Current Perspectives in Prediabetic Neuropathy

D. Ziegler[1], A. Holz[2], I. Gurieva[3], V. Horvath[4], B.N. Mankovsky[4], G. Radulian[5], O. Schnell[6,7], V. Spallone[8], A. Stirban[9], S. Tesfaye[10], P. Kempler[4]

Diabetes Stoffw Herz 2021; 30: 36 – 48

Summary

Diabetic neuropathies are prevalent in people with type 1 or type 2 diabetes and are characterised by long-term progressive dysfunction and loss of sensory, motor, and autonomic nerve fibres. Evidence has accumulated suggesting an increased prevalence of peripheral neuropathies as early as in prediabetes and newly diagnosed diabetes, so that the term frequently used for neuropathy as a 'late' diabetic complication is misleading. This review will elaborate on the existence of prediabetic neuropathies and discuss the risk factors for their development. Our aim is to raise awareness of prediabetic neuropathy in clinical practice and encourage early screening for peripheral neuropathies to enable management opportunities.

Key words
prediabetic neuropathy, distal sensorimotor polyneuropathy, cardiovascular autonomic neuropathy, diabetes mellitus

Prädiabetische Neuropathie – aktuelle Perspektiven

Zusammenfassung

Diabetische Neuropathien sind häufige Komplikationen des Diabetes mellitus und weisen eine hohe Prävalenz sowohl bei Menschen mit Typ-1- als auch bei Menschen mit Typ-2-Diabetes auf. Sie sind charakterisiert durch eine langfristig fortschreitende Dysfunktion und den Verlust von sensorischen, motorischen und autonomen Nervenfasern. Es mehren sich Hinweise darauf, dass periphere Neuropathien bereits bei Menschen mit Prädiabetes und neu diagnostiziertem Diabetes auftreten. Daher ist die Annahme, dass Neuropathien „späte" Komplikationen im Diabetesverlauf sind, irreführend. In diesem Übersichtsartikel stellen wir die Evidenz zur Existenz prädiabetischer Neuropathien vor und diskutieren mögliche Risikofaktoren für ihr Entstehen. Wir möchten das Bewusstsein für die prädiabetische Neuropathie in der klinischen Praxis schärfen und somit auf die Bedeutung eines frühen Screenings auf periphere Neuropathien sowie deren Behandlung hinweisen.

Schlüsselwörter
prädiabetische Neuropathie, distal-sensomotorische Polyneuropathie, kardiovaskuläre autonome Neuropathie, Diabetes mellitus

Diabetic neuropathy – a common and fatal complication

Peripheral neuropathies, specifically distal sensorimotor polyneuropathy (DSPN) and cardiovascular autonomic neuropathy (CAN), are amongst the most common complications of both type 1 and type 2 diabetes mellitus (T1DM and T2DM, respectively). Risk factors for both DSPN and CAN include diabetes duration, poor glycaemic control, and cardiovascular risk factors such as hypertension, obesity, smoking, and hypertriglyceridaemia [Andersen 2018, Moţăţăianu 2018, Tesfaye 1996, Tesfaye 2005]. Prevalence estimates for DSPN in the literature vary depending on the definitions and methodology used, but are assumed to be around 30 % in people with T1DM and T2DM and up to 50 % in elderly people with T2DM [Boulton 2004, Ziegler 2014, Ziegler 2018]. Similarly, estimates of CAN prevalence show a wide range in both T1DM and T2DM [Dimitropoulos 2014, Fisher 2017, Karayannis 2012, Spallone 2011, Tesfaye 2010, Verrotti 2009, Vinik 2013 (a), Vinik 2013 (b)].

1) Institute for Clinical Diabetology, German Diabetes Centre, Leibniz Centre for Diabetes Research at Heinrich Heine University; Division of Endocrinology and Diabetology, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany
2) WÖRWAG Pharma GmbH & Co. KG, Böblingen, Germany
3) Department of Endocrinology, Russian Medical Academy of Continuous Professional Education, Moscow, Russia
4) Semmelweis University, 1st Dept. of Medicine, Budapest, Hungary
5) Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
6) Sciarc GmbH, Baierbrunn, Germany
7) Forschergruppe Diabetes e.V., München-Neuherberg, Germany
8) Endocrinology, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
9) Internistische Fachklinik Dr. Steger, Nürnberg, Germany
10) Diabetes Research Unit, Sheffield Teaching Hospitals and University of Sheffield, Sheffield, UK

for internal use only – © Kirchheim Publishers

	Impaired glucose tolerance (IGT)	Impaired fasting glucose (IFG)
World Health Organization, International Diabetes Federation [World Health Organization 2006]		
Fasting plasma glucose	< 7.0 mmol/l (< 126 mg/dl)	6.1 – 6.9 mmol/l (110 – 125 mg/dl)
Two-hour plasma glucose	≥ 7.8 and < 11.1 mmol/l (≥ 140 and < 200 mg/dl)	< 7.8 mmol/l (< 140 mg/dl)
American Diabetes Association [Genuth 2003]		
Fasting plasma glucose	-	5.6 – 6.9 mmol/l (100 – 125 mg/dl)
Two-hour plasma glucose	7.8 – 11.0 mmol/l (140 – 199 mg/dl)	-

Tab. 1: Diagnostic thresholds for impaired glucose regulation.

Diabetic neuropathies are characterised by a dysfunction and loss of nerve fibres of the somatic and autonomic nervous systems [Pop-Busui 2017, Spallone 2011, Tesfaye 2010]. DSPN may manifest in a multitude of symptoms including pain, dysaesthesiae, numbness, tingling, and impaired balance with increased risk of falls. Patients with painful DSPN are often limited in their daily activities and frequently have mood disorders, including depression and anxiety, leading to chronic insomnia and impaired quality of life [Pop-Busui 2017]. Foot ulcers are also a common complication in people with DSPN [Boulton 2014] associated with increased risk of not only amputation but also death [Vadiveloo 2018]. In patients with CAN, the damaged autonomic fibres innervating the heart may have an adverse impact on the regulation of heart rate, cardiac output, myocardial contractility, cardiac electrophysiology, and coronary blood flow [Balcıoğlu 2015], which may culminate in serious clinical sequelae such as arrhythmias, silent myocardial ischaemia or sudden death [Verrotti 2014].

Both DSPN and CAN are associated with an increased risk of all-cause mortality and cardiovascular mortality in diabetes patients [Brownrigg 2014, Forsblom 1998, Hsu 2012]. The Michigan Neuropathy Screening Instrument (MNSI) questionnaire for neuropathic symptoms has been shown to predict all-cause and cardiovascular mortality in individuals with T2DM. In a post-hoc analysis of the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints) trial, Seferovic and colleagues identified three core questions from the MNSI – "Are your legs numb?", "Have you ever had an open sore on your foot?" and "Do your legs hurt when you walk?" – to which a positive answer was associated with major adverse cardiovascular events. These questions may therefore be suitable to identify high-risk individuals in clinical practice, but further studies are needed to confirm this [Seferovic 2018].

The exact mechanisms underlying the increased risk of mortality in indi-

Abbreviations

ACE	angiotensin-converting-enzyme
ADRA2B	alpha2b adrenergic receptor
ADA	American Diabetes Association
AGEs	advanced glycation end products
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints
BRS	baroreflex sensitivity
CAN	cardiovascular autonomic neuropathy
CNBD	corneal nerve branch density
CNFD	corneal nerve fibre density
CNFL	corneal nerve fibre length
DCCT/EDIC	Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications
DM	diabetes mellitus
DPPOS	Diabetes Prevention Program Outcomes Study
DSPN	distal sensorimotor polyneuropathy
Glo1	glyoxalase 1
GST	glutathione S-transferase
HbA_{1c}	glycosylated haemoglobin A_{1c}
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HF	high frequency power in the R-R interval spectrum between 0.12 and 0.40 Hz
HRV	heart rate variability
IDF	International Diabetes Federation
IENFD	intra-epidermal nerve fibre density
IFG-1	fasting glucose 5.6 – 6.0 mmol/l
IFG-2	fasting glucose 6.1 – 6.9 mmol/l
(i-)IFG	(isolated) impaired fasting glucose
(i-)IGT	(isolated) impaired glucose tolerance
IL-4	interleukin-4
k-DM	known diabetes mellitus
KORA	Cooperative Health Research in the Augsburg Region
LF	low frequency power in the R-R interval spectrum between 0.04 and 0.12 Hz
Look AHEAD	Look Action for Health in Diabetes
MetS	metabolic syndrome
MNSI	Michigan Neuropathy Screening Instrument
MTHFR	methylenetetrahydrofolate reductase
NAFLD	non-alcoholic fatty liver disease
NC	nerve conduction
n-DM	newly diagnosed/detected diabetes mellitus
NDS	Neuropathy Deficit Score
NGT	normal glucose tolerance
NSS	Neuropathy Symptom Score
n-T2DM	newly diagnosed/detected type 2 diabetes mellitus
OSA	obstructive sleep apnoea
PKC	protein kinase C
PNSS	positive neuropathic sensory symptoms
PS	pressure sensation
RMSSD	square root of the mean of the squares of successive differences in normal-to-normal intervals
30:15 R-R	ratio between 30th and 15th R-R interval after standing from supine position
SDANN	standard deviation of 5-min averaged normal-to-normal intervals
SDNN	standard deviation of normal-to-normal intervals
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TCF7L2	transcription factor 7-like2
VEGF	vascular endothelial growth factor
VP	vibration perception
WHO	World Health Organization

for internal use only – © Kirchheim Publishers

viduals with DSPN and CAN remain largely unknown. It has been suggested that the progression of microvascular and macrovascular complications may play a role in increased mortality rates amongst individuals with DSPN [Dietrich 2017]. A number of cardiovascular alterations associated with CAN may contribute to the increased risk of mortality; these alterations include resting tachycardia, QT interval prolongation, orthostatic hypotension, reverse dipping, and silent myocardial ischaemia [Spallone 2019].

