Journal of Research in Clinical Medicine

J Res Clin Med, 2020, 8: 49
doi: 10.34172/jrcm.2020.049
https://jrcm.tbzmed.ac.ir

TUOMS PRESS

Original Article

Evaluation of autonomic neuropathy in newly diagnosed and chronic type 2 diabetic patients: A retrospective cross-sectional study

Mahsa Esmaeillou[1], Jalil Houshyar[2], Fariborz Akbarzadeh[1], Akbar Aliasgarzadeh[2,3*]

[1]Department of Internal Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Endocrine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Imam Reza hospital, Tabriz University of Medical Sciences, Tabriz, Iran

Article info

Article History:
Received: 29 Aug. 2020
Accepted: 4 Oct. 2020
e-Published: 23 Dec. 2020

Keywords:
- Diabetes mellitus
- Cardiovascular autonomic Disorder
- Gastrointestinal autonomic disorder
- Urinary tract autonomic dysfunction

Abstract

Introduction: Diabetic autonomic neuropathy is one of the most important complications of diabetes mellitus (DM) that ultimately occurs in most patients. The purpose of this study was to screen and diagnose latent cases of autonomic neuropathy among patients with a history of DM for over 10 years, and recently diagnosed diabetic patients.

Methods: This cross-sectional study was performed on 104 patients, consisting of 52 type 2 DM (T2DM) patients diagnosed in the last 6 months; and 52 T2DM patients with a history of DM for more than 10 years) referred to outpatient endocrine clinic of Imam Reza Medical Center in Tabriz University of Medical Sciences between 2015-2016. Blood pressure, resting heart rate and corrected QT interval were evaluated according to standard methods. The history of gastrointestinal and urinary tract neuropathy was extracted from patients' history and physical exam.

Results: Of the 104 patients studied, 54 were male and 50 were female. Standing heart rate ($P=0.02$), resting ($P<0.0002$) and standing ($P<0.0001$) systolic blood pressure, and resting diastolic blood pressure ($P=0.03$) were significantly higher in chronic diabetic patients compared with newly diagnosed group. Additionally, blood glucose levels ($P=0.03$) and body mass index (BMI) ($P<0.0001$) were significantly higher in patients with neuropathy.

Conclusion: Overall, the results of this study showed that in patients with T2DM, cardiac autonomic dysfunction is more common in patients with a longer history of DM.

Introduction

Nowadays, due to population growth, aging, urbanization growth, increasing prevalence of obesity and lack of movement, the number of people with type 2 diabetes mellitus (T2DM) is constantly increasing.[1] Diabetic autonomic neuropathy is one of the most important complications of DM which occurs in the early stages in most asymptomatic patients.[2-5] Despite the negative effects of autonomic neuropathy on diabetic patients' survival and quality of life, this complication is less studied compared to other complications of DM.[6]

Several studies reported a relationship between cardiovascular autonomic neuropathy and microvascular complications of DM. High concurrent prevalence of genitourinary autonomic neuropathy, gastrointestinal autonomic neuropathy, and cardiac autonomic neuropathy with elevated levels of albumin excretion have been reported. The relationship between sensory neuropathy and autonomic neuropathy has been reported in some studies.[7-9]

Gastrointestinal autonomic neuropathy occurs in 40% of diabetic patients and is characterized as delayed esophageal transit, regurgitation, dysphagia, esophageal stricture and gastroparesis.[10,11] The prevalence of large and small bowel and anorectal motor disorders is high, and bacterial overgrowth occurs due to decreased bowel movements and constipation.[10,11] Fecal incontinence also occurs in diabetics, mainly due to a decrease in anal sphincter tone. Evaluation of autonomic function of the gastrointestinal system is difficult in humans and cannot be recognized in most patients. The incidence of bladder dysfunction is around 42% to 87% in type 1 diabetic patient and 25% in T2DM patients.[10,11] The bladder dysfunction in diabetics is due to changes in bladder detrusor muscle, bladder nerve dysfunction or urethral dysfunction. The common symptoms include dysuria, urinary frequency, urinary incontinence, enuresis, incomplete bladder emptying, weak urine stream, urinary hesitancy, recurrent cystitis and stress incontinence.[10,11]

