

## REVIEW

# Cardiac Autonomic Neuropathy in Diabetes Mellitus Patients – Are We Aware of the Consequences?

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Cardiovascular autonomic neuropathy is the most frequent clinical form of autonomous diabetic neuropathy and appears secondary to cardiac autonomous fibre involvement, actively involved in cardiac rhythm impairment. Type 2 diabetes mellitus patients can present cardiac autonomic neuropathy early in the disease. Autonomous nerve function in DM patients should be assessed as early as the diagnosis is set in order to establish the optimal therapeutic strategy. The most frequent cardio-vagal test used is heart rate variability. An abnormal heart rate variability in the presence of orthostatic arterial hypotension indicates a severe cardiac autonomic neuropathy diagnosis. The development of cardiac autonomic neuropathy is subjected to glycaemic control, duration of the disease and associated risk factors. The glycaemic control is extremely important, especially early in the disease. Therefore, a poor glycaemic control carries unfavourable long-term effects, despite an ulterior optimal control, a phenomenon named “hyperglycaemic memory”. In type 2 diabetes mellitus patients, the association of cardiac autonomic neuropathy with intensive glycaemic control increases the mortality rate, due to the fact, that, secondary to autonomous impairment, the patients do not present the typical symptoms associated with hypoglycaemia. Stratifying the cardiac autonomic neuropathy aids the clinician in assessing the morbidity and mortality risk of diabetes mellitus patients, because it is an independent risk factor for mortality, associated with silent myocardial infarctions and the risk of sudden death.

**Keywords:** cardiac autonomic neuropathy, diabetes mellitus, hyperglycaemia, hyperglycaemic memory, diabetic neuropathy

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## Introduction

Autonomous diabetic neuropathy is the least recognised and understood type of diabetic neuropathy (DN), despite a significant negative impact on long-term survival and quality of life of these patients. The autonomous nervous system virtually regulates the functions of all the organs, therefore, the autonomous diabetic neuropathy can lead to mild or dire consequences [1].

Cardiovascular autonomic diabetic neuropathy (CAN) is the most frequent clinical form of autonomous diabetic neuropathy, defined as an impairment of the autonomous control upon the cardiovascular system in diabetes mellitus patients (DM), after the exclusion of other systemic causes. The autonomous nervous system closely integrates vital processes such as cardiac rhythm, blood pressure (BP), myocardial contractility and in consequence, plays a primordial role in cardiovascular regulation. CAN, probably one of the most severe and neglected complications, appears secondary to cardiac autonomic fibre involvement, leading to an impairment of the cardiac rhythm and of the vascular dynamic [2,3,4,5].

The clinical manifestations of CAN have a significant impact upon the quality of life of these patients and are associated with a poor outcome, due to orthostatic arterial hypotension, intolerance to physical activity, silent myocardial infarctions, malignant cardiac arrhythmias and sudden death. Usually, the symptoms of CAN appear in the

late stages of DM, but a subclinical CAN can be detected in DM patients one year after the initial diagnosis. This aspect underlines the importance of CAN screening [1,6,7]. Once the diagnosis of CAN has been established, the patients need to be closely monitored for physical activity, early identification of silent myocardial ischemia, assessment of the current medication and careful control of the associated cardiovascular risk factors [7,8].

Globally, the diagnosis of DM is an extremely important public health issue. The past decades recognised an increasing and dramatic change in this aspect, due to a continuous increase in the prevalence. This is most likely secondary to population ageing and a decrease in physical activity. Furthermore, the diagnosis of DM started to appear in younger individuals (40-64 years old), which leads to a longer duration of the disease and a higher risk of mortality and morbidity secondary to DM complications, especially due to cardiovascular diseases [9].

According to FID data, in Romania, the prevalence of DM for 2011 was 9.2% and is estimated that by the end of 2030, the prevalence will reach 11.1%. Globally, for each individual that receives the DM diagnosis, another one remains undiagnosed. Romania is in the top 10 in Europe for undiagnosed DM patients [10,11].

Considering these disquieting epidemiological data, together with the severity of CAN, this diagnosis needs to be prioritised by the clinicians involved: neurologists, diabetologists and cardiologists. The efforts must be joined together in order to extend the area of expertise and to

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positively influence the clinical evolution, for a better long-term prognosis of DM patients.