Prediabetes

Prediabetes or intermediate hyperglycaemia [Beulens 2019] are terms used for individuals with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) [International Dia-

Study and publication	Measure	Population	Number (n)	Prevalence (%)	Statistics
[Fujimoto 1987]	DSPN (abnormal NC)	NGT IGT DM	79 72 78	5.1 2.9 46.2 [a]	[a] $p<0.05$ for DM vs. NGT and DM vs. IGT
Hoorn study [de Neeling 1996]	DSPN (absent VP/ankle reflex)	NGT IGT n-DM k-DM	267 167 90 73	10.5 [a], 6.0 [b] 16.2 [a], 15.6 [b] 43.3 [a], 32.2 [b] 68.5 [a], 67.1 [b]	[a] $p<0.01$ for k-DM vs. NGT [b] $p<0.05$ for IGT vs. NGT and n-DM vs. NGT; $p<0.001$ for k-DM vs. NGT
MONICA/KORA Augsburg Surveys S2 and S3 [Ziegler 2008]	DSPN (MNSI > 2)	NGT i-IFG IGT k-DM	81 71 46 195	7.4 11.3 13.0 28.0	$p \leq 0.05$ for k-DM vs. NGT, k-DM vs. IFG, and k-DM vs. IGT
MONICA/KORA Augsburg Surveys S2 and S3) [Ziegler 2009 (a)]	Painful DSPN (MNSI > 2)	NGT i-IFG IGT k-DM	81 71 46 195	1.2 4.2 8.7 13.3	Overall $p=0.003$
KORA Myocardial Infarction Registry [Ziegler 2009 (b)]	Painful DSPN (MNSI > 2)	NGT i-IFG IGT k-DM	81 70 61 214	3.7 5.7 14.8 21.0	Overall $p<0.001$
OC IGTrial [Dyck 2012]	DSPN (abnormal NC plus neuropathic signs and symptoms)	NGT IFG and/or IGT n-DM	150 174 218	2.0 1.7 7.8 [a]	[a] $p=0.02$ for n-DM vs. NGT and $p<0.01$ for n-DM vs. IFG and/or IGT
SH-DREAMS study [Lu 2013]	DSPN (NDS ≥ 6 or NDS ≥ 3 + NSS ≥ 5)	NGT IFG and/or IGT DM	458 1043 534	1.5 2.8 8.4 [a]	[a] $p<0.05$ for DM vs. NGT and for DM vs. IFG and/or IGT
KORA S4 study [Bongaerts 2013]	DSPN (bilaterally impaired VP and/or PS)	NGT i-IFG i-IGT IFG + IGT n-DM k-DM	577 55 183 46 62 177	11.1 5.5 14.8 23.9 16.1 22.0	Not determined
PROMISE cohort [Lee 2015] *	DSPN (MNSI > 2)	NGT IFG and/or IGT n-DM	344 101 22	29.0 49.0 50.0	$p<0.001$ for trend
OC IGTrial [Kassardjian 2015]	Symptomatic small fibre DSPN (PNSS score >1/ HP-5 ≥ 95th/HP-5 ≤ 5th)	NGT IFG and/or IGT n-DM	138 165 195	5.1/13.4/7.5 5.5/20.5/9.3 6.2/22.8/9.8	Not significant
Health ABC study [Callaghan 2016 (a)]	Symptomatic DSPN (symptoms plus ≥ 1 of 3 tests abnormal)	NGT IFG and/or IGT DM	1145 699 490	8.6/11.4 ** 5.6/10.6 ** 16.7/17.1 **	Not determined $p<0.05$ for effect of diabetes
[Callaghan 2018]	DSPN (MNSI ≥ 2.5)	NGT IFG and/or IGT DM	1487 1758 757	3.25 6.29 15.12	Overall $p<0.0001$
[Kurisu 2019]	DSPN (Toronto criteria: possible/probable/confirmed)	NGT IFG n-DM k-DM	430 120 13 62	17.4/2.1/2.1 19.2/0.8/1.7 7.7/0/0 41.9 [a]/9.7 [a]/16.1 [a]	Overall $p<0.001/=0.002/<0.001$ [a] $p<0.01$ for k-DM vs. all other groups

* Study including individuals at high risk for T2DM, three-year follow-up examination; ** Prevalance rates for subjects with no/4 additional MetS components are depicted

Tab. 2: Population-based DSPN prevalence in individuals with prediabetes in comparison to normoglycaemic controls and patients with diabetes; DM: diabetes mellitus, DSPN: distal sensorimotor polyneuropathy, HP-5 ≥ 95th: hypoalgesia (HP-5 ≥ 95th percentile), HP-5 ≤ 5th: hyperalgesia (HP-5 ≤ 5th percentile), (i-)IFG: (isolated) impaired fasting glucose, IFG + IGT: combined impaired fasting glucose and impaired glucose tolerance, (i-)IGT: (isolated) impaired glucose tolerance, k-DM: known diabetes mellitus, MetS: metabolic syndrome, MNSI: Michigan Neuropathy Screening Instrument, NC: nerve conduction, n-DM, newly diagnosed/detected diabetes mellitus, NDS: Neuropathy Deficit Score, NGT: normal glucose tolerance, NSS: Neuropathy Symptom Score, PNSS: positive neuropathic sensory symptoms, PS: pressure sensation, VP: vibration perception.

for internal use only – © Kirchheim Publishers

betes Federation 2019]. The American Diabetes Association (ADA) and World Health Organization (WHO) have provided frequently used cut-off values for IGT and IFG; these are summarised in Table 1. The most recent International Diabetes Federation (IDF) Atlas estimated a global IGT prevalence of 7.5 % in adults (20–79 years) [International Diabetes Federation 2019]. The population-based Hoorn study cohort showed an IFG prevalence of 33.2 % according to ADA criteria and 10.1 % based on WHO/IDF criteria [Rijkelijkhuizen 2007]. In the Euro Heart Survey, oral glucose tolerance tests in patients with acute or stable coronary heart disease referred to a cardiologist revealed that 5 % of the participants had IFG and 32 % had IGT [Bartnik 2007]. Similarly, a German study found that 1 % of patients with coronary artery disease had IFG and 34 % had IGT [Doerr 2011].

Prediabetes is associated with a marked increase in risk of developing T2DM [International Diabetes Federation 2019]. A review of 103 prospective cohort studies estimated the rate of progression from IGT or IFG towards manifestation of T2DM between 26 % and 50 % (follow-up period ranging from 1 to 24 years) [Richter 2018], with some studies showing around 70 % to develop T2DM within 10 years [DeJesus 2017]. On average, it took 8.5 years to develop manifest T2DM in men compared to 10.3 years in women [Bertram 2010]. Thus, not everyone with intermediate hyperglycaemia necessarily progresses to T2DM, and regression to normoglycaemia has also been observed [Richter 2018, Vistisen 2019].

Prediabetes appears to be associated with an increased risk of cardiovascular disease [Huang 2016, International Diabetes Federation 2019] comparable to T2DM [DeFronzo 2011], although not all studies have ultimately validated such a relationship for IFG per se [Yeboah 2011]. However, reversion from increased two-hour glucose values to normoglycaemia has been associated with reduced risk of developing cardiovascular disease [Vistisen 2019].

The concept of metabolic memory suggests that early glycaemic normalisation may be relatively beneficial to postpone hyperglycaemia-induced vascular processes in the longer term [Otto-Buczkowska 2010, Reddy 2015]. With regard to diabetic neuropathies, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study showed that in contrast to conventional therapy, early intensive therapy in patients with T1DM resulted in long-term lower prevalence and incidence of DSPN and CAN even after the prior glycaemic separation vanished [Martin 2014, Pop-Busui 2010]. Early preventive measures in individuals with prediabetes appear desirable in view of the proposed concept of metabolic memory and its impact on outcomes [Roman 2009, Testa 2010].

Does prediabetic neuropathy exist?

Several studies identified varying relationships between peripheral neuropathies and IFG and/or IGT. Table 2 summarises the results from larger population-based studies including at least 200 participants with various degrees of glucose tolerance reporting prevalence rates of DSPN. Several studies have reported increased prevalence rates of DSPN in people with prediabetes compared to those with normal glucose tolerance (NGT), which were comparable to the prevalence rates observed in newly diagnosed T2DM [Bongaerts 2013, de Neeling 1996, Lee 2015, Ziegler 2008, Ziegler 2009 (a), Ziegler 2009 (b)]. Variable neuropathy testing and the diagnostic thresholds used may explain the high variability of prevalence rates in different studies [Ziegler 2014]. Especially the presence of IGT seems to be a major determinant in the development of nerve damage in people with prediabetes [Bongaerts 2013, Ziegler 2008, Ziegler 2009 (a), Ziegler 2009 (b)]. DSPN prevalence was assessed in six groups with different degrees of glucose tolerance in the KORA S4 (Cooperative Health Research in the Augsburg Region) study. The prevalence of clinical DSPN was particularly high in people with combined IFG and IGT, reaching 23.9 % compared to 5.5 % in people with isolated IFG and 14.8 % in those with isolated IGT [Bongaerts 2013]. However, some studies found no difference in DSPN prevalence between individuals with prediabetes and NGT [Callaghan 2016 (a), Callaghan 2018, Dyck 2012, Fujimoto 1987, Kassardjian 2015, Kurisu 2019, Lu 2013]. The reasons for these discrepancies have been discussed previously [Papanas 2011] and may include the following: focus on large fibre impairment only [Dyck 2012, Fujimoto 1987], very low DSPN prevalence in the population examined [Dyck 2012, Kassardjian 2015, Lu 2013], problems of generalisability [Callaghan 2018, Kurisu 2019, Lu 2013], and variable definitions of symptomatic DSPN [Dyck 2011].