Correlation between diabetic cystopathy and peripheral neuropathy has been reported in 1% to 5% of patients.[12] Autonomic neuropathy in the early stages is usually

***Corresponding Author:** Akbar Ali-Asgarzadeh, Email: Asgharzadeha@gmail.com

asymptomatic and is usually not included in the initial evaluation and follow-up of diabetic patients.[12] There is no reliable data in Iran on the prevalence of autonomic neuropathy among newly diagnosed T2DM patients. This study was designed to screen and diagnose latent cases of autonomic neuropathy in newly diagnosed diabetic patients and compare it with those with a history of more than ten years of T2DM.

Methods

Patients

This retrospective cross-sectional study was performed on 104 diabetic patients, including 52 T2DM patients diagnosed in the last 6 months and 52 patients with a history of T2DM for more than 10 years, referred to outpatient endocrinology clinic of Imam Reza hospital in Tabriz University of Medical Sciences. Cochrane formula with the power of 95% and a significance level of less than 0.05 was used for sample size calculation, based on the 7% prevalence of T2DM.[13] The study lasted for one year from April 1, 2015 to April 1, 2016.

The inclusion criteria were age >18 years, and having the ability to perform the tests correctly. Cases with ischemic heart, brain, renal or respiratory diseases, and malignancy; and the patients under insulin and alpha and beta blocker agents, and alcohol or caffeine users were excluded from the study.

After selecting patients, they were asked to avoid any intense physical activity before the tests and wait sitting on the chair for at least ten minutes. Then, they were taken to the examination room and were asked to lie in supine position on the bed and breathe in with normal rhythms and avoid moving on and speaking during the tests. Blood pressure measured from the left arm, and electrocardiogram (ECG) was recorded using bipolar limb leads. Data collection was performed after a minimum of 5 minutes of rest in lying position.

Determination of the average resting heart rate

The average heart rate after 5 minutes of completing rest in lying position was determined based on the records of electrocardiogram on lead II. Heart rates more than 100 beats/minute were considered as abnormal without correction for age and sex. In addition, the changes in heart rates were estimated through standing up position based on a ratio of 15 to 30.[14] The length of two consecutive sinusoidal waves at 15 and 30 beats after standing up was determined and their ratio was reported.

Determination of the corrected QT interval

For this purpose, the Q and T wavelengths were measured in the electrocardiogram on lead II and calculated by the Bazett's formula ($QTc = QT/\sqrt{RR}$). QTc, QT and RR represent the corrected QT, duration of QT interval and duration of RR interval, respectively.[15] The QT intervals >440 milliseconds were considered as abnormal.[16]

Orthostatic hypotension test

Two minutes after changing from lying to standing position, the systolic and diastolic blood pressures were measured and then compared to systolic and diastolic blood pressures in lying position. A reduction >20 mmHg in systolic pressure and 10 mmHg in diastolic pressure was considered as abnormal.[17]

The test score was calculated for patients who fully completed all of five tests. For quantitative evaluation of cardiac autonomic neuropathy, the results of each test were scored between 0 (normal value) and 1 (abnormal value). Then, patients were allocated to one of the three groups including: without neuropathy (final sum of zero), intermediate (final sum of 1) and neuropathic (final sum of 2-5).[6,18,19]

Evaluation of gastrointestinal and genitourinary neuropathy status

Gastrointestinal and genitourinary neuropathies were determined through patients' medical history. Any compliant of autonomic system disorders such as benign paroxysmal positional vertigo, night sweats, sweating during eating, dry skin of the lower extremity, dysuria, urinary frequency, urinary incontinence, sexual problems, early satiety, reflux, diarrhea, constipation, and fecal incontinence were questioned from each patient.[20,21]

Examining peripheral neuropathy

Peripheral neuropathy was assessed by United Kingdom Screening Test.[18] This test includes the patient's symptoms (burning sensation, itching, pain, location of symptoms, timing of symptoms and how symptoms resolve) and clinical examination (achilles tendon reflex, vibration sensation and pain and temperature sensation).