### CAN diagnosis

Symptoms and clinical signs of autonomic cardiac involvement

The symptoms of cardiovagal involvement can be tachycardia, dizziness, visual impairment and positional fainting when passing from a supine to a standing position [12]. A decrease in the heart rate variability (HRV) can be one of the first symptoms in CAN, reflecting the vagal dysfunction. In healthy subjects, an increase of the sympathetic activity will determine a reactive increase in the parasympathetic activity. In consequence, any increase in the sympathetic activity will lead to a reduced acceleration of the heart rhythm if the autonomic functions are intact. The rest tachycardia, with an occasional increase of the heart beats up to 130 beats per minute is characteristic for the late stages and is secondary to an increase in the sympathetic tonus associated with a vagal dysfunction. Clinically speaking, tachycardia in DM patients has to be considered a sign of autonomic dysfunction, even if any other potential cause has been ruled out (hyperthyroidism, anaemia, infections, cardiac insufficiency) [13,14,15]. "Fixed" tachycardia, which doesn't modify as a response to moderate physical activity, stress or sleep, indicates an almost complete cardiac denervation and has to be considered a sign of severe autonomic cardiovascular impairment [6].

Additionally, besides "fixed" tachycardia, the lack of an increase in the cardiac rhythm from passing from a supine to a standing position has significant clinical repercussions, due to the fact it involves a compensatory increase in the cardiac ejection, aggravating the orthostatic arterial hypotension, which usually accompanies the resting tachycardia [16,17]. Also, it has been demonstrated that the resting tachycardia is involved in the genesis of ventricular arrhythmias, with the consequence of sudden death [18].

### Cardiovascular reflex tests (Ewing tests)

The clinical research of the cardiovascular autonomic function significantly progressed based on the studies of Ewing and Clarke [19], who introduced a battery of cardiovascular reflex tests that have been successfully reproduced in a large number of studies. By using these tests in current clinical practice, the subclinical forms of CAN can be early detected, by identifying a reduction in the HRV [20, 21, 22].

Cardiovascular reflex tests record the HRV, notably the variability of the R-R interval during the Valsalva manoeuvre. This is recorded during deep breathing or during the change in posture, from a supine to a standing position, together with BP variability from a supine to a standing position during a sustained contraction of the dynamometer. The HRV predominantly (but not exclusively) records the parasympathetic nervous system function, and BP variability records the sympathetic nervous system function [5,

23]. Pafili et al, (2015) reported that deep breathing HRV is the best indicator for CAN, and that the accuracy of the diagnosis is increased if this technique is combined with HRV by deep breathing Valsalva manoeuvre [24].

### Spectral analysis of HRV

The spectral analysis of HRV represents a more advanced method of CAN diagnosis. This can be evaluated by breaking down the R-R interval and estimating the magnitude of the variability according to frequency. There are two main wavelength frequencies: (1) low-frequency (0.04-0.15 Hz) – vasomotor activity; (2) high-frequency (0.15-0.4 Hz) – synchronized with the breathing. The sympathetic system modulates the low-frequency HRV and the parasympathetic nervous system modulates the high-frequency. The magnitude of the spectral variation reflects the amplitude of cardiac rhythm fluctuation in different frequencies, during the breathing-in and breathing-out manoeuvre. This technique has the advantage that it doesn't require active participation from the patient, being evaluated in resting conditions [6, 25].

### Arterial baroreflex sensitivity assessment

The arterial baroreceptor reflex is responsible for maintaining short-term BP. By stimulating the baroreceptors, two major effector mechanisms are activated. The cardiac vagal fibre stimulation decreases the cardiac rhythm and in consequence, it increases the cardiac flow, while the inhibition of the sympathetic vasoconstrictor activity reduces the peripheral vascular resistance. The vagal tonus is maintained by various reflex mechanisms which are continuously activated by the stimulation of the baroreceptors. Therefore, the level of the vagal tonus is proportional to the sensitivity of the baroreceptors. The vagus nerve carries cardioprotective effects in order to maintain the electric stability of the myocardial muscle. An impairment in the baroreceptor sensitivity represents, therefore, a cardiovascular risk factor. In order to assess the sensitivity of the baroreceptors, the spectral analysis of the length of the R-R interval induced by spontaneous BP fluctuations is used. A specialised software analyses the sequences in which both the BP and the R-R interval simultaneously increase or decrease during three cardiac cycles [26, 27, 28].

