Review

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1338395
J Health Sci Med. 2024;7(1):137-142

Exploring the relationship between orthostatic hypertension and diabetes mellitus: a literature review

Serhat Öcal

Department of Internal Medicine, VM Medicalpark Ankara Hospital, Ankara, Turkiye

Cite this article as: Öcal S. Exploring the relationship between orthostatic hypertension and diabetes mellitus: a literature review. *J Health Sci Med.* 2024;7(1):137-142.

Received: 08.08.2023 ◆ **Accepted**: 23.08.2023 ◆ **Published**: 15.01.2024

ABSTRACT

Diabetes mellitus is a swiftly escalating health problem both nationally and internationally. Diabetic neuropathy, a prominent microvascular complication of diabetes, frequently occurs. Autonomic cardiac neuropathy, which arises from diabetic neuropathy, is a substantial cause of mortality and morbidity. It is also linked with orthostatic hypertension, a condition characterized by an abnormal increase in blood pressure upon standing. There is, however, no consensus on the clinical and pathological characteristics of orthostatic hypertension. Blood pressure and pulse display a circadian rhythm, varying throughout the day. This literature review seeks to explore the intricate relationship between diabetes mellitus and orthostatic hypertension. Special attention is given to the potential impact of circadian rhythm on these conditions, as this aspect could provide essential insights into the disease mechanism and patient management. The review will cover the existing literature, aiming to identify knowledge gaps and illuminate potential areas for future research. Such exploration could lead to the development of enhanced preventive measures and therapeutic strategies, improving patient outcomes in these prevalent and interconnected conditions.

Keywords: Diabetes mellitus, orthostatic hypertension, autonomic cardiac neuropathy, diabetic neuropathy

INTRODUCTION

Today, diabetes is emerging as a health problem of increasing importance worldwide, due to its prevalence and the issues it creates. Alongside lifestyle changes and shifts in dietary habits, the prevalence of diabetes is rapidly rising in all countries.[1]

Autonomic neuropathy, a chronic microvascular complication of diabetes mellitus, can clinically manifest as unawareness of hypoglycemia, resting tachycardia, orthostatic hypotension, reduced heart rate variability, silent myocardial infarction, sudden cardiac death, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction.[2] Autonomic cardiac neuropathy is associated with significant morbidity and mortality in diabetes mellitus.[3] Unlike postural hypotension, a common feature of advanced autonomic neuropathy in diabetes mellitus, the prevalence and clinical importance of early-onset orthostatic hypertension in diabetic patients have not been fully understood.[4,5] Orthostatic hypertension, defined as a consistent increase in blood pressure occurring 1 to 5 minutes after standing up, is a cardiovascular disorder that has been less studied and is increasingly recognized. As one transitions from a supine to standing position, a rapid increase compensates for the transient drop in blood pressure, facilitated by autoregulatory mechanisms modulated by the autonomic nervous system. Despite representing the opposite of OHT, OHT similarly arises from autonomic nervous system (ANS) dysfunction.[6] Pathophysiology of orthostatic hypertension is considered responsible for increased peripheral vascular resistance, high levels of norepinephrine, impaired arterial and cardiopulmonary baroreceptor sensitivity, increased activation of the renin-angiotensin-aldosterone system (RAAS), and increased vasopressin secretion.[7]

Cardiovascular parameters such as blood pressure, pulse, and coronary tone are influenced by circadian rhythms throughout the day.[8] According to ambulatory blood pressure monitoring data of healthy individuals, blood pressure reaches its highest values in the morning, shows a slow decrease throughout the day, and is at its lowest at night.[9] This circadian rhythm in blood pressure has led to a new classification. In this classification made with ambulatory blood pressure monitoring, a decrease of 10% or more in blood pressure values measured at night compared to daytime values is named dipper hypertension, and a decrease of less than 10% is named

Corresponding Author: Serhat Öcal, serhatocal73@hotmail.com

non-dipper hypertension.[10] Recently, it has been shown that 24-hour ambulatory blood pressure measurements (ABPM) are more valuable than clinic measurements in assessing cardiovascular risk.[11]