Each of these cases is scored between 0-2. Patients were ranked according to the total score in one of the four groups including 0 to 2 points: Normal, 3 to 4 points: Mild polyneuropathy, 5to 6 points: Moderate polyneuropathy, 7 to 9 points: Severe polyneuropathy.

Statistical analysis

Data were analyzed using SPSS version 22 software. The mean values of the study groups were evaluated using the independent sample *t* test. The values of $P < 0.05$ were considered significant. The examining person and statistical analyzer were blinded to the newly diagnosed or chronic patient's groups.

Results

Demographic characteristics of the studied patients

Of 104 patients under study, 54 (51.7%) were male and 50 (48.3%) were female. The mean age of the patients was 60.4 ± 17.2. Fifty-two subjects were newly diagnosed T2DM patients (less than 6 months) and 52 had a history of T2DM for more than ten years. As shown in Table 1, high blood pressure (64.4%), recent physical inactivity

Table 1. Frequency of risk factors in patients under study

Risk Factors	No. (%) (n=104)
History of high BP	65 (64.4)
Hyperglycemia >200	60 (57.6)
BMI >27	37 (35.5)
Smoking	23 (22.2)
Recent physical inactivity	29 (28.7)

Note. BP: blood pressure; BMI: Body mass index.

(28.7%) and smoking (26.5%) were the most frequent risk factors, respectively.

The comparison of heart rates in resting and standing positions in study groups

The mean resting heart rates in newly diagnosed and chronic T2DM patients did not show a significant difference between two groups (80±16.87 versus 84±12.54, $P=0.173$, respectively). However, a significant difference was observed in the mean standing heart rates in mentioned groups (88±19.21 versus 96±15.74, $P=0.02$, respectively) (Figure 1).

The comparison of systolic blood pressure in resting and standing positions

The mean resting systolic blood pressure in newly diagnosed and chronic T2DM patients showed a significant statistical difference between groups (110±31.21 mm Hg versus 128±11.65 mm Hg, $P<0.0002$, respectively). Moreover, similar results were also observed in comparison of the standing systolic blood pressure between mentioned groups (112±29.11 mm Hg versus 131±13.79 mm Hg, $P<0.0001$, respectively) (Figure 2).

The comparison of diastolic blood pressure in resting and standing positions

As it is presented in Figure 3, a significant difference was observed in resting diastolic blood pressure between newly diagnosed and chronic T2DM patients (71±21.37 mm Hg versus 80±21.43 mm Hg, $P=0.03$, respectively). No significant statistical differences were observed in standing diastolic blood pressure between mentioned groups (75±57.61 mm Hg versus 84±11.34 mm Hg, $P=0.334$, respectively) (Figure 3).

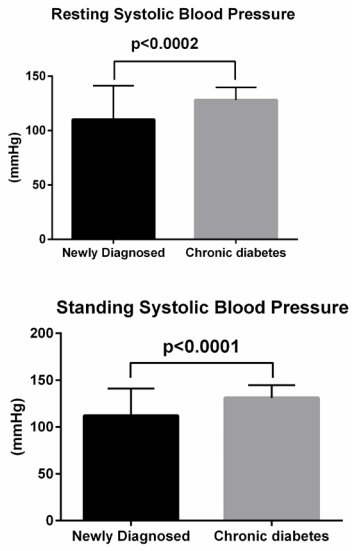

Figure 2. Resting and standing systolic blood pressure in newly diagnosed and chronic type 2 diabetic patients. Data are presented as mean ± standard deviation. $P<0.05$ was considered as statistically significant.