### Measuring the corrected QT interval

The length of the QT interval is widely influenced by the autonomous nervous system tonus and a prolonged QT interval increases the risk of both severe cardiac arrhythmias and sudden death. A corrected QT over 440 milliseconds is considered abnormal. Evaluating the corrected QT interval can be a simple and useful instrument that can identify the patients that carry a high cardiovascular risk [29]. For the past years, the dispersion of the QT interval has been used – it analyses the difference between the longest and the shortest QT interval measured in a 12 lead EKG [30].

### Cardiac scintigraphy

Cardiac scintigraphy allows a complex imagistic assessment of the cardiac sympathetic innervation, by using sympathetic neurotransmitters analogues, such as I-metaiodobenzylguanidine (MIBG). A reduced or abnormal MIBG capture suggests an early sign of myocardial adrenergic innervation impairment. A good metabolic control improves these anomalies [27, 31, 32]. This method is far more sensible than the Ewing's battery and spectral analysis for the early CAN detection, but it requires advanced machinery and cannot be performed at a large scale.

### Stages of CAN and screening diagnostic tests

The presence of one abnormal cardiovagal test, such as HRV, indicates early, subclinical or probable CAN, which needs to be confirmed in time. In order to establish the diagnosis of definite CAN at least two serially cardiovagal tests need to be abnormal. The presence of orthostatic arterial hypotension (symptomatic or asymptomatic) indicates advanced or severe CAN diagnosis [20, 22].

The diagnostic protocol for CAN needs to be carried out in the following instances: (1) DM type 2 patients at the moment of diagnosis; (2) DM type 1 diagnosis at 5 years after diagnosis; (3) independent on the DM duration if there are signs of autonomic dysfunction; (4) diabetic patients that need to follow a restricted programme of physical exercises with moderate-high intensity, especially in the presence of associated cardiovascular risk factors; (5) DM patients with a history of impaired metabolic control, high cardiovascular risk and microvascular complications, especially before a major surgical intervention [33,34].

### Risk factors for CAN development

A poor glycaemic control and the duration of the DM diagnosis play an important role, both for triggering the physio-pathological mechanisms of CAN development (cellular destruction secondary to oxidative stress, accumulation of advanced glycosylation products, activation of the polyol dependent metabolic pathway, depletion of the nitric oxide in the microcirculatory endothelium that impairs the nerve vascularisations) and in the progression of the disease [4, 5, 33, 35, 36].

The DCCT study demonstrated, in type 1 DM patients, the favourable and substantial effect of the strict glycaemic control upon preventing diabetic microvascular complications, especially for DN. The strict glycaemic control and intensive DM treatment, together with a good metabolic control slowed down the progression of autonomic dysfunction and reduced the incidence of CAN with 53% compared to conventional therapy [37, 38]. The EDIC study, which followed-up the patients included in DCCT study, confirmed the beneficial effects of the strict therapies for hyperglycaemia. They carried a protective role upon the occurrence and progression of DN for at least 8 years after the DCCT ended. The lesser prevalence and incidence of DN was noted in the DCCT study in the lot of patients

intensively treated with insulin and can be explained by a strict glycaemic control as a part of "metabolic memory". The results of these clinical studies support the need for a strict glycaemic control in type 1 DM patients in order to prevent CAN [3, 35, 39,40].

The EURODIAB study that followed type 1 DM patients for more than 8 months demonstrated that the risk for CAN development is higher in patients with poor glycaemic control, associated with arterial hypertension and various other microvascular complications [41].

A poor glycaemic control carries unfavourable long-term effects. An increase in the glycaemic levels increases the risk for diabetic complications. If the glycaemic control was inadequate in the first years of DM evolution, the incidence of complications will rise, despite an ulterior optimal control. This phenomenon is described as a "hyperglycaemic memory" or "metabolic memory" and plays a very important role, especially in type 2 DM, where patients are usually diagnosed after a variable number of years of asymptomatic evolution. At the basis of this "metabolic memory" stand epigenetic changes that arise in the silent DM period, determined by undiagnosed or untreated hyperglycaemias [42, 43].

In type 2 DM, the effects of strict glycaemic control are less conclusive, therefore CAN development is subjected to the complex interaction between the optimal glycaemic control, duration of the disease, age-dependent neuronal usage and the co-existence of cardiovascular risk factors (arterial hypertension, dyslipidaemia, obesity, smoking) [41, 44].