The objective of this review is to comprehensively analyze the existing literature on the relationship between diabetes mellitus and orthostatic hypertension, placing particular emphasis on autonomic neuropathy and the effects of circadian rhythms on these conditions. Despite growing acknowledgment of orthostatic hypertension as a prevalent complication in diabetic patients, there remains a considerable gap in comprehensive literature reviews exploring its prevalence and clinical implications. This lack of holistic understanding hampers the progression towards formulating effective treatment and preventative measures for diabetic patients susceptible to orthostatic hypertension. By synthesizing the findings on the nuances of this relationship, including the impacts of circadian rhythms on blood pressure and pulse, we intend to illuminate a facet of research that has often been overshadowed. Highlighting these connections can guide improved patient management protocols, aiming to reduce the morbidity and mortality associated with these intertwined conditions. Furthermore, with the global rise in diabetes cases, grasping its complications such as orthostatic hypertension is vital for worldwide health. Consequently, this review holds considerable relevance in the realm of diabetes research and its practical application, offering insights that might shape policy and healthcare directives.

DIABETIC NEUROPATHY

It is defined as symptoms and signs of the peripheral nervous system that cannot be attributed to anything other than diabetes in a diabetic patient. It is the most common microvascular complication in diabetes. Neuropathy is seen in at least half of the patients who have had diabetes for more than ten years.[12]

Prevalence

The prevalence in diabetic patients is on average 30%, and symptomatic peripheral neuropathy develops in about half of the patients during follow-up. Autonomic neuropathy accompanies peripheral neuropathy in 30 to 50% of patients.[13]

The most common form of neuropathy is distal sensory and autonomic polyneuropathy. The most common of the mononeuropathies is carpal tunnel syndrome. Other causes of neuropathy should be ruled out for diagnosis.[14]

Pathogenesis

Metabolic and vascular factors are considered together responsible for the pathogenesis of diabetic neuropathy. However, the most significant metabolic factor is undoubtedly chronic hyperglycemia. There is plenty of evidence that hyperglycemia increases this risk.[15,16]

Multiple mechanisms are held responsible for the development of microvascular complications. One of the pathological reactions triggered by hyperglycemia is the activation of the polyol pathway. With the activation of the polyol pathway, sorbitol increases in the tissues, while myo-inositol levels decrease. As a result of these two parameters, there is a slowdown in nerve conduction speed.[17]

When there is prolonged high blood sugar, or chronic hyperglycemia, compounds called Advanced Glycation End Products (AGEs) are formed. A commonly referenced example of an AGE is HbA1c. What happens is that glucose attaches to proteins in a way that can't be reversed. This attachment can disrupt the normal structure and function of these proteins. Additionally, when AGEs interact with their designated receptor, known as RAGE, it triggers an increase in the production of certain inflammatory substances like cytokines and molecules that help cells stick together, which are released from monocytes and the lining of blood vessels, the endothelium. When RAGE is activated, it also impacts the creation of enzymes called matrix metalloproteinases, which can, in turn, harm nerve fibers.[18]

Other pathological mechanisms triggered by hyperglycemia are decreases in growth factors, activation of protein kinase C, and increased oxidative stress. [19]

One of the most important factors implicated in neuropathy is neural ischemia. Studies have found that the presence of macrovascular disease is a risk factor for the development of neuropathy. The increases in nerve conduction speed after revascularization interventions on large vessels are direct evidence for the role of ischemic factors in neuropathy pathogenesis.[20,21]

Oxidative stress, both experimental data and mitochondrial (SOD2) and extracellular (SOD3) superoxide dismutase gene polymorphism, increase the risk of neuropathy. Some data on the positive effects of antioxidant agents support the role of this mechanism.[22-25]

Symptoms vary according to the affected sensory fiber class. While small fiber involvement leads to pain, burning and tingling, large fiber involvement results in numbness and loss of sensation.[26]

Risk Factors

In type 1 and type 2 diabetes, advanced age, the duration and severity of hyperglycemia are major risk factors for the development of diabetic neuropathy. Additionally, obesity, metabolic syndrome, glycemic variability, dyslipidemia, and smoking are considered risk factors.[27]

Screening

In type 1 DM, it is recommended to perform neuropathy screening every year, starting 5 years after the diagnosis, and in type 2 DM, starting from the time of diagnosis. Neuropathy screening should be done with physical examination, 10-gram (10-g) monofilament, and tests like tuning fork.[28]