The high proportion of individuals with painless or asymptomatic DSPN entities complicates the situation in clinical practice [Bongaerts 2013, Kasznicki 2014]. The PROTECT study showed that the condition was previously undiagnosed in 75 % of the participants without any history of diabetes despite signs of DSPN. Among participants without a history of diabetes, 39.2 % had glycosylated haemoglobin A_{1c} (HbA_{1c}) levels in the prediabetic or even diabetic ranges [Ziegler 2018], while 77 % of individuals with diabetes and 91 % of those with prediabetes were unaware of having DSPN in the KORA F4 study [Bongaerts 2013].

Table 3 summarises the results from larger population-based studies including data on various measures of CAN from at least 200 participants with prediabetes, diabetes and healthy controls. The only study reporting prevalence rates of CAN is the KORA S4 study. This cohort showed a prevalence of 8.1 % and 5.9 % for CAN in subjects with isolated IFG and isolated IGT, respectively, compared to 4.5 % in NGT and 11.7 % in newly diagnosed diabetes. Similar to DSPN, CAN prevalence was particularly high in people with combined IFG and IGT, reaching 11.4 % [Dyck 2011]. Other studies comparing mean levels of measures of heart rate variability (HRV) and baroreflex sensitivity (BRS) consistently confirmed reduced cardiac autonomic function in people with prediabetes and an association with worsening glycaemic control [Coopmans 2020, Gerritsen 2000, Schroeder 2005, Singh 2000, Stein 2007, Wu 2007, Wu 2014, Ziegler 2015 (c)]. Impaired BRS was detected in IGT but not isolated IFG [Wu 2014]. Meyer and colleagues reported data from 11 994 non-diabetic US Hispanics from

for internal use only – © Kirchheim Publishers

Study and publication	Measure	Population	Number (n)	Prevalence (%)	Statistics
KORA S4 study [Ziegler 2015 (c)]	CAN (≥2 of 4 HRV indices abnormal)	NGT i-IFG i-IGT IFG+IGT n-DM k-DM	565 336 72 151 78 130	4.5 8.1 5.9 11.4 11.7 17.5	p<0.05 for i-IFG vs. NGT, IFG+IGT vs. NGT, n-DM vs. NGT, and k-DM vs. NGT

Study and publication	Measure	Population	Number (n)	Median (range)/ geometric mean±SD	Statistics
Hoorn study [Gerritsen 2000]	SDNN (ms)	NGT IGT n-DM k-DM	288 169 95 79	34.8 (33.0–36.7) 31.3 (29.1–33.5) 28.2 (25.0–31.8) 25.0 (22.2–28.0)	SDNN: p<0.01 for trend p<0.05 for NGT vs. all
	LF (ms^2)	NGT IGT n-DM k-DM	288 169 95 79	251 (220–286) 224 (190–264) 163 (123–215) 148 (109–202)	LF, HF, and BRS: p<0.01 for trend p<0.05 for n-DM vs. NGT and vs. k-DM NGT
	HF (ms^2)	NGT IGT n-DM k-DM	288 169 95 79	202 (174–234) 172 (142–208) 135 (102–180) 113 (83–155)	
	BRS (ms/mmHg)	NGT IGT n-DM k-DM	288 169 95 79	8.0 (7.5–8.6) 7.2 (6.5–8.0) 6.1 (5.3–7.0) 6.3 (5.4–7.5)	
Framingham Heart study [Singh 2000]	SDNN (ms)	NGT IFG DM	1,779 56 84	4.51±0.01 4.37±0.04 4.28±0.03	SDNN, LF, and HF: p<0.05 for DM vs. NGT and IFG vs. NGT
	LF (ms^2)	NGT IFG DM	1,779 56 84	6.77±0.02 6.26±0.10 6.03±0.08	
	HF (ms^2)	NGT IFG DM	1,779 56 84	5.55±0.02 5.06±0.11 4.95±0.09	
ARIC study [Schroeder 2005]	SDNN (ms)	NGT IFG DM	5410 3561 969	31.46 (31.00–31.92) 31.42 (30.85–32.00) 27.95 (26.67–29.23)	SDNN: p<0.05 for DM vs. NGT
	R-R interval (mm)	NGT IFG DM	5410 3561 969	976 (971–980) 955 (949–960) 908 (895–921)	R-R interval: p<0.05 for DM vs. NGT and IFG vs. NGT
	RMSSD (ms)	NGT IFG DM	5410 3561 969	24.98 (24.45–25.50) 24.83 (24.16–25.49) 21.09 (19.62–22.57)	RMSSD: p<0.05 for DM vs. NGT
[Wu 2007]	SDNN (ms)	NGT i-IFG IGT DM	983 163 188 106	39.5±24.3 33.1±18.8 29.6±17.2 23.5±15.6	SDNN: p<0.001 (ANOVA); p<0.001 for DM vs. NGT p<0.01 for DM vs. i-IFG p<0.001 for IGT vs. NGT p<0.01 for i-IFG vs. NGT
	30:15 R-R	NGT i-IFG IGT DM	983 163 188 106	1.10±0.13 1.07±0.10 1.06±0.11 1.04±0.09	30:15 R-R: p<0.001 (ANOVA) p<0.001 for DM vs. NGT and IGT vs. NGT
Cardiovascular Health study [Stein 2007]	SDNN (ms)	NGT IFG-1 IFG-2 DM	536 363 182 178	123±2 121±2 112±3 110±3	SDNN: p<0.001 for DM vs. NGT, p=0.001 for IFG-2 vs. NGT, p=0.024 for IFG-2 vs. IFG-1
	SDANN (ms)	NGT IFG-1 IFG-2 DM	536 363 182 178	110±2 109±2 101±3 99±3	SDANN: p=0.001 for DM vs. NGT, p=0.005 for IFG-2 vs. NGT, p=0.042 for IFG-2 vs. IFG-1

for internal use only – © Kirchheim Publishers

Study and publication	Measure	Population	Number (n)	Median (range)/ geometric mean ± SD	Statistics
[Wu 2014]	BRS (ms/mmHg)	NGT i-IFG IGT n-DM	498 61 126 83	11.71 ± 6.09 11.50 ± 5.44 9.49 ± 5.27 8.53 ± 5.03	BRS and Valsalva ratio: p < 0.001 (ANOVA) p < 0.001 for trend p < 0.001 for n-DM vs. NGT, p < 0.01 for IGT vs. NGT, p < 0.05 for n-DM vs. i-IFG
	Valsalva ratio	NGT i-IFG IGT n-DM	498 61 126 83	1.54 ± 0.24 1.50 ± 0.24 1.45 ± 0.23 1.40 ± 0.21	
Maastricht study [Coopmans 2020]	HRV (time domain, composite score SD)	NGT IFG and/or IGT DM	1,226 331 550	0.15 ± 0.93 –0.10 ± 0.84 –0.33 ± 0.95	p < 0.001 for trend in HRV (time domain and frequency domain)
	HRV (frequency domain, composite score, SD)	NGT IFG and/or IGT DM	1,226 331 550	0.16 ± 0.99 –0.10 ± 0.80 –0.32 ± 0.91	

Tab. 3: Population-based prevalence of CAN (KORA S4 study) and averaged levels of HRV indices in individuals with prediabetes in comparison to normoglycaemic controls and patients with diabetes; BRS: baroreflex sensitivity (ms/mmHg), CAN: cardiac autonomic neuropathy, DM: diabetes mellitus, HF: high frequency power spectrum, HRV: heart rate variability, (i-)IFG: (isolated) impaired fasting glucose, IFG-1: fasting glucose 5.6–6.0 mmol/l, IFG-2: fasting glucose 6.1–6.9 mmol/l, IFG + IGT: combined impaired fasting glucose and impaired glucose tolerance, (i-)IGT: (isolated) impaired glucose tolerance, k-DM: known diabetes mellitus, LF: low frequency power spectrum, n-DM: newly diagnosed/detected diabetes mellitus, NGT: normal glucose tolerance, RMSSD: square root of the mean of the squares of successive differences in normal-to-normal intervals, SDANN, standard deviation of 5 min averaged normal-to-normal intervals, SDNN: standard deviation of normal-to-normal intervals, 30:15 R-R: ratio between 30th and the 15th R-R interval after standing from supine position.

the US (HCHS/SOL [Hispanic Community Health Study/Study of Latinos] cohort). This study showed an association between impairment in glucose homeostasis such as IFG and lower HRV, suggesting that reduced cardiac autonomic function may be present even before the onset of overt diabetes [Meyer 2016].

In addition to population-based data, a large hospital-based study by Dimova and colleagues showed DSPN prevalence, defined as abnormal nerve conduction (NC), of 0 % in NGT, 5.7 % in IFG and/or IGT and 28.6 % in newly diagnosed T2DM. Prevalence of CAN, defined as reduced HRV (ANX-3.0 method), was 19.8 % in individuals with IFG and/or IGT compared to 12.3 % in NGT and 32.2 % in n-T2DM [Dimova 2017]. In line with observations in the KORA S4 survey and the study by Coopmans et al., Dimova and colleagues showed that CAN prevalence was particularly high in people with isolated IGT reaching 20.6 % compared to 13.2 % in subjects with IFG [Dimova 2017].

Overall, associations have been observed between increased glucose intolerance and both DSPN and CAN. Even though the prevalence may vary in different populations, evidence points towards the occurrence of prediabetic neuropathies. A recent review summarising data from the surveys of the KORA cohort concluded that prevalence rates in both DSPN and CAN in individuals with combined IFG and IGT reach levels comparable to those found in newly diagnosed T2DM [Herder 2019]. This emerging evidence prompted the ADA to recognise the relevance of peripheral neuropathies in people with prediabetes in 2017. The ADA position statement on diabetic neuropathy included a recommendation to screen patients with prediabetes who have neuropathic symptoms. This recommendation has been further fostered by the related comorbidities of DSPN such as cardiovascular risk, foot ulceration and amputation as mentioned above, alongside of falls and fractures [Pop-Busui 2017]. Thus, DSPN and CAN can no longer be considered "late" complications of diabetes.

Which factors determine the development of prediabetic neuropathy?