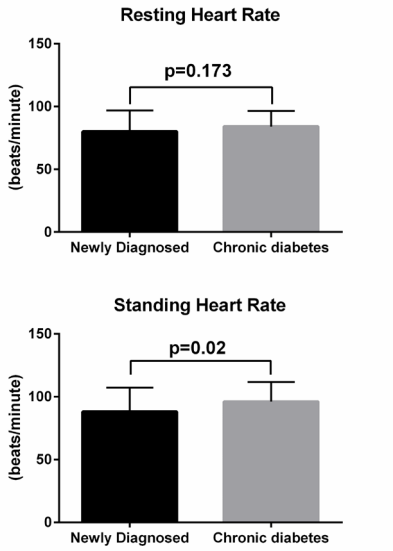

Figure 1. Resting and Standing heart rate in newly diagnosed and chronic type 2 diabetic patients. Data are presented as mean ± standard deviation. $P<0.05$ was considered as statistically significant.

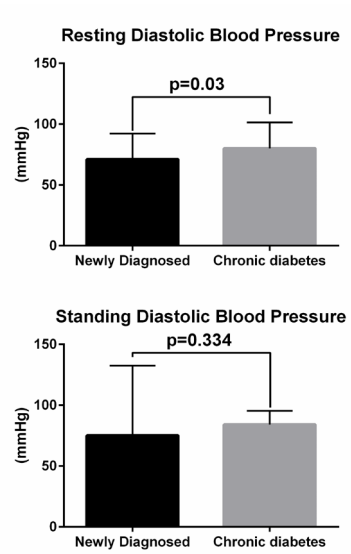

Figure 3. Resting and standing diastolic blood pressure in newly diagnosed and chronic type 2 diabetic patients. Data are presented as mean ± standard deviation. $P<0.05$ was considered as statistically significant.

The comparison of corrected QT interval in study groups

The mean QT intervals in newly diagnosed and chronic T2DM patients showed a significant difference (462±46.51 versus 482±17.72 ms/s, $P=0.106$) (Figure 4).

The frequency of autonomic neuropathies in study groups

As shown in Table 2, of 52 newly diagnosed T2DM patients, 4, 2 and 5 subjects had cardiovascular autonomic impairment, gastrointestinal autonomic disorder, and genitourinary autonomic disorder, respectively. In contrast, of 52 patients with T2DM for more than 10 years, 16, 6 and 8 subjects had cardiovascular autonomic impairment, gastrointestinal autonomic disorder and genitourinary autonomic disorder, respectively.

The association between serum glucose and body mass index with frequency of autonomic neuropathy in study groups

Autonomic neuropathy was observed in 41 patients who were accounted for 39.42% of study population. A significant higher level of blood glucose was observed in patients with autonomic neuropathy in comparison to the patients without autonomic neuropathy (312±52.61 versus 131±24.7, $P<0.0001$, respectively); indicating a significant association between the lack of blood glucose control and the presence of autonomic neuropathy in patients with T2DM. In addition, the mean level of body mass index (BMI) in patients with and without autonomic neuropathy were 33.3±5.3 and 28±4.7, $P<0.0001$, respectively (Figure 5).

Discussion

This study investigated the incidence of autonomic dysfunction in patients with T2DM for more than 10 years in comparison to the patients with newly diagnosed T2DM, using the non-invasive criteria of Ewing et al.[22] These tests are extensively used worldwide to examine the presence of cardiac autonomic neuropathy. Due to their simplicity, these tests are reliable and the results in the different studies have been reproducible. Ewing et al[22] considered the presence of autonomic cardiac neuropathy with abnormal results in any one of these tests, but we performed this study based on recommendations of the reference book.[19]

In this study, we investigated the prevalence of microvascular complications (neuropathies) in diabetic patients with autonomic diabetic neuropathy. We separated patients based on the number of years since the onset of diabetes.