Diagnosis

Early diagnosis of diabetic polyneuropathy is important in preventing many complications. Patients should be questioned about the type of symptoms, onset time, progression duration, symmetry, alcohol use, family history. The presence of autonomic symptoms such as constipation, urinary retention, changes in sweating pattern, blurred vision, and bloating in the abdomen should be evaluated. Neuropathy screening, in addition to the physical examination, can be done with simple clinical tests like the monofilament test, which evaluates small nerve fiber function by applying 10 g pressure once a year, and the tuning fork test, which evaluates large nerve fiber function by testing the vibration sense. Electrophysiological tests or referral to a neurologist is rarely required except in cases with atypical symptoms or unclear diagnosis. In all patients with diabetic neuropathy, causes of neuropathy other than diabetes, toxins, neurotoxic drugs, vitamin B12 deficiency, hypothyroidism, kidney disease, malignancies, infections, chronic inflammatory demyelinating neuropathies, hereditary neuropathies, and vasculitis should be ruled out.[26]

Classification

Diabetic neuropathies:[29]

A. A. Diffuse
   1. Distal symmetric polyneuropathy
      - Primary small fiber neuropathy
      - Primary large fiber neuropathy
      - Mixed small and large fiber neuropathy (most common)
   2. Autonomic
      - Cardiovascular
      - Decreased heart rate variability
      - Resting tachycardia
      - Orthostatic hypotension
      - Sudden death
      - Gastrointestinal
      - Diabetic gastroparesis
      - Diabetic enteropathy
      - Chronic hypomotility
      - Urogenital
      - Diabetic cystopathy
      - Erectile dysfunction
      - Female sexual dysfunction
      - Sudomotor dysfunction
      - Distal hypohidrosis/anhidrosis
      - Unawareness of hypoglycemia
      - Abnormal pupillary function

B. Mononeuropathy
   - Isolated cranial or peripheral nerve
   - Mononeuritis multiplex

C. Radiculopathy or polyradiculopathy
   - Radiculoplexus neuropathy
   - Thoracic radiculopathy

DIABETIC AUTONOMIC NEUROPATHY

The signs and symptoms of autonomic neuropathy should be carefully identified during the history taking and physical examination. The main symptoms of diabetic autonomic neuropathy include unawareness of hypoglycemia, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with increased/decreased sweating.[28]

The clinical symptoms of autonomic neuropathy usually appear long after the onset of diabetes. While symptoms suggestive of autonomic dysfunction can be common, they are often due to reasons other than actual autonomic neuropathy. Nevertheless, subclinical autonomic dysfunction can emerge within one year after diagnosis in type 2 diabetic patients and within two years in type 1 diabetic patients.[30]

Cardiac Autonomic Neuropathy

Cardiac autonomic neuropathy is associated with mortality, independent of other cardiovascular risk factors.[31,32] It is suggested that a significant portion of sudden cardiac death cases in diabetic patients is due to silent cardiac autonomic neuropathy.[33]

In its early stages, cardiac autonomic neuropathy may be entirely asymptomatic. Advanced disease can be associated with resting tachycardia (>100 beats/min) and orthostatic hypotension.[28]

In most patients, parasympathetic dysfunction is detected before sympathetic dysfunction. Ewing and colleagues developed an assessment scale that evaluates both sympathetic and parasympathetic autonomic dysfunction together.[34]

In epidemiological studies, diabetes has been found to be an independent risk factor for cardiac hypertrophy, systolic dysfunction, and heart failure.[35,36]

ORTHOSTATIC HYPERTENSION

Contrary to postural hypotension, a common feature of advanced autonomic neuropathy in diabetes mellitus, the prevalence and clinical significance of orthostatic hypertension in diabetic patients have not yet been

fully understood. The difficulty in determining the true prevalence of OHT is due to various factors, such as different definitions used and differences among the populations studied to date.[37]

Definition of Orthostatic Hypertension

Most researchers have suggested that OHT can be defined as an increase of at least 20 mmHg in systolic blood pressure (SBP) after standing.[38] However, recent large-scale studies and in line with the definition of orthostatic hypotension, an orthostatic increase of at least 10 mmHg in diastolic blood pressure (DBP) has also been included in the OHT definition.[39,40] It emerges as a result of abnormal regulation of blood pressure during postural changes and was first defined in 1980.[41]