The detailed mechanisms responsible for the development of peripheral neuropathies in prediabetes remain to be elucidated. Several factors are considered in the ongoing studies aimed at further understanding the impact of metabolic imbalance on the vascular system. A number of non-modifiable risk factors such as age and height, but also modifiable risk factors such as glycaemic control are associated not only with diabetic neuropathy but also prediabetic neuropathy [Lee 2015, Németh 2017]. Other traditional cardiovascular risk factors such as hypertriglyceridaemia may also play a role in the development of peripheral neuropathies in individuals with prediabetes [Stino 2017].

Postprandial glucose levels and other risk factors

The KORA F4 study demonstrated a relationship between elevated two-hour postprandial glucose levels and increased risk of DSPN in people with IFG, IGT and known diabetes [Bongaerts 2012]. Dimova and colleagues found a relationship between two-hour postprandial glucose and increased CAN prevalence [Dimova 2017]. A similar relationship was observed for two-hour postprandial glucose and cardiovascular disease, specifically coronary artery disease, even in the absence of a diabetes diagnosis [Fu 2018].

Obesity

Obesity has been identified as a risk factor for DSPN in individuals with T1DM and T2DM, and also in people with

for internal use only – © Kirchheim Publishers

prediabetes and normoglycaemia [Callaghan 2016 (b), Grisold 2017, Papanas 2015]. Obese but normoglycaemic individuals showed a DSPN prevalence of up to 11 % compared to 3.8 % in lean controls [Callaghan 2016 (b)]. The increased risk of peripheral neuropathy appears to correlate with small fibre integrity [Smith 2013]. Recent studies suggest that the relationship between obesity and DSPN in individuals with and without diabetes might be mediated by subclinical inflammation [Schlesinger 2019]. Higher levels of pro-inflammatory biomarkers as a consequence of obesity may directly affect neuronal cells and increase the risk of DSPN [Schlesinger 2019]. However, a direct correlation of obesity with the development of peripheral neuropathies is difficult to decipher as obesity is strongly associated with glycaemic imbalance and other cardiovascular risk factors.

Inflammation

Inflammation has been frequently addressed as a factor in the development of diabetic neuropathy. Prooxidant and antioxidant markers have both been implicated in the development of DSPN at early stages of diabetes [Herder 2018, Herder 2019]. One prospective study showed that oxidative stress, characterised by increased superoxide anion generation, preceded the decline in sensory and cardiac autonomic nerve function [Ziegler 2015 (a)]. Intracellular hyperglycaemia may result in tissue damage via alteration of several molecular pathways. The increased activation of the polyol pathway depletes the cellular antioxidant capacity and thus exposes the cell to oxidative stress; the formation of advanced glycation end products (AGEs) triggers the expression of cytokines and growth factors; the protein kinase C (PKC) pathway alters the expression of inflammation markers as well as reactive oxygen species. Other pathways such as the hexosamine pathway may additionally modify proteins and alter gene expression to target tissue damage (reviewed in [Brannick 2016]). Data on inflammation and CAN are limited in individuals with either prediabetes or diabetes [Herder 2019].

Genetic predisposition

Aside from modifiable risk factors, genetic predisposition appears to be an important factor in the development of diabetic neuropathy [Politi 2016]. Genes found to be associated with diabetic neuropathy include angiotensin-converting-enzyme (ACE), a potent vasoconstrictor; methylenetetrahydrofolate reductase (MTHFR); glutathione S-transferase (GST), which is involved in protection against oxidative stress; and glyoxalase 1 (Glo1), which is associated with the formation of AGEs [Politi 2016]. Apart from that, transcription factor 7-like2 (TCF7L2), a mediator of the Wnt signalling pathway; vascular endothelial growth factor (VEGF), which promotes vascular endothelial cell proliferation; interleukin-4 (IL-4), which is involved in anti-inflammation inter alia; and glutathione peroxidase-1 and alpha2b adrenergic receptor (ADRA2B) are associated with diabetic neuropathy (reviewed in [Politi 2016]). The respective products of these genes are mainly involved in inflammation, oxidative stress, and neuronal function and development [Politi 2016]. Other studies have indicated that polymorphisms in enzymes such as transketolase involved in metabolic pathways are associated with neuropathic symptoms in recent-onset diabetes [Ziegler 2017]. Taking genetic predisposition into account might explain why some individuals with diabetes are more prone to develop peripheral neuropathies than others.

What are the characteristics of prediabetic neuropathy?

Generally, peripheral neuropathies associated with prediabetes are clinically similar to early diabetic neuropathies [Smith 2008]. Metabolic alterations trigger pathogenic mechanisms, which in turn lead to neuronal damage [Yagihashi 2011]. Prediabetic neuropathy is associated with reduced endothelium-dependent vasodilation and axon-reflex elicited flare areas [Caballero 1999, Green 2010]. The capillary luminal area appears lower in subjects with NGT progressing to IGT or those with IGT progressing to diabetes compared to persons with constant NGT or constant IGT [Thrainsdottir 2003]. Early neuropathic features in people with prediabetes may include impaired warm/cold perception [Putz 2009] and neuropathic pain [Papanas 2011]. Less pronounced impairments in sural nerve amplitudes, conduction velocities and distal leg intra-epidermal nerve fibre density (IENFD) have been reported in prediabetes compared to diabetic polyneuropathy [Papanas 2011, Singleton 2001, Sumner 2003].

Improvements in corneal nerve fibre density (CNFD), corneal nerve branch density (CNBD), and corneal nerve fibre length (CNFL) compared to baseline have been observed in individuals with IGT who converted to NGT within 36 months. Neuropathy assessments in people remaining with IGT and those developing T2DM over 36 months were comparable or deteriorated, respectively [Azmi 2015], between baseline and study end, suggesting that an improvement in glucose tolerance coincides with improving nerve pathology [Azmi 2015].

A progressive course of nerve fibre damage has been suggested in diabetic neuropathy reflected by symptoms progressing from pure small to large nerve fibre symptoms. Some studies indicate that small fibres may be affected more than large fibres in prediabetic neuropathy compared to diabetic neuropathy [Groener 2020, Papanas 2011, Putz 2009, Singleton 2001, Sumner 2003]. Small nerve fibres lack a myelin sheath, and may therefore be more susceptible to damage [Papanas 2011, Papanas 2012, Singleton 2001, Sumner 2003]. Information varies on the course of nerve fibre damage in prediabetic and diabetic neuropathies; a clear phenotype has not been determined and should be focus of further investigation. The potentially less severe clinical manifestation of prediabetic neuropathy compared to diabetic neuropathy may induce less pronounced neuropathic symptoms and deficits; this may result in reduced awareness of prediabetic neuropathy [Groener 2020, Ziegler 2018].

Implications for clinical practice

Nerve function may deteriorate progressively without any intervention, so that timely peripheral neuropathy diagno-

for internal use only – © Kirchheim Publishers

sis is crucial in slowing down and halting progression or even restoring nerve function as early as possible [Pfeifer 1995]. The potential link of prediabetic neuropathy to the damage of small nerve fibres might be advantageous when considering that these may also be more amenable to regeneration, even if these nerve fibres may also be more prone to injury [Singleton 2015].

Treatment of prediabetic neuropathy has not been frequently addressed. The long-term follow-up of the Diabetes Prevention Program Outcomes Study (DPPOS) indicated that lifestyle modification may reduce diabetes incidence in a population at high risk of developing diabetes. Participants who did not develop diabetes showed a 28 % lower prevalence of microvascular complications, including neuropathy [Diabetes Prevention Program Research Group 2015]. One small uncontrolled one-year study demonstrated that lifestyle interventions consisting of individualised diet and exercise counselling was associated with improvements in innervation and neuropathic pain in individuals with prediabetes and DSPN [Smith 2006]. A number of studies on obese individuals have shown that weight loss, achieved either by lifestyle changes, diet, or bariatric surgery may reverse reductions in HRV, indicating improvement in cardiac autonomic dysfunction [Alam 2009, Casellini 2016, de Jonge 2010, Kokkinos 2013, Lips 2013, Rissanen 2001, Sjoberg 2011, Straznicky 2016, Wasmund 2011, Ziegler 2015 (b)]. It was suggested that the improvements in autonomic function may have a positive impact on diabetes outcomes, specifically on cardiovascular mortality. Of note, the positive impact of weight loss on CAN appears to be independent of glycaemic status [Casellini 2016, Lips 2013, Sjoberg 2011, Straznicki 2016, Ziegler 2015 (b)]. Aside from weight loss, exercise was observed to positively influence autonomic function in individuals with T2DM [Bhati 2018, Villafaina 2017]. A meta-analysis concluded that long-term and regular exercise improves cardiac autonomic function, especially in individuals with T2DM. The Look AHEAD (Look Action for Health in Diabetes) study showed that intensive lifestyle intervention resulted in a modest improvement in neuropathic symptoms assessed by the MNSI questionnaire after 12 years in overweight or obese people with T2DM [Look AHEAD Research Group 2017]. Some studies have shown a reversal of neuropathic damage in individuals with prediabetes [Singleton 2015, Smith 2006], but the overall evidence for an effect of physical exercise on CAN is less robust in people with T1DM or prediabetes than in those with T2DM [Röhling 2017].

It should be kept in mind that some studies investigating lifestyle intervention in individuals with metabolic syndrome and CAN did not show any improvement in autonomic function, even though markers of oxidative stress and components of the metabolic syndrome were positively influenced [Pennathur 2017]. Moreover, analysing CAN in relation to prediabetes, diagnosis of CAN in most of these studies relied on HRV indices rather than the more commonly used cardiovascular autonomic reflex tests. It should be further noted that most improvements mediated by weight loss were observed for small fibre function, but not large fibre function. Nevertheless, a positive effect of weight loss on large fibres is also conceivable as improvement of neuropathic signs may take several years, and might therefore not be observed in clinical trials with shorter time periods [Casellini 2016, Ziegler 2011, Ziegler 2016].