The UKPDS study included type 2 DM patients at the onset and evaluated the effect of the metabolic control upon the chronic complications, demonstrating that even a slight HbA1c reduction is beneficial for preventing micro- and macrovascular complications [45]. A cohort of patients included in the UKPDS study were annually monitored, both clinically and paraclinical, in order to assess the evolution of chronic complications and mortality. A decade of monitoring noted that the incidence of microvascular complications, myocardial infarction and general mortality were lower in the intensively treated group compared to conventionally treated group (at the onset of the study), although the metabolic control in the follow-up period did not differ significantly between the two groups. The UKPDS investigators named this phenomenon "metabolic inheritance". Therefore, an early optimal metabolic control for type 2 DM patients will carry beneficial long-term effects. This evidence can be attributed to the "metabolic memory" [46, 47].

Ohkubo et al. (1995) showed that type 2 DM patients with good glycaemic control on intensive insulin therapy have a lower rate of microvascular complications, including DN [48]. The VA Cooperative study revealed that there are no differences in CAN prevalence in type 2 DM patients with a strict glycaemic control compared to those without [49]. The Steno-2 study showed that the inten-

sive-aggressive intervention upon the glycaemic control, but also upon the associated cardiovascular risk factors (arterial hypertension, obesity and dyslipidaemia) reduces the CAN and microalbuminuria prevalence by up to 60% in type 2 DM patients [50].

### **Cardiovascular autonomic neuropathy – an increase in cardiovascular risk and mortality**

The presence of CAN in type 2 DM patients is strongly associated with the risk of malignant arrhythmias, cardiovascular events, myocardial dysfunction, silent myocardial ischemia and an increase of cardiovascular mortality [15, 51, 52].

In DM patients, due to the presence of autonomic dysfunction, the regulatory hypoglycaemic mechanisms are impaired and the patients do not perceive the typical symptoms of hypoglycaemia [53]. Hypoglycaemia can induce arrhythmias by prolonging the QT interval, by lowering the cardiovagal baroreflex function and by the means of sympathetic activation. DM and the cardiac disease accompany this phenomenon [54, 55]. In the EURODIAB study, autonomous involvement was named to be an independent risk factor for severe hypoglycaemias. Autonomous impairment contribution was demonstrated by a reduction in the secretory response of the glucagon, adrenalin and cortisol in this category of patients, therefore increasing the risk of severe hypoglycaemias [56, 57].

The ACCORD study demonstrated that in type 2 DM patients, an intensive glycaemic control, compared to standard glycaemic control, lead to an increase of general and cardiovascular mortality. Mortality was higher in the group of patients that carried a larger number of cardiovascular risk factors, and the existence of CAN at the beginning of the study doubled the mortality rate [15, 58].

Over a third of the deaths from the ACCORD study were secondary to sudden cardiac death. Therefore, the ACCORD study was the first large scale, controlled study that raised the suspicion that hypoglycaemia facilitates the onset of malignant ventricular arrhythmias [59]. A potential cause for the difference in mortality between the two groups, besides the episodes of severe hypoglycaemia, can be the existence of CAN and sensory-motor DN at the beginning of the study. The existence of CAN doubled the risk of mortality and the association between autonomic and somatic nervous impairment increases the risk of cardiovascular mortality by almost three-fold [15, 60]. A number of important conclusions were the result of the abovementioned study and they were included in the standard treatment care for type 2 DM patients:

Type 2 DM patients without cardiovascular impairment or macrovascular complications need to be encouraged to maintain an optimal glycaemic control ( $HbA1c \leq 7\%$ );

Besides the glycaemic control, in order to decrease the risk of macrovascular complications and death, there needs to be an optimal control for the other cardiovascular risk

factors (smoking, arterial hypertension, dyslipidaemia, sedentarism);

In DM patients with a long history of the disease, with advanced micro- and macrovascular complications, the level of the glycaemic control needs to be less strict compared to previous recommendations, in which the HbA1c level was indicated to be under 7% [61].

The lesson learned from the ACCORD study is that the autonomous and somatic nervous dysfunction represent risk factors for the cardiovascular disease and lead to an increase in mortality. The early identification of CAN is crucial in order to establish future treatment strategies, targeted against the mortality rate in these patients [62]. The window of opportunity for an aggressive control of the entire array of cardiovascular risk factors is defined by early diagnosis and the absence of cardiovascular disease or autonomic cardiac dysfunction [63].