Pathogenesis of Orthostatic Hypertension

The pathophysiology of orthostatic hypertension is not yet fully understood. Orthostatic hypertension represents the hemodynamic opposite of hypotension but similarly originates from ANS dysfunction. Opposite functioning common mechanisms play a role in both disorders. The reason why common triggering factors and mechanisms support the development of orthostatic hypertension in some patients and orthostatic hypotension in others remains unclear. OHT is closely associated with cardiovascular, cerebrovascular diseases and central nervous system damage, and is considered a new risk factor for cardiovascular and cerebrovascular diseases in adults. It is thought that conditions that increase ANS degeneration are factors supporting the development of OH.[7] These factors are;

- Activation of the Sympathetic Nervous System
- Aging
- Essential hypertension
- Diabetes mellitus
- Neurological disorders

When moving from a supine to a standing position, approximately 500-1000 ml of blood pools below the diaphragm, and hydrostatic pressure shifts fluids from the intravascular area to the interstitial area. In healthy individuals, compensatory autonomic reflex mechanisms withdraw cardiac parasympathetic impulses and increase cardiac and vascular sympathetic activity, leading to an increase in heart rate, a decrease of <20 mmHg in systolic blood pressure, and a small increase in diastolic blood pressure. Studies suggest that orthostatic hypertension results from an excessive increase in vascular resistance when standing. Observations that plasma norepinephrine increases more with standing in patients with orthostatic hypertension suggest that the response is mediated through excessive sympathetic activation while standing.[42] In patients with orthostatic hypertension, due to higher sympathetic activity, vasoconstriction is also greater, and as a result, blood pressure increases. Autonomic nervous system dysfunction leads to insensitivity of arterial and cardiopulmonary baroreceptors and/or inability to adjust the baroreflex to normal blood pressure values, while excessive vasoconstriction mediated by alpha-adrenergic vascular hyperactivity is believed to be another important mechanism. Another proposed mechanism is nephroptosis. In these patients, the renal artery is strained and bent when standing up. As a result, renal blood flow decreases and RAAS is activated.[43]

Signs and Symptoms of Orthostatic Hypertension

Unlike orthostatic hypotension, orthostatic hypertension (OHT) is usually asymptomatic and does not produce any symptoms. Rarely, syncope, feelings of emptiness, dizziness, headaches, palpitations, nausea, and sweating may occur.[44]

Orthostatic Hypertension Treatment

Due to the lack of evidence associated with negative outcomes, there are no specific recommendations for the management and treatment of OHT. There is no direct evidence that the treatment of OHT improves prognosis. If it is considered that OHT is linked to masked and future hypertension, patients with OHT should be closely monitored for the rapid detection of essential hypertension.[7]

Ambulatory Blood Pressure Measurement

Ambulatory blood pressure measurement (ABPM) is considered the gold standard for the diagnosis of hypertension. In healthy individuals, nighttime blood pressure values are usually lower than daytime values, and a reduction of the night-time blood pressure by 10-20% or more compared to the daytime average is considered as a 'dipper' pattern. Non-dipper refers to less than a 10% decrease, while reverse dipper is defined as no decrease or even an increase in nighttime pressure values. It has been reported that non-dipper and reverse dipper patterns are associated with increased cardiovascular mortality.[45]

CONCLUSION

Diabetic neuropathy, the most common microvascular complication in diabetic patients, presents a significant challenge in terms of its diagnosis, management, and long-term impact on patient quality of life. It is a multifaceted disorder, with a prevalence rate of approximately 30% among diabetic patients and often accompanied by symptomatic peripheral and autonomic neuropathy.

The complex pathogenesis of diabetic neuropathy involves both metabolic and vascular factors, with chronic hyperglycemia being the most significant metabolic factor. Various mechanisms contribute to the development of microvascular complications, such as the

activation of the polyol pathway, advanced glycosylation end products (AGEs), oxidative stress, and alterations in growth factors. Furthermore, neural ischemia and the presence of macrovascular disease contribute to the risk of neuropathy development.