Intensive glycaemic control is the most effective way of preventing or slowing the progression of diabetic neuropathy in individuals with T1DM [Ang 2014, Callaghan 2012 (c), Dimitropoulos 2014, Ismail-Beigi 2010, Pambianco 2006, Pop-Busui 2010], so that optimising glycaemic control is considered the basis in the management of diabetic neuropathy. Disease-modifying treatments for DSPN are limited. Treatment with the antioxidant α-lipoic acid for four years has been shown to improve neuropathic deficits in patients with DSPN. Benfotiamine may interfere with pathogenetic glucose-metabolising pathways, such as the formation of AGEs, and short-term clinical trials with this vitamin B_1 derivative have shown improvements in neuropathic symptoms [Bönhof 2019, Haupt 2005, Stracke 2008, Ziegler 2004, Ziegler 2006, Ziegler 2011]. Symptomatic treatment options for painful DSPN include mainly serotonin-noradrenaline reuptake inhibitors, anticonvulsants and opioids [Alam 2020]. A study specifically focusing on individuals with prediabetes and neuropathic pain showed treatment with the α2δ ligand pregabalin to result in pain relief. However, increasing severity of nerve damage reduced patient responsiveness to pregabalin [González-Duarte 2016]. The similarities between prediabetic and diabetic neuropathy point to therapeutic approaches comparable to those suggested in the management of cardiovascular risk factors in prediabetes, but evidence to support this notion is lacking [DeFronzo 2011].

Considerations for the future

Although the clinical manifestations of diabetic neuropathy in T1DM and T2DM are similar, they appear to be based on partly divergent concepts [Callaghan 2012 (a), Callaghan 2012 (b)]. One of the major differences could be the positive impact of improved glycaemic control on the incidence of DSPN in individuals with T1DM which was not observed in T2DM [Amthor 1994, Callaghan 2012 (c), Diabetes Control and Complications (DCCT) Research Group 1995, Holman 1983, Ismail-Beigi 2010, Jakobsen 1988, Linn 1996]. This should be kept in mind when addressing DSPN in clinical practice. The multifactorial impact of risk factors such as hyperglycaemia, obesity, age, gender, height, and genetics are important to consider, especially in view of currently established therapies for diabetic neuropathy. These mostly address neuropathic pain or target hyperglycaemia [Grisold 2017].

Metabolic syndrome, prediabetes and diabetes are all risk factors for and associated with a number of comorbidities such as obstructive sleep apnoea (OSA), non-alcoholic fatty liver disease (NAFLD) and others, and may have a direct impact on microvascular or macrovascular complications. Lifestyle intervention does not

for internal use only – © Kirchheim Publishers

only address the underlying metabolic disorders such as hyperglycaemia and inflammation, but also have a positive impact on many of the comorbidities. Understanding the interplay of metabolic factors with diabetic complications may support prevention and treatment optimisation [Greco 2015].

Overall, data gathered from patients with prediabetes and peripheral neuropathies is limited. Randomised controlled trials would play a pivotal role in understanding the impact of approaches such as lifestyle management and therapeutic interventions towards developing recommendations for clinical practice. Additional prospective data should improve the current understanding of associations between prediabetes, its risk factors and the development of peripheral neuropathies. The available studies provide some preliminary insights but vary considerably in participant selection as well as definitions and diagnostic procedures for both prediabetes and neuropathy.

Conclusions

Peripheral neuropathy has been reported to be prevalent in the prediabetic state. Individuals with prediabetes should be screened for peripheral neuropathies such as DSPN and autonomic dysfunction to detect nerve damage as early as possible. A timely diagnosis might provide the opportunity to address both prediabetes and peripheral neuropathy to allow for a pathophysiological reversal. Apart from lifestyle modification and despite the lack of evidence, both symptomatic and pathogenesis-oriented treatment merit consideration to maintain the patients' quality of life rather than await the transition to clinically manifest diabetes.

Acknowledgement
The authors thank Katharina Fritzen and Badreddine Mecheri of Sciarc GmbH, Baierbrunn, for their assistance in the preparation of the manuscript.

for internal use only – © Kirchheim Publishers

References

1. Alam I, Lewis MJ, Lewis KE, Stephens JW, Baxter JN: Influence of bariatric surgery on indices of cardiac autonomic control. Auton Neurosci 2009; 151: 168-173
2. Alam U, Sloan G, Tesfaye S: Treating pain in diabetic neuropathy: current and developmental drugs. Drugs 2020; 80: 363-384
3. Amthor KF, Dahl-Jørgensen K, Berg TJ, Heier MS, Sandvik L, Aagenaes O, Hanssen KF: The effect of 8 years of strict glycaemic control on peripheral nerve function in IDDM patients: the Oslo Study. Diabetologia 1994; 37: 579-584
4. Andersen ST, Witte DR, Fleischer J, Andersen H, Lauritzen T, Jørgensen ME, Jensen TS, Pop-Busui R, Charles M: Risk factors for the presence and progression of cardiovascular autonomic neuropathy in type 2 diabetes: ADDITION-Denmark. Diabetes Care 2018; 41: 2586-2594
5. Ang L, Jaiswal M, Martin C, Pop-Busui R: Glucose control and diabetic neuropathy: lessons from recent large clinical trials. Curr Diab Rep 2014; 14: 528
6. Azmi S, Ferdousi M, Petropoulos IN, Ponirakis G, Alam U, Fadavi H, Asghar O, Marshall A, Atkinson AJ, Jones W, Boulton AJ, Tavakoli M, Jeziorska M, Malik RA: Corneal confocal microscopy identifies small-fiber neuropathy in subjects with impaired glucose tolerance who develop type 2 diabetes. Diabetes Care 2015; 38: 1502-1508
7. Balcıoğlu AS, Müderrisoğlu H: Diabetes and cardiac autonomic neuropathy: clinical manifestations, cardiovascular consequences, diagnosis and treatment. World J Diabetes 2015; 6: 80-91
8. Bartnik M, Rydén L, Malmberg K, Ohrvik J, Pyörälä K, Standl E, Ferrari R, Simoons M, Soler-Soler J; Euro Heart Survey Investigators: Oral glucose tolerance test is needed for appropriate classification of glucose regulation in patients with coronary artery disease: a report from the Euro Heart Survey on Diabetes and the Heart. Heart 2007; 93: 72-77
9. Bertram MY, Vos T: Quantifying the duration of pre-diabetes. Aust N Z J Public Health 2010; 34: 311-314
10. Beulens J, Rutters F, Rydén L, Schnell O, Mellbin L, Hart HE, Vos RC: Risk and management of pre-diabetes. Eur J Prev Cardiol 2019; 26 (2_suppl): 47-54
11. Bhati P, Shenoy S, Hussain ME: Exercise training and cardiac autonomic function in type 2 diabetes mellitus: a systematic review. Diabetes Metab Syndr 2018; 12: 69-78
12. Bongaerts BW, Rathmann W, Heier M, Kowall B, Herder C, Stöckl D, Meisinger C, Ziegler D: Older subjects with diabetes and prediabetes are frequently unaware of having distal sensorimotor polyneuropathy: the KORA F4 study. Diabetes Care 2013; 36: 1141-1146
13. Bongaerts BW, Rathmann W, Kowall B, Herder C, Stöckl D, Meisinger C, Ziegler D: Postchallenge hyperglycemia is positively associated with diabetic polyneuropathy: the KORA F4 study. Diabetes Care 2012; 35: 1891-1893
14. Bönhof GJ, Herder C, Strom A, Papanas N, Roden M, Ziegler D: Emerging biomarkers, tools, and treatments for diabetic polyneuropathy. Endocr Rev 2019; 40: 153-192
15. Boulton AJ, Malik RA, Arezzo JC, Sosenko JM: Diabetic somatic neuropathies. Diabetes Care 2004; 27: 1458-1486
16. Boulton AJ: Diabetic neuropathy and foot complications. Handb Clin Neurol 2014; 126: 97-107
17. Brannick B, Wynn A, Dagogo-Jack S: Prediabetes as a toxic environment for the initiation of microvascular and macrovascular complications. Exp Biol Med (Maywood) 2016; 241: 1323-1331
18. Brownrigg JR, de Lusignan S, McGovern A, Hughes C, Thompson MM, Ray KK, Hinchliffe RJ: Peripheral neuropathy and the risk of cardiovascular events in type 2 diabetes mellitus. Heart 2014; 100: 1837-1843
19. Caballero AE, Arora S, Saouaf R, Lim SC, Smakowski P, Park JY, King GL, LoGerfo FW, Horton ES, Veves A: Microvascular and macrovascular reactivity is reduced in subjects at risk for type 2 diabetes. Diabetes 1999; 48: 1856-1862
20. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL: Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol 2012 (a); 11: 521-534
21. Callaghan BC, Gao L, Li Y, Zhou X, Reynolds E, Banerjee M, Pop-Busui R, Feldman EL, Ji L: Diabetes and obesity are the main metabolic drivers of peripheral neuropathy. Ann Clin Transl Neurol 2018; 5: 397-405
22. Callaghan BC, Hur J, Feldman EL: Diabetic neuropathy: one disease or two? Curr Opin Neurol 2012 (b); 25: 536-541
23. Callaghan BC, Little AA, Feldman EL, Hughes RA: Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev 2012 (c); 6: CD007543
24. Callaghan BC, Xia R, Banerjee M, de Rekeneire N, Harris TB, Newman AB, Satterfield S, Schwartz AV, Vinik AI, Feldman EL, Strotmeyer ES; Health ABC Study: Metabolic syndrome components are associated with symptomatic polyneuropathy independent of glycemic status. Diabetes Care 2016 (a); 39: 801-807
25. Callaghan BC, Xia R, Reynolds E, Banerjee M, Rothberg AE, Burant CF, Villegas-Umana E, Pop-Busui R, Feldman EL: Association between metabolic syndrome components and polyneuropathy in an obese population. JAMA Neurol 2016 (b); 73: 1468-1476
26. Casellini CM, Parson HK, Hodges K, Edwards JF, Lieb DC, Wohlgemuth SD, Vinik AI: Bariatric surgery restores cardiac and sudomotor autonomic C-fiber dysfunction towards normal in obese subjects with type 2 diabetes. PLoS One 2016; 11: e0154211
27. Coopmans C, Zhou TL, Henry RMA, Heijman J, Schaper NC, Koster A, Schram MT, van der Kallen CJH, Wesselius A, den Engelsman RJA, Crijns HJGM, Stehouwer CDA: Both prediabetes and type 2 diabetes are associated with lower heart rate variability: the Maastricht Study. Diabetes Care 2020; 43: 1126-1133
28. de Jonge L, Moreira EA, Martin CK, Ravussin E; Pennington CALERIE Team: Impact of 6-month caloric restriction on autonomic nervous system activity in healthy, overweight, individuals. Obesity (Silver Spring) 2010; 18: 414-416
29. de Neeling JN, Beks PJ, Bertelsmann FW, Heine RJ, Bouter LM: Peripheral somatic