A similar study conducted on 53 diabetic patients in Turkey, indicated similar results with our study. In this study, cardiovascular autonomic neuropathy was considered as an impairment in one of the tests. Based on patients' impairment rates in the tests, they were divided into three groups of mild, moderate, and severe cardiovascular autonomic neuropathies. Although, there was no relationship between severity of cardiovascular autonomic neuropathy and BMI in our patients, it was also observed that a large proportion of patients with heart cardiovascular autonomic neuropathy have other microvascular complications of DM. On the other hand, diabetic autonomic neuropathy has a high prevalence

Table 2. Frequency of autonomic neuropathies in newly diagnosed and chronic type 2 diabetic patients

Neuropathies	Newly diagnosed (n=52) No. (%)	Chronic diabetes (n=52) No. (%)
Cardiovascular autonomic impairment	4 (7.69)	16 (30.76)
Gastrointestinal autonomic disorder	2 (3.84)	6 (11.55)
Genitourinary autonomic disorder	5 (9.61)	8 (15.38)

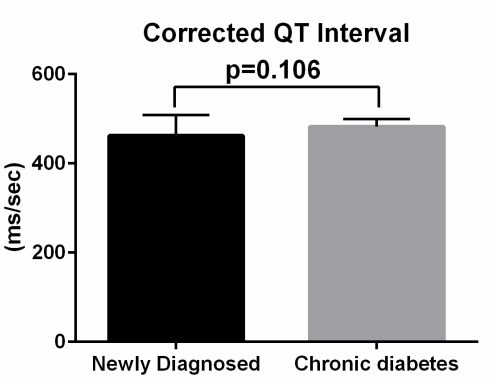

Figure 4. Corrected QT interval in newly diagnosed and chronic type 2 diabetic patients. Data are presented as mean ± standard deviation. $P<0.05$ was considered as statistically significant.

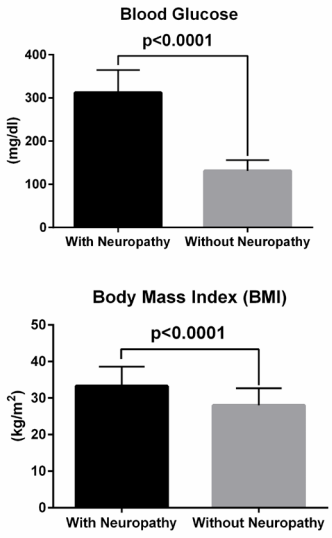

Figure 5. Comparison of blood glucose levels and body mass index (BMI) between patients with (n=41) or without (n=63) neuropathy. Data are presented as mean ± standard deviation. $P<0.05$ was considered as statistically significant.

in comparison to other microvascular complications of DM.[14]

In our study groups, the incidence of cardiovascular autonomic neuropathy was about 19%; while the incidence of cardiovascular autonomic neuropathy in a study conducted by Valensi et al[9] in the French Research Center of Diabetes yielded a 24.5% incidence; although, they accordingly included the type 1 diabetic patients in their study. Given the fact that resting heart rate measurement is a simple and fast test and is known as the first symptom of cardiovascular autonomic neuropathy in many studies; it can be a warning sign in patients for other complications of DM, including sensory neuropathy and nephropathy.[9]

In study of Ko et al,[20] the prevalence of gastrointestinal symptoms was estimated as 70% in 149 T2DM patients. In the Mjörnheim et al[23] and Krishnan et al[24] studies on T2DM patients, the prevalence of gastrointestinal symptoms were estimated to be 59% and 60%, respectively. However, their findings were in contradiction with our findings. In Quan et al[25] and Clouse et al[26] studies, the frequency of gastrointestinal symptoms in diabetic patients were estimated as 15%-25%, and 35%, respectively. Different sample sizes may be the cause of difference in findings of the mentioned studies with the others; since those two studies also included type 1 diabetic patients. Among the findings in the current study, the symptoms of gastrointestinal autonomic dysfunction were lower than that of previous studies, and there were no significant differences between recently diagnosed and chronic diabetic patients.