Diagnosis of diabetic neuropathy is particularly challenging due to its varied symptoms, which depend on the type of affected sensory fiber. Early diagnosis can prevent many complications, so understanding the type and onset of symptoms, progression, alcohol usage, family history, and the presence of autonomic symptoms can be crucial for diagnosis.

Screening is recommended yearly starting 5 years after diagnosis for Type 1 diabetes and at the time of diagnosis for Type 2 diabetes. Various risk factors can contribute to the development of diabetic neuropathy, including older age, duration and severity of hyperglycemia, obesity, metabolic syndrome, glycemic variability, dyslipidemia, and smoking.

Finally, diabetic neuropathy can be classified into diffused neuropathy (distal symmetric polyneuropathy and autonomic neuropathy), mononeuropathy (isolated cranial or peripheral nerve or mononeuritis multiplex), and radiculopathy or polyradiculopathy (radiculoplexus neuropathy and thoracic radiculopathy).

Understanding the intricate pathophysiology of diabetic neuropathy is vital for the development of effective treatments and interventions. There remains a need for more comprehensive research to further illuminate the mechanisms involved and potentially discover novel therapeutic strategies. Improving patient outcomes will require ongoing efforts in early diagnosis, personalized treatment plans, and disease management education for patients. Ultimately, the objective should be not just to treat diabetic neuropathy, but also to prevent its onset through effective management of diabetes and its associated risk factors.

HIGHLIGHT KEY POINTS

Diabetic neuropathy is a common microvascular complication in diabetic patients, with a prevalence rate of around 30%. Its complex pathogenesis involves both metabolic and vascular factors, with chronic hyperglycemia being the most significant metabolic factor.Different mechanisms including the activation of the polyol pathway, advanced glycosylation end products (AGEs), oxidative stress, and alterations in growth factors contribute to neuropathy development.Diagnosis is challenging due to the varied symptoms, which depend on the type of affected sensory fiber.Screening is recommended yearly starting 5 years after diagnosis for Type 1 diabetes and at the time of diagnosis for Type 2 diabetes.Numerous risk factors contribute to the development of diabetic neuropathy, including older age, duration and severity of hyperglycemia, obesity, metabolic syndrome, glycemic variability, dyslipidemia, and smoking.

Diabetic neuropathy can be classified into diffused neuropathy, mononeuropathy, and radiculopathy or polyradiculopathy.Further comprehensive research is needed to understand the intricate pathophysiology of diabetic neuropathy and develop effective treatments. The ultimate goal should be not just to treat diabetic neuropathy, but also to prevent its onset through effective management of diabetes and its associated risk factors.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Türkiye Halk Sağlığı Kurumu/Türkiye Diyabet Programı 2015-2020. 2020.Accessed July 23, https://www.diyabetimben.com/turkiye-diyabet-programi-2015-2020/
2. Türkiye Endokrinoloji ve Metabolizma Derneği. Diabetes mellitus ve komplikasyonlarının tanı, tedavi ve izlem kılavuzu; 2022. Accessed July 23, https://file.temd.org.tr/Uploads/publications/guides/documents/diabetes-mellitus_2022.pdf
3. Istenes I, Keresztes K, Hermányi Z, et al. Relationship between autonomic neuropathy and hypertension--are we underestimating the problem?. *Diabet Med.* 2008;25(7):863-866. doi:10.1111/j.1464-5491.2008.02458.x
4. Yoshinari M, Wakisaka M, Nakamura U, Yoshioka M, Uchizono Y, Iwase M. Orthostatic hypertension in patients with type 2 diabetes. *Diabetes Care.* 2001;24(10):1783-1786. doi:10.2337/diacare.24.10.1783
5. Jarmuzewska EA, Rocchi R, Mangoni AA. Predictors of impaired blood pressure homeostasis during acute and sustained orthostasis in patients with type 2 diabetes. *Panminerva Med.* 2006;48(1):67-72.
6. Ricci F, De Caterina R, Fedorowski A. Orthostatic hypotension: epidemiology, prognosis, and treatment. *J Am Coll Cardiol.* 2015;66(7):848-860. doi:10.1016/j.jacc.2015.06.1084
7. Magkas N, Tsioufis C, Thomopoulos C, et al. Orthostatic hypertension: From pathophysiology to clinical applications and therapeutic considerations. *J Clin Hypertens (Greenwich).* 2019;21(3):426-433. doi:10.1111/jch.13491
8. Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood-pressure. *Lancet.* 1978;1(8068):795-797. doi:10.1016/s0140-6736(78)92998-7