nerve function in relation to glucose tolerance in an elderly Caucasian population: the Hoorn study. Diabet Med 1996; 13: 960-966
30. DeFronzo RA, Abdul-Ghani M: Assessment and treatment of cardiovascular risk in prediabetes: impaired glucose tolerance and impaired fasting glucose. Am J Cardiol 2011; 108 (3 Suppl): 3B-24B
31. DeJesus RS, Breitkopf CR, Rutten LJ, Jacobson DJ, Wilson PM, Sauver JS: Incidence rate of prediabetes progression to diabetes: modeling an optimum target group for intervention. Popul Health Manag 2017; 20: 216-223
32. Diabetes Control and Complications (DCCT) Research Group: Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. Kidney Int 1995; 47: 1703-1720
33. Diabetes Prevention Program Research Group: Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol 2015; 3: 866-875
34. Dietrich I, Braga GA, de Melo FG, da Costa Silva Silva ACC: The diabetic foot as a proxy for cardiovascular events and mortality review. Curr Atheroscler Rep 2017; 19: 44
35. Dimitropoulos G, Tahrani AA, Stevens MJ: Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes 2014; 5: 17-39
36. Dimova R, Tankova T, Guergueltcheva V, Tournev I, Chakarova N, Grozeva G, Dakovska L: Risk factors for autonomic and somatic nerve dysfunction in different stages of glucose tolerance. J Diabetes Complications 2017; 31: 537-543
37. Doerr R, Hoffmann U, Otter W, Heinemann L, Hunger-Battefeld W, Kulzer B, Klinge A, Lodwig V, Amann-Zalan I, Sturm D, Tschoepe D, Spitzer SG, Stumpf J, Lohmann T, Schnell O: Oral glucose tolerance test and HbA_{1c} for diagnosis of diabetes in patients undergoing coronary angiography: [corrected] the Silent Diabetes Study. Diabetologia 2011; 54: 2923-2930
38. Dyck PJ, Albers JW, Andersen H, Arezzo JC, Biessels GJ, Bril V, Feldman EL, Litchy WJ, O'Brien PC, Russell JW; Toronto Expert Panel on Diabetic Neuropathy: Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes Metab Res Rev 2011; 27: 620-628
39. Dyck PJ, Clark VM, Overland CJ, Davies JL, Pach JM, Dyck PJ, Klein CJ, Rizza RA, Melton LJ 3rd, Carter RE, Klein R, Litchy WJ: Impaired glycemia and diabetic polyneuropathy: the OC IG Survey. Diabetes Care 2012; 35: 584-591
40. Fisher VL, Tahrani AA: Cardiac autonomic neuropathy in patients with diabetes mellitus: current perspectives. Diabetes Metab Syndr Obes 2017; 10: 419-434
41. Forsblom CM, Sane T, Groop PH, Tötterman KJ, Kallio M, Saloranta C, Laasonen L, Summanen P, Lepäntalo M, Laatikainen L, Matikainen E, Teppo AM, Koskimies S, Groop L: Risk factors for mortality in type II (non-insulin-dependent) diabetes: evidence of a role for neuropathy and a protective effect of HLA-DR4. Diabetologia 1998; 41: 1253-1262
42. Fu CP, Sheu WH, Lee WL, Lee WJ, Wang JS, Lin SY, Lee IT: Two-hour post-challenge hyperglycemia, but not fasting plasma glucose, associated with severity of coronary artery disease in patients with angina. PLoS One 2018; 13: e0202280
43. Fujimoto WY, Leonetti DL, Kinyoun JL, Shuman WP, Stolov WC, Wahl PW: Prevalence of complications among second-generation Japanese-American men with diabetes, impaired glucose tolerance, or normal glucose tolerance. Diabetes 1987; 36: 730-739
44. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003; 26: 3160-3167
45. Gerritsen J, Dekker JM, TenVoorde BJ, Bertelsmann FW, Kostense PJ, Stehouwer CD, Heine RJ, Nijpels G, Heethaar RM, Bouter LM: Glucose tolerance and other determinants of cardiovascular autonomic function: the Hoorn Study. Diabetologia 2000; 43: 561-570
46. González-Duarte A, Lem M, Díaz-Díaz E, Castillo C, Cárdenas-Soto K: The efficacy of pregabalin in the treatment of prediabetic neuropathic pain. Clin J Pain 2016; 32: 927-932
47. Greco C, Spallone V: Obstructive sleep apnoea syndrome and diabetes. Fortuitous association or interaction? Curr Diabetes Rev 2015; 12: 129-155
48. Green AQ, Krishnan S, Finucane FM, Rayman G: Altered C-fiber function as an indicator of early peripheral neuropathy in individuals with impaired glucose tolerance. Diabetes Care 2010; 33: 174-176
49. Grisold A, Callaghan BC, Feldman EL: Mediators of diabetic neuropathy: is hyperglycemia the only culprit? Curr Opin Endocrinol Diabetes Obes 2017; 24: 103-111
50. Groener JB, Jende JME, Kurz FT, Kender Z, Treede RD, Schuh-Hofer S, Nawroth PP, Bendszus M, Kopf S: Understanding diabetic neuropathy – from subclinical nerve lesions to severe nerve fiber deficits: a cross-sectional study in patients with type 2 diabetes and healthy control subjects. Diabetes 2020; 69: 436-447
51. Haupt E, Ledermann H, Köpcke W: Benfotiamine in the treatment of diabetic polyneuropathy – a three-week randomized, controlled pilot study (BEDIP study). Int J Clin Pharmacol Ther 2005; 43: 71-77
52. Herder C, Kannenberg JM, Huth C, Carstensen-Kirberg M, Rathmann W, Koenig W, Strom A, Bönhof GJ, Heier M, Thorand B, Peters A, Roden M, Meisinger C, Ziegler D: Myeloperoxidase, superoxide dismutase-3, cardiometabolic risk factors, and distal sensorimotor polyneuropathy: the KORA F4/FF4 study. Diabetes Metab Res Rev 2018; 34: e3000
53. Herder C, Roden M, Ziegler D: Novel insights into sensorimotor and cardiovascular autonomic neuropathy from recent-onset diabetes and population-based cohorts. Trends Endocrinol Metab 2019; 30: 286-298
54. Holman RR, Dornan TL, Mayon-White V, Howard-Williams J, Orde-Peckar C, Jenkins L, Steemson J, Rolfe R, Smith B, Barbour D, McPherson K, Poon P, Rizza C, Mann JI, Knight AH, Bron AJ, Turner RC: Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients. A two-year randomised prospective study. Lancet 1983; 321 (8318): 204-208
55. Hsu WC, Chiu SY, Yen AM, Chen LS, Fann CY, Liao CS, Chen HH: Somatic neuropathy is an independent predictor of all- and diabetes-related mortality in type 2 diabetic patients: a population-based 5-year follow-up study (KCIS No. 29). Eur J Neurol 2012; 19: 1192-1198
56. Huang Y, Cai X, Mai W, Li M, Hu Y: Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ 2016; 355: i5953
57. International Diabetes Federation: IDF Diabetes Atlas, 9th ed. IDF, Brussels, 2019
58. Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH Jr, Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian A, O'Connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D, Hramiak I; ACCORD trial group: Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010; 376 (9739): 419-430
59. Jakobsen J, Christiansen JS, Kristoffersen I, Christensen CK, Hermansen K, Schmitz A, Mogensen CE: Autonomic and somatosensory nerve function after 2 years of continuous subcutaneous insulin infusion in type I diabetes. Diabetes 1988; 37: 452-455
60. Karayannis G, Giamouzis G, Cokkinos DV, Skoularigis J, Triposkiadis F: Diabetic cardiovascular autonomic neuropathy: clinical implications. Expert Rev Cardiovasc Ther 2012; 10: 747-765
61. Kassardjian CD, Dyck PJ, Davies JL, Carter RE, Dyck PJ: Does prediabetes cause small fiber sensory polyneuropathy? Does it matter? J Neurol Sci 2015; 355: 196-198
62. Kasznicki J: Advances in the diagnosis and management of diabetic distal symmetric polyneuropathy. Arch Med Sci 2014; 10: 345-354
63. Kokkinos A, Alexiadou K, Liaskos C, Argyrakopoulou G, Balla I, Tentolouris N, Moyssakis I, Katsilambros N, Vafiadis I, Alexandrou A, Diamantis T: Improvement in cardiovascular indices after Roux-en-Y gastric bypass or sleeve gastrectomy for morbid obesity. Obes Surg 2013; 23: 31-38
64. Kurisu S, Sasaki H, Kishimoto S, Hirayasu K, Ogawa K, Matsuno S, Furuta H, Arita M, Naka K, Nanjo K, Akamizu T: Clinical polyneuropathy does not increase with prediabetes or metabolic syndrome in the Japanese general population. J Diabetes Investig 2019; 10: 1565-1575
65. Lee CC, Perkins BA, Kayaniyil S, Harris SB, Retnakaran R, Gerstein HC, Zinman B, Hanley AJ: Peripheral neuropathy and nerve dysfunction in individuals at high risk for type 2 diabetes: the PROMISE cohort. Diabetes Care 2015; 38: 793-800
66. Linn T, Ortac K, Laube H, Federlin K: Intensive therapy in adult insulin-depend-