### **The utility of CAN diagnosis in current clinical practice**

The necessity of early CAN diagnosis is due to the following:

1. Early CAN diagnosis is useful in order to establish an adequate therapeutical strategy for glycaemic control and personalised treatment [64].
2. The diagnosis of CAN has to be established before performing physical activity, and if moderate to severe CAN exists, certain physical activities will be contraindicated [6, 35].
3. The presence of CAN has to be considered as a marker for hemodynamic instability during anaesthesia, this specific lot of patients needs additional monitoring during and post-surgery [65].
4. CAN detection is necessary in order to stratify the morbidity and mortality risk. CAN is an independent risk factor for general and cardiac mortality, myocardial infarction, cardiac arrhythmias, sudden death and a progression of nephropathy [5, 6, 66, 67, 68, 69].
5. Identifying CAN patients is useful for selecting DM patients that need to be screened for coronary artery disease, in order to prevent silent myocardial infarctions, and to enhance treatment adherence [66, 70].
6. The presence of CAN can identify the DM patients that are predisposed to developing dangerous events during hypoglycaemic periods, therefore being highly useful in defining a glycaemic target (important use for assessing the risk profile of the patients, the CAN diagnosis being a contraindication for strict glycaemic control) [34].

### **Conclusions**

Cardiovascular autonomous dysfunction is recognised as an important cardiovascular risk factor. The importance of recognising this entity, as a predictor for increased morbidity and mortality during intensive treatment for hypergly-

caemia suggests that all type 2 DM patients need to be tested for CAN, as soon as the diagnosis is confirmed. This assessment aids the adequate management of type 2 DM patients, in order to prevent mortality.

### Authors' contribution

AM (Conceptualization; Methodology; Writing – original draft)

LB (Investigation; Writing – review & editing)

SM (Investigation; Writing – review & editing)

AB (Investigation)

AS (Conceptualization; Writing – original draft)

### Conflict of interest

None to declare.