9. Seo WS, Oh HS. The circadian rhythms of blood pressure and heart rate in the hypertensive subjects: dippers and non-dippers. *Yonsei Med J.* 2002;43(3):320-328. doi:10.3349/ymj.2002.43.3.320
10. Fujii T, Uzu T, Nishimura M, et al. Circadian rhythm of natriuresis is disturbed in nondipper type of essential hypertension. *Am J Kidney Dis.* 1999;33(1):29-35. doi:10.1016/s0272-6386(99)70254-4
11. Clement DL, De Buyzere ML, De Bacquer DA, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med.* 2003;348(24):2407-2415. doi:10.1056/NEJMoa022273
12. Boulton AJ, Gries FA, Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med.* 1998;15(6):508-514. doi:10.1002/(SICI)1096-9136(199806)15:6<508::AID-DIA613>3.0.CO;2-L
13. Volmer-Thole M, Lobmann R. Neuropathy and diabetic foot syndrome. *Int J Mol Sci.* 2016;17(6):917. doi:10.3390/ijms17060917
14. Younger DS, Bronfin L. Overview of diabetic neuropathy. *Semin Neurol.* 1996;16(2):107-113. doi:10.1055/s-2008-1040965
15. American Diabetes Association; American Academy of Neurology. Report and recommendations of the San Antonio Conference on diabetic neuropathy. *Diabetes Care.* 1988;11(7):592-597. doi: 10.2337/dc22-S002.
16. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352(9131):837-853.
17. The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group. *Ann Intern Med.* 1995;122(8):561-568. doi:10.7326/0003-4819-122-8-199504150-00001
18. Sundkvist G, Dahlin LB, Nilsson H, et al. Sorbitol and myo-inositol levels and morphology of sural nerve in relation to peripheral nerve function and clinical neuropathy in men with diabetic, impaired, and normal glucose tolerance. *Diabet Med.* 2000;17(4):259-268. doi:10.1046/j.1464-5491.2000.00261.x
19. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature.* 2001;414(6865):813-820. doi:10.1038/414813a
20. Boulton AJM, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. Accessed July 23, http://diabetesjournals.org/care/article-pdf/27/6/1458/646055/zdc00604001458.pdf
21. Tesfaye S, Chaturvedi N, Eaton SE, et al. Vascular risk factors and diabetic neuropathy. *N Engl J Med.* 2005;352(4):341-350. doi:10.1056/NEJMoa032782
22. Ziegler D. Treatment of diabetic neuropathy and neuropathic pain: how far have we come?. *Diabetes Care.* 2008;31 Suppl 2:S255-S261. doi:10.2337/dc08-s263
23. Jensen TS, Backonja MM, Hernández Jiménez S, Tesfaye S, Valensi P, Ziegler D. New perspectives on the management of diabetic peripheral neuropathic pain. *Diab Vasc Dis Res.* 2006;3(2):108-119. doi:10.3132/dvdr.2006.013
24. American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* 2022;45(Suppl 1):S17-S38. doi:10.2337/dc22-S002
25. Clair C, Cohen MJ, Eichler F, Selby KJ, Rigotti NA. The effect of cigarette smoking on diabetic peripheral neuropathy: a systematic review and meta-analysis. *J Gen Intern Med.* 2015;30(8):1193-1203. doi:10.1007/s11606-015-3354-y
26. American Diabetes Association Professional Practice Committee. 12. Retinopathy, Neuropathy, and Foot Care: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* 2022;45(Suppl 1):S185-S194. doi:10.2337/dc22-S012
27. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care.* 2017;40(1):136-154. doi:10.2337/dc16-2042
28. Pfeifer MA, Weinberg CR, Cook DL, et al. Autonomic neural dysfunction in recently diagnosed diabetic subjects. *Diabetes Care.* 1984;7(5):447-453. doi:10.2337/diacare.7.5.447