for internal use only – © Kirchheim Publishers

ent diabetes mellitus is associated with improved insulin sensitivity and reserve: a randomized, controlled, prospective study over 5 years in newly diagnosed patients. Metabolism 1996; 45: 1508-1513
67. Lips MA, de Groot GH, De Kam M, Berends FJ, Wiezer R, Van Wagensveld BA, Swank DJ, Luijten A, Pijl H, Burggraaf J: Autonomic nervous system activity in diabetic and healthy obese female subjects and the effect of distinct weight loss strategies. Eur J Endocrinol 2013; 169: 383-390
68. Look AHEAD Research Group: Effects of a long-term lifestyle modification programme on peripheral neuropathy in overweight or obese adults with type 2 diabetes: the Look AHEAD study. Diabetologia 2017; 60: 980-988
69. Lu B, Hu J, Wen J, Zhang Z, Zhou L, Li Y, Hu R: Determination of peripheral neuropathy prevalence and associated factors in Chinese subjects with diabetes and prediabetes – ShangHai Diabetic neuRopathy Epidemiology and Molecular Genetics Study (SH-DREAMS). PLoS One 2013; 8: e61053
70. Martin CL, Albers JW, Pop-Busui R; DCCT/EDIC Research Group: Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 2014; 37: 31-38
71. Meyer ML, Gotman NM, Soliman EZ, Whitsel EA, Arens R, Cai J, Daviglus ML, Denes P, González HM, Moreiras J, Talavera GA, Heiss G: Association of glucose homeostasis measures with heart rate variability among Hispanic/Latino adults without diabetes: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Cardiovasc Diabetol 2016; 15: 45
72. Moţăţăianu A, Maier S, Bajko Z, Voidazan S, Bălaşa R, Stoian A: Cardiac autonomic neuropathy in type 1 and type 2 diabetes patients. BMC Neurol 2018; 18: 126
73. Németh N, Putz Z, Istenes I, Körei AE, Vági OE, Kempler M, Gandhi R, Jermendy G, Tesfaye S, Tabák ÁG, Kempler P: Is there a connection between postprandial hyperglycemia and IGT related sensory nerve dysfunction? Nutr Metab Cardiovasc Dis 2017; 27: 609-614
74. Otto-Buczkowska E, Machnica L: Metabolic memory – the implications for diabetic complications. Endokrynol Pol 2010; 61: 700-703
75. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ: The 30-year natural history of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study experience. Diabetes 2006; 55: 1463-1469
76. Papanas N, Vinik AI, Ziegler D: Neuropathy in prediabetes: does the clock start ticking early? Nat Rev Endocrinol 2011; 7: 682-690
77. Papanas N, Ziegler D: Prediabetic neuropathy: does it exist? Curr Diab Rep 2012; 12: 376-383
78. Papanas N, Ziegler D: Risk factors and comorbidities in diabetic neuropathy: an update 2015. Rev Diabet Stud 2015; 12: 48-62
79. Pennathur S, Jaiswal M, Vivekanandan-Giri A, White EA, Ang L, Raffel DM, Rubenfire M, Pop-Busui R: Structured lifestyle intervention in patients with the metabolic syndrome mitigates oxidative stress but fails to improve measures of cardiovascular autonomic neuropathy. J Diabetes Complications 2017; 31: 1437-1443
80. Pfeifer MA, Schumer MP: Clinical trials of diabetic neuropathy: past, present, and future. Diabetes 1995; 44: 1355-1361
81. Politi C, Ciccacci C, D'Amato C, Novelli G, Borgiani P, Spallone V: Recent advances in exploring the genetic susceptibility to diabetic neuropathy. Diabetes Res Clin Pract 2016; 120: 198-208
82. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D: Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care 2017; 40: 136-154
83. Pop-Busui R, Herman WH, Feldman EL, Low PA, Martin CL, Cleary PA, Waberski BH, Lachin JM, Albers JW; DCCT/EDIC Research Group: DCCT and EDIC studies in type 1 diabetes: lessons for diabetic neuropathy regarding metabolic memory and natural history. Curr Diab Rep 2010; 10: 276-282
84. Putz Z, Tabák AG, Tóth N, Istenes I, Németh N, Gandhi RA, Hermányi Z, Keresztes K, Jermendy G, Tesfaye S, Kempler P: Noninvasive evaluation of neural impairment in subjects with impaired glucose tolerance. Diabetes Care 2009; 32: 181-183
85. Reddy MA, Zhang E, Natarajan R: Epigenetic mechanisms in diabetic complications and metabolic memory. Diabetologia 2015; 58: 443-455
86. Richter B, Hemmingsen B, Metzendorf MI, Takwoingi Y: Development of type 2 diabetes mellitus in people with intermediate hyperglycaemia. Cochrane Database Syst Rev 2018; 10: CD012661
87. Rijkelijkhuizen JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD, Dekker JM: High risk of cardiovascular mortality in individuals with impaired fasting glucose is explained by conversion to diabetes: the Hoorn study. Diabetes Care 2007; 30: 332-336
88. Rissanen P, Franssila-Kallunki A, Rissanen A: Cardiac parasympathetic activity is increased by weight loss in healthy obese women. Obes Res 2001; 9: 637-643
89. Röhling M, Strom A, Bönhof GJ, Roden M, Ziegler D: Cardiorespiratory fitness and cardiac autonomic function in diabetes. Curr Diab Rep 2017; 17: 125
90. Roman G, Hancu N: Early insulin treatment to prevent cardiovascular disease in prediabetes and overt diabetes. Horm Metab Res 2009; 41: 116-122
91. Schlesinger S, Herder C, Kannenberg JM, Huth C, Carstensen-Kirberg M, Rathmann W, Bönhof GJ, Koenig W, Heier M, Peters A, Meisinger C, Roden M, Thorand B, Ziegler D: General and abdominal obesity and incident distal sensorimotor polyneuropathy: insights into inflammatory biomarkers as potential mediators in the KORA F4/FF4 cohort. Diabetes Care 2019; 42: 240-247
92. Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, Heiss G; Atherosclerosis Risk in Communities (ARIC) study: Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care 2005; 28: 668-674
93. Seferovic JP, Pfeffer MA, Claggett B, Desai AS, de Zeeuw D, Haffner SM, McMurray JJV, Parving HH, Solomon SD, Chaturvedi N: Three-question set from Michigan Neuropathy Screening Instrument adds independent prognostic information on cardiovascular outcomes: analysis of ALTITUDE trial. Diabetologia 2018; 61: 581-588
94. Singh JP, Larson MG, O'Donnell CJ, Wilson PF, Tsuji H, Lloyd-Jones DM, Levy D: Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). Am J Cardiol 2000; 86: 309-312
95. Singleton JR, Marcus RL, Lessard MK, Jackson JE, Smith AG: Supervised exercise improves cutaneous reinnervation capacity in metabolic syndrome patients. Ann Neurol 2015; 77: 146-153
96. Singleton JR, Smith AG, Bromberg MB: Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. Diabetes Care 2001; 24: 1448-1453
97. Sjoberg N, Brinkworth GD, Wycherley TP, Noakes M, Saint DA: Moderate weight loss improves heart rate variability in overweight and obese adults with type 2 diabetes. J Appl Physiol (1985) 2011; 110: 1060-1064
98. Smith AG, Russell J, Feldman EL, Goldstein J, Peltier A, Smith S, Hamwi J, Pollari D, Bixby B, Howard J, Singleton JR: Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care 2006; 29: 1294-1299
99. Smith AG, Singleton JR: Impaired glucose tolerance and neuropathy. Neurologist 2008; 14: 23-29
100. Smith AG, Singleton JR: Obesity and hyperlipidemia are risk factors for early diabetic neuropathy. J Diabetes Complications 2013; 27: 436-442
101. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, Stevens M, Kempler P, Hilsted J, Tesfaye S, Low P, Valensi P; Toronto Consensus Panel on Diabetic Neuropathy: Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev 2011; 27: 639-653
102. Spallone V: Update on the impact, diagnosis and management of cardiovascular autonomic neuropathy in diabetes: what is defined, what is new, and what is unmet. Diabetes Metab J 2019; 43: 3-30
103. Stein PK, Barzilay JI, Domitrovich PP, Chaves PM, Gottdiener JS, Heckbert SR, Kronmal RA: The relationship of heart rate and heart rate variability to non-diabetic fasting glucose levels and the metabolic syndrome: the Cardiovascular Health Study. Diabet Med 2007; 24: 855-863
104. Stino AM, Smith AG: Peripheral neuropathy in prediabetes and the metabolic syndrome. J Diabetes Investig 2017; 8: 646-655
105. Stracke H, Gaus W, Achenbach U, Federlin K, Bretzel RG: Benfotiamine in diabetic polyneuropathy (BENDIP): results of a randomised, double blind, placebo-controlled clinical study. Exp Clin Endocrinol Diabetes 2008; 116: 600-605
106. Straznicky NE, Grima MT, Sari CI, Lambert EA, Phillips SE, Eikelis N, Mariani JA, Kobayashi D, Hering D, Dixon JB,