### References

- Edwards JL, Vicent AM, Cheng HT et al. Diabetic neuropathy: mechanism to management. *Pharmacol Ther* 2008; 120: 1-34.
- Kempler P. Cardiac autonomic neuropathy: Is it a cardiovascular risk factor in type 2 diabetes? In: Hâncu N [Ed]. *Cardiovascular Risk in Type 2 Diabetes Mellitus: assessment and control*, Springer-Verlag, Berlin Heidelberg 2003:181-192.
- DCCT Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 1998; 41: 416-423.
- Pop-Busui R. What do we know and we do not know about cardiovascular autonomic neuropathy. *J Cardiovasc Transl Res* 2012; 5: 463-478.
- Vinik AI, Maser RE, Mitchell BD et al. Diabetic autonomic neuropathy. *Diabetes Care* 2003; 26: 1553-1579.
- Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007; 115: 387-397.
- Maser RE, Lenhard MJ. Cardiovascular autonomic neuropathy due to diabetes mellitus: clinical manifestations, consequences and treatment. *J Clin Endocrinol Metab* 2005; 90: 5896-5903.
- Freeman R. Autonomic peripheral neuropathy. *Lancet* 2005; 365: 1259-1270.
- Rett K. Diabetes Therapy on the Move: Is glucocentric view outdated? In: Rett K [Ed]. *Better chances for nerves and vessels*, Georg Thieme Verlag KG Stuttgart 2011:1-8.
- Vlad I, Popa AR. Epidemiology of diabetes mellitus: a current review. *Rom J Diabetes Nutr Metab Dis*. 2012; 19: 433-440
- King H, Rewers M. Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. *Diabetes Care* 1993;16:157-177.
- Low PA, Tomalia VA. Orthostatic hypotension: mechanisms, causes, management. *J Clin Neurol* 2015;11:220-226
- Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular diseases: physiological basis and prognostic implications. *J Am Coll Cardiol* 2008; 51:1725-1733.
- Ewing DJ, Clarke BF. Diabetic autonomic neuropathy: present insights and future prospects. *Diabetes Care* 1986; 9: 648-665.
- Pop-Busui R, Evans GW, Gerstein HC et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial. *Diabetes Care* 2010; 33:1578-1584.
- Fedorowski A, Stavenow L, Hedblad B et al. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals. *Eur Heart J* 2010; 31: 85-91.
- Mancia M, Grassi G. Orthostatic hypotension and cardiovascular risk: defining the epidemiological and prognostic relevance. *Eur Heart J* 2010; 31: 12-14.
- Soliman EZ, Elsalam MA, Li Y. The relationship between high resting heart rate and ventricular arrhythmogenesis in patients referred to ambulatory 24 h electrocardiographic recording. *Europace* 2010; 12: 261-265.
- Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J (Clin Res Ed)* 1982; 285:916-918.
- Tesfaye S, Boulton AJ, Dyck PJ et al. Diabetic Neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; 33: 2285-2293.
- Ewing DJ, Martyn CN, Young RJ et al. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 1985; 8:491-498.
- American Academy of Neurology. Assessment: clinical autonomic testing report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 1996; 46:873-880.
- Spallone V, Morganti R, Fedele T et al. Reappraisal of the diagnostic role of orthostatic hypotension in diabetes. *Clin Auton Res* 2009; 19: 58-64.
- Pafilis K, Trypsianis G, Papzoglou D, Maltezos E, Papanas N. Simplified diagnosis of cardiovascular autonomic neuropathy in type 2 diabetes using Ewing's battery. *Rev Diabet Stud*. 2015;12(1-2):213-219
- Vinik AI, Maser RE, Ziegler D. Autonomic imbalance: prophet of doom or scope for hope. *Diabet Med* 2011; 28: 643-651.
- Jermendy G, Kempler P, Keresztes K et al. The clinical features and diagnosis of autonomic neuropathy. In: Kempler P, Varkonyi T [Eds]. *Neuropathies: A Global Clinical Guide*, Zafir Press, Budapest 2012: 69-130.
- Dimitropoulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. *World J Diabetes* 2014;5(1):17-39.
- La Rovere M, Maestri R, Pinna G. Baroreflex sensitivity assessment: latest advances and strategies. *Eur Cardiol* 2011;7(2):89-92.
- Kempler P, Varadi A, Szalay F et al. Autonomic neuropathy and corrected QT interval prolongation. There is a relationship. *Diabetes Care* 1994; 17: 454-456.
- Schneider CA, Baer FM, Erdmann E. QT-dispersion - analysis and prognostic implications. *Dtsch Med Wochenschr* 1999; 124:396-402.
- Ziegler D, Weise F, Langen KJ et al. Effect of glycaemic control on myocardial sympathetic innervation assessed by 123 I-metaiodobenzylguanidine scintigraphy: a 4-year prospective study in IDDM patients. *Diabetologia* 1998; 41: 443-451.
- Kuehl M, Stevens MJ. Cardiovascular autonomic neuropathies as complications of diabetes mellitus. *Nat Rev Endocrinol* 2012; 8(7):405-416
- Spallone V, Ziegler D, Freeman R et al. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis and management. *Diabetes Metab Res Rev* 2011; 27: 639-653
- Buse JB, Ginsberg HN, Bakris GL et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from American Heart Association and the American Diabetes Association. *Circulation* 2007; 115: 114-126.
- Pop-Busui R, Low PA, Waberski BH et al. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC). *Circulation* 2009; 119: 2886-2893.
- Pop-Busui R. Cardiac autonomic neuropathy in diabetes: a clinical perspective. *Diabetes Care* 2010; 2:434-441.
- Nathan DM, Genuth S, Lachin J et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977-986.
- The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on the development and progression of neuropathy. *Ann Intern Med* 1995; 122: 561-568.
- Martin CL, Albers J, Herman WH et al. Neuropathy among diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care* 2006; 29: 340-344.
- Pop-Busui R, Herman WH, Feldman EL et al. 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.
- Witte DR, Tesfaye S, Chaturvedi N et al. Risk factors for cardiac autonomic neuropathy in type 1 diabetes mellitus. *Diabetologia* 2005; 48: 164-171.
- Brownlee M. Diabetic complications: pathobiology of hyperglycemic damage and potential impact on treatment. In: Thornalley PJ, Kempler P [Eds]. *Complications of diabetes mellitus: pathophysiology and pathogenetically-based treatment options*, Georg Thieme Verlag KG Stuttgart 2009: 1-8.
- Hammes HP. Diabetic nerve, vascular and organ damage from the pathogenetic key to new therapeutic approaches. In: Rett K [Ed]. *Better chances for nerves and vessels*, Georg Thieme Verlag KG Stuttgart 2011: 9-19.
- Pop Busui R. What do we know and what we do not know about cardiovascular autonomic neuropathy in diabetes. *J Cardiovasc Trans Res* 2012; 5: 463-478.
- Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with

- macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321: 405-412.
46. Holman RR, Paul SK, Bethel MA et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359: 1577-1589.
  47. Jermendy G. Late effect of treatment for reducing cardiovascular risk- a hypothesis on cardiometabolic therapeutic memory. *Med Hypotheses* 2009; 73: 73-79.
  48. Ohkubo Y, Kishikawa H, Araki E, Miyata T et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995; 28:103-117
  49. Azad N, Emanuele NV, Abaira C et al. The effects of intensive glycemic control on neuropathy in the VA Cooperative Study on type II diabetes mellitus. *J Diabetes Complications* 1999; 13: 307-313.
  50. Gaede P, Vedel P, Larsen GV et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348: 383-393.
  51. Maser RE, Mitchell BD, Vinik AI et al. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care* 2003; 26:1895-1901.
  52. Ziegler D, Zentai CP, Perz S et al. Prediction of mortality using measures of cardiac autonomic dysfunction in the diabetic and nondiabetic population: the MONICA/KORA Augsburg Cohort Study. *Diabetes Care* 2008; 31: 556-561
  53. Bolli GB, Fanelli CG, Porcellati F et al. Diabetic autonomic neuropathy. Response to hypoglycemia. In: Gries FA, Cameron NE, Low PA, Ziegler D [Eds]. *Textbook of diabetic neuropathy*, Georg Thieme Verlag, Stuttgart 2003:286-295.
  54. Adler GK, Bonyhay I, Failing H et al. Antecedent hypoglycemia impairs autonomic cardiovascular function: implications for rigorous glycemic control. *Diabetes* 2009; 58: 360-366.
  55. Nordin C. The case for hypoglycaemia as a proarrhythmic event: basic and clinical evidence. *Diabetologia* 2010; 53: 1552-1561.
  56. Stephenson JM, Kempler P, Perin PC et al. Is autonomic neuropathy a risk factor for severe hypoglycaemia? The EURODIAB IDDM Complications Study. *Diabetologia* 1996; 39: 1372-1376.
  57. Meyer C, Grossman R, Mitrakou A et al. Effects of autonomic neuropathy on counterregulation and awareness of hypoglycemia in type 1 diabetic patients. *Diabetes Care* 1998; 21:1960-1966.
  58. Gerstein HC, Miller ME, Byington RP et al. Effects of intensive glucose lowering in type 2 diabetes. *New Engl J Med* 2008; 358: 2545-2559.
  59. Gerstein HC, Riddle MC, Kendall DM et al. Glycemia treatment strategies in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Am J Cardiol* 2007; 99: 34-43.
  60. Calles-Escandon J, Lovato LC, Simons-Morton DG et al. Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010; 33: 721-727.
  61. Skyler JS, Bergenstal R, Bonow RO et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE and VA Diabetes Trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 2009; 32:187-192.
  62. Vinik AI, Maser RE, Ziegler D. Neuropathy: the crystal ball for cardiovascular disease. *Diabetes Care* 2010; 33: 1688-1690.
  63. Vinik AI. The conductor of the autonomic orchestra. *Frontiers in Endocrinology* 2012; ID 103389.
  64. Palatini P, Benetos A, Grassi G et al. Identification and management of the hypertensive patient with elevated heart rate: statement of a European Society of Hypertension Consensus Meeting. *J Hypertens* 2006; 24: 603-610.
  65. Kadoi Y. Anesthetic considerations in diabetic patients. Part I: preoperative considerations of patients with diabetes mellitus. *J Anesth* 2010; 24: 739-747.
  66. Young LH, Wackers FJ, Chyun DA et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 2009; 301:1547-1555.
  67. Maser RE, Mitchell BD, Vinik AI et al. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care* 2003; 26:1895-1901.
  68. Dinh W, Futh R, Lankisch M et al. Cardiovascular autonomic neuropathy contributes to left ventricular diastolic dysfunction in subjects with type 2 diabetes and impaired glucose tolerance undergoing coronary angiography. *Diabet Med* 2011; 28: 311-318.
  69. Brotman DJ, Bash LD, Qayyum R et al. Heart rate variability predicts ESRD and CKD-related hospitalization. *J Am Soc Nephrol* 2010; 21: 1560-1570.
  70. Valensi P, Cosson E. It is not yet the time to stop screening diabetic patients for silent myocardial ischaemia. *Diabetes Metab* 2010; 36: 91-96.