29. Pop-BusuiR, 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(7): 1578-1584.
30. Maser RE, Pfeifer MA, Dorman JS, Kuller LH, Becker DJ, Orchard TJ. Diabetic autonomic neuropathy and cardiovascular risk. Pittsburgh Epidemiology of Diabetes Complications Study III. *Arch Intern Med.* 1990;150(6):1218-1222.
31. Singh N. Diabetes, Heart Rate, and Mortality. *J Cardiovasc Pharmacol Ther.* 2002;7(2):117-129.
32. Güçlü S, Aydinlar A, Kaderli AA, GüllülüS, Özdemir B, ŞentürkT. Tip II diyabetes mellituslu hastalarda kardiyak otonom nöropati ile diyastolik kalp fonksiyonlarının ilişkisi. *Uludağ Tıp Derg.* 2007;33(2): 55-59.
33. Vinik AI, Erbas T, Park TS, Stansberry KB, Scanelli JA, Pittenger GL. Dermal neurovascular dysfunction in type 2 diabetes. *Diabetes Care.* 2001;24(8):1468-1475. doi:10.2337/diacare.24.8.1468
34. Mesquita P, Queiroz D, Lamartine de Lima Silva V, et al. Prevalence of orthostatic hypertension in elderly patients with type 2 diabetes. *Int J Endocrinol.* 2015. doi: 10.1155/2015/463487
35. Fessel J, Robertson D. Orthostatic hypertension: when pressor reflexes overcompensate. *Nat Clin Pract Nephrol.* 2006;2(8):424-431. doi:10.1038/ncpneph0228
36. Townsend RR, Chang TI, Cohen DL, et al. Orthostatic changes in systolic blood pressure among SPRINT participants at baseline. *J Am Soc Hypertens.* 2016;10(11):847-856. doi:10.1016/j.jash.2016.08.005
37. Bhuachalla BN, McGarrigle CA, O'Leary N, et al. Orthostatic hypertension as a risk factor for age-related macular degeneration: Evidence from the Irish longitudinal study on ageing. *Exp Gerontol.* 2018;106:80-87. doi:10.1016/j.exger.2018.02.029
38. Streeten DH, Auchincloss JH Jr, Anderson GH Jr, Richardson RL, Thomas FD, Miller JW. orthostatic hypertension. pathogenetic studies. *Hypertension.* 1985;7(2):196-203. doi:10.1161/01.hyp.7.2.196
39. Jordan J, Biaggioni I, Kotsis V, et al. Consensus statement on the definition of orthostatic hypertension endorsed by the American Autonomic Society and the Japanese Society of Hypertension. *Clin Auton Res.* 2023;33(1):69-73. doi:10.1007/s10286-022-00897-8
40. Schiefer J, Amthauer H, Genseke P, Mertens PR, Chatzikyrkou C. Position-related renal perfusion disturbances as a possible underestimated mechanism in patients with resistant hypertension: a case vignette. *Int Urol Nephrol.* 2017;49(10):1823-1833. doi:10.1007/s11255-017-1656-1
41. Lee H, Kim HA. Orthostatic hypertension: An underestimated cause of orthostatic intolerance. *Clin Neurophysiol.* 2016;127(4):2102-2107. doi:10.1016/j.clinph.2015.12.017
42. Birkenhäger AM, van den Meiracker AH. Causes and consequences of a non-dipping blood pressure profile. *Neth J Med.* 2007;65(4):127-131.
43. Selvi NMK, Nandhini S, Sakthivadivel V, Lokesh S, Srinivasan AR, Sumathi S. Association of Triglyceride-Glucose Index (TyG index) with HbA1c and insulin resistance in type 2 diabetes mellitus. *Maedica (Bucur).* 2021;16(3):375-381. doi:10.26574/maedica.2021.16.3.375
44. Alizargar J, Hsieh NC, Wu SV. The correct formula to calculate triglyceride-glucose index (TyG). *J Pediatr Endocrinol Metab.* 2020;33(7):945-946. doi:10.1515/jpem-2019-0579
45. Zhixiang Y, Cheng W, Jibing X, Bisheng G, Ming X, Deyu L. Ambulatory blood pressure monitoring in children suffering from orthostatic hypertension. *Biomed Eng Online.* 2018;17(1):129. doi:10.1186/s12938-018-0530-4