for internal use only – © Kirchheim Publishers

Lambert GW: Comparable attenuation of sympathetic nervous system activity in obese subjects with normal glucose tolerance, impaired glucose tolerance, and treatment naïve type 2 diabetes following equivalent weight loss. Front Physiol 2016; 7: 516
107. Sumner CJ, Sheth S, Griffin JW, Cornblath DR, Polydefkis M: The spectrum of neuropathy in diabetes and impaired glucose tolerance. Neurology 2003; 60: 108-111
108. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P; Toronto Diabetic Neuropathy Expert Group: Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010; 33: 2285-2293
109. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, Witte DR, Fuller JH; EURODIAB Prospective Complications Study Group: Vascular risk factors and diabetic neuropathy. N Engl J Med 2005; 352: 341-350
110. Tesfaye S, Stevens LK, Stephenson JM, Fuller JH, Plater M, Ionescu-Tirgoviste C, Nuber A, Pozza G, Ward JD: Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. Diabetologia 1996; 39: 1377-1384
111. Testa R, Bonfigli AR, Marra M, Testa I: In the light of the metabolic memory theory, should not all aged people with dysglycemia be treated? Rejuvenation Res 2010; 13: 599-605
112. Thrainsdottir S, Malik RA, Dahlin LB, Wiksell P, Eriksson KF, Rosén I, Petersson J, Greene DA, Sundkvist G: Endoneurial capillary abnormalities presage deterioration of glucose tolerance and accompany peripheral neuropathy in man. Diabetes 2003; 52: 2615-2622
113. Vadiveloo T, Jeffcoate W, Donnan PT, Colhoun HC, McGurnaghan S, Wild S, McCrimmon R, Leese GP; Scottish Diabetes Research Network Epidemiology Group: Amputation-free survival in 17,353 people at high risk for foot ulceration in diabetes: a national observational study. Diabetologia 2018; 61: 2590-2597
114. Verrotti A, Loiacono G, Mohn A, Chiarelli F: New insights in diabetic autonomic neuropathy in children and adolescents. Eur J Endocrinol 2009; 161: 811-818
115. Verrotti A, Prezioso G, Scattoni R, Chiarelli F: Autonomic neuropathy in diabetes mellitus. Front Endocrinol (Lausanne) 2014; 5: 205
116. Villafaina S, Collado-Mateo D, Fuentes JP, Merellano-Navarro E, Gusi N: Physical exercise improves heart rate variability in patients with type 2 diabetes: a systematic review. Curr Diab Rep 2017; 17: 110
117. Vinik AI, Erbas T: Diabetic autonomic neuropathy. Handb Clin Neurol 2013 (a); 117: 279-294
118. Vinik AI, Nevoret ML, Casellini C, Parson H: Diabetic neuropathy. Endocrinol Metab Clin North Am 2013 (b); 42: 747-787
119. Vistisen D, Kivimäki M, Perreault L, Hulman A, Witte DR, Brunner EJ, Tabák A, Jørgensen ME, Færch K: Reversion from prediabetes to normoglycaemia and risk of cardiovascular disease and mortality: the Whitehall II cohort study. Diabetologia 2019; 62: 1385-1390
120. Wasmund SL, Owan T, Yanowitz FG, Adams TD, Hunt SC, Hamdan MH, Litwin SE: Improved heart rate recovery after marked weight loss induced by gastric bypass surgery: two-year follow up in the Utah Obesity Study. Heart Rhythm 2011; 8: 84-90
121. World Health Organization, International Diabetes Federation: Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. WHO Press, Geneva, 2006
122. Wu JS, Lu FH, Yang YC, Chang SH, Huang YH, Chen JJ, Chang CJ: Impaired baroreflex sensitivity in subjects with impaired glucose tolerance, but not isolated impaired fasting glucose. Acta Diabetol 2014; 51: 535-541
123. Wu JS, Yang YC, Lin TS, Huang YH, Chen JJ, Lu FH, Wu CH, Chang CJ: Epidemiological evidence of altered cardiac autonomic function in subjects with impaired glucose tolerance but not isolated impaired fasting glucose. J Clin Endocrinol Metab 2007; 92: 3885-3889
124. Yagihashi S, Mizukami H, Sugimoto K: Mechanism of diabetic neuropathy: Where are we now and where to go? J Diabetes Investig 2011; 2: 18-32
125. Yeboah J, Bertoni AG, Herrington DM, Post WS, Burke GL: Impaired fasting glucose and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2011; 58: 140-146
126. Ziegler D, Ametov A, Barinov A, Dyck PJ, Gurieva I, Low PA, Munzel U, Yakhno N, Raz I, Novosadova M, Maus J, Samigullin R: Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care 2006; 29: 2365-2370
127. Ziegler D, Buchholz S, Sohr C, Nourooz-Zadeh J, Roden M: Oxidative stress predicts progression of peripheral and cardiac autonomic nerve dysfunction over 6 years in diabetic patients. Acta Diabetol 2015 (a); 52: 65-72
128. Ziegler D, Landgraf R, Lobmann R, Reiners K, Rett K, Schnell O, Strom A: Painful and painless neuropathies are distinct and largely undiagnosed entities in subjects participating in an educational initiative (PROTECT study). Diabetes Res Clin Pract 2018; 139: 147-154
129. Ziegler D, Low PA, Freeman R, Tritschler H, Vinik AI: Predictors of improvement and progression of diabetic polyneuropathy following treatment with α-lipoic acid for 4 years in the NATHAN 1 trial. J Diabetes Complications 2016; 30: 350-356
130. Ziegler D, Low PA, Litchy WJ, Boulton AJ, Vinik AI, Freeman R, Samigullin R, Tritschler H, Munzel U, Maus J, Schütte K, Dyck PJ: Efficacy and safety of anti-oxidant treatment with α-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. Diabetes Care 2011; 34: 2054-2060
131. Ziegler D, Nowak H, Kempler P, Vargha P, Low PA: Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. Diabet Med 2004; 21: 114-121
132. Ziegler D, Papanas N, Vinik AI, Shaw JE: Epidemiology of polyneuropathy in diabetes and prediabetes. Handb Clin Neurol 2014; 126: 3-22
133. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A; KORA Study Group: Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. Diabetes Care 2008; 31: 464-469
134. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A; KORA Study Group: Neuropathic pain in diabetes, prediabetes and normal glucose tolerance: the MONICA/KORA Augsburg Surveys S2 and S3. Pain Med 2009 (a); 10: 393-400
135. Ziegler D, Rathmann W, Meisinger C, Dickhaus T, Mielck A; KORA Study Group: Prevalence and risk factors of neuropathic pain in survivors of myocardial infarction with pre-diabetes and diabetes. The KORA Myocardial Infarction Registry. Eur J Pain 2009 (b); 13: 582-587
136. Ziegler D, Schleicher E, Strom A, Knebel B, Fleming T, Nawroth P, Häring HU, Papanas N, Szendrödi J, Müssig K, Al-Hasani H, Roden M; GDS Group: Association of transketolase polymorphisms with measures of polyneuropathy in patients with recently diagnosed diabetes. Diabetes Metab Res Rev 2017; 33: e2811
137. Ziegler D, Strom A, Nowotny B, Zahiragic L, Nowotny PJ, Carstensen-Kirberg M, Herder C, Roden M: Effect of low-energy diets differing in fiber, red meat, and coffee intake on cardiac autonomic function in obese individuals with type 2 diabetes. Diabetes Care 2015 (b); 38: 1750-1757
138. Ziegler D, Voss A, Rathmann W, Strom A, Perz S, Roden M, Peters A, Meisinger C; KORA Study Group: Increased prevalence of cardiac autonomic dysfunction at different degrees of glucose intolerance in the general population: the KORA S4 survey. Diabetologia 2015 (c); 58: 1118-1128

Address for correspondence
Prof. Dr. Dan Ziegler
Institute for Clinical Diabetology
German Diabetes Centre
Leibniz Centre for Diabetes Research at Heinrich Heine University
Division of Endocrinology and Diabetology,
Medical Faculty, Heinrich Heine University
Auf'm Hennekamp 65
40225 Düsseldorf
Germany
E-Mail: dan.ziegler@ddz.de

Manuscript received: 28 July 2020
Manuscript accepted: 18 August 2020

for internal use only – © Kirchheim Publishers

Conflicts of interest
Dan Ziegler declares to be an advisory board member of the companies Wörwag Pharma, Teva and Astellas, to own shares/equity of the companies Bayer and Pfizer, to have received remuneration or fees for activities on behalf of the companies Wörwag Pharma, Meda, AstraZeneca, Mitsubishi Tanabe, Takeda, Pfizer, Lilly, Trigocare, Allergan, Novartis, Biogen, Berlin-Chemie, Novaremed, Mundipharma, and Astellas, and to have received third-party funds/project grants from Wörwag Pharma.
Anja Holz is a full-time employee of Wörwag Pharma GmbH & Co. KG.
Irina Gurieva declares to be an advisory board member of the company Wörwag Pharma and to have received remuneration or fees for activities on behalf of the companies Wörwag Pharma, Meda, Takeda and Pfizer.
Viktor Horvath declares to be an advisory board member of the company Wörwag Pharma.
Boris N. Mankovsky declares to be an advisory board member of the company Wörwag Pharma.
Gabriela Radulian declares to be an advisory board member of the company Wörwag Pharma.
Oliver Schnell declares to be an advisory board member of the company Wörwag Pharma and is CEO and founder of Sciarc GmbH.
Vincenza Spallone declares to be an advisory board member of the companies Trigocare and Wörwag Pharma, and to have received remuneration or fees for activities on behalf of the companies Daiichi Sankyo, IRIS Servier, Eli Lilly and ACRAF.
Alin Stirban declares to be an advisory board member of Wörwag Pharma and to have received remuneration or fees for activities on behalf of the companies Wörwag Pharma, Sanofi, Novo Nordisk, Berlin-Chemie, Lilly and Pfizer.
Solomon Tesfaye declares to be an advisory board member of the company Wörwag Pharma and Bayer and to have received remuneration or fees for activities on behalf of Wörwag Pharma, Novo Nordisk, Pfizer, Merck, Eva Pharma, Grünenthal, Abbott, AstraZeneca and Trigocare International.
Peter Kempler declares to be an advisory board member of the companies Wörwag Pharma and Lilly, and to have received remuneration or fees for activities on behalf of the companies Wörwag Pharma, Lilly and Pfizer.

for internal use only – © Kirchheim Publishers