In a study by Papatheodoridis and Karamanolis,[21] 700 adults from the general population of Greece were investigated, of whom 53% presented at least one gastrointestinal complaint. In Sweden, Agréus et al[27] examined the incidence of gastrointestinal symptoms on 1290 normal individuals, of whom 54% indicated a minimal gastrointestinal complaint. Since, no study investigated the prevalence of gastrointestinal disorders in Iranian population, it cannot be concluded that the prevalence of gastrointestinal symptoms in diabetic patients in the present study is higher than the normal population.

Small sample size of the studied population was one of the main limitations of the present study. Additionally, correlation analysis between albuminuria and nephropathy with cardiovascular autonomic neuropathy seems to be an important issue which was not evaluated in this study.

Conclusion

According to the findings of current study, the most common autonomic disorder in newly diagnosed T2DM patients and patients with a history of T2DM for more than 10 years was cardiovascular autonomic impairment which was more common in patients with longer history of diabetes. However, the comparison of gastrointestinal autonomic and genitourinary autonomic disorders in newly diagnosed diabetic patients and patients with a history of T2DM for more than 10 years had no significant differences. The overall incidence of gastrointestinal autonomic and genitourinary autonomic disorders was lower than the incidence of cardiovascular autonomic impairment.

Study Highlights

What is current knowledge?

- Diabetic autonomic neuropathy is one of the most important complications of DM which occurs in the early stages in most asymptomatic patients. Despite the negative effects of autonomic neuropathy on diabetic patients' survival and quality of life, this complication is less studied compared to other complications of DM.

What is new here?

- There is no reliable data in Iran on the prevalence of autonomic neuropathy among newly diagnosed T2DM patients. This study was designed to screen and diagnose latent cases of autonomic neuropathy in newly diagnosed diabetic patients and compare it with those with a history of more than ten years of T2DM.

Conflict of Interest

All authors declare no conflict of interests.

Ethic Approval

Written informed consent was obtained from all participants prior to any action; and the study was approved by the ethics committee of Tabriz University of Medical Sciences (Code: IR.TBZMED.REC.1396.565).

Authors' Contribution

In this study ME wrote the manuscript. JH selected the patients. FA analysed the data. AA supervised all the study processes. All authors have read and approved the final manuscript.

Acknowledgments

This work has been done as part of the specialty Dissertation for Mahsa Esmaeillou. Authors would acknowledge Endocrine Research Center for their great help.

Funding

This study was supported by Endocrine Research Center at Tabriz University of Medical Sciences, Iran [Grant No.: 94/3-27/24].

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047-53. doi: 10.2337/diacare.27.5.1047.
2. Asbury AK, Porte D, Asbury A, Prote D, Griffin J, Ward J, et al. Proceedings of a consensus development conference on standardized measures in diabetic neuropathy. Neurology

1992;42:1823-39.
3. Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. J Diabetes Investig. 2013;4(1):4-18. doi: 10.1111/jdi.12042.
4. Trotta D, Verrotti A, Salladini C, Chiarelli F. Diabetic neuropathy in children and adolescents. Pediatr Diabetes. 2004;5(1):44-57. doi: 10.1111/j.1399-543X.2004.00041.x.
5. Vinik AI, Maser RE, Ziegler D. Autonomic imbalance: prophet of doom or scope for hope? Diabet Med. 2011;28(6):643-51. doi: 10.1111/j.1464-5491.2010.03184.x.
6. Vinik AI, Erbas T. Cardiovascular autonomic neuropathy: diagnosis and management. Curr Diab Rep. 2006;6(6):424. doi: 10.1007/s11892-006-0074-z.
7. Savage S, Estacio RO, Jeffers B, Schrier RW. Urinary albumin excretion as a predictor of diabetic retinopathy, neuropathy, and cardiovascular disease in NIDDM. Diabetes Care. 1996;19(11):1243-8. doi: 10.2337/diacare.19.11.1243.
8. Valensi P, Huard JP, Giroux C, Attali JR. Factors involved in cardiac autonomic neuropathy in diabetic patients. J Diabetes Complications. 1997;11(3):180-7. doi: 10.1016/S1056-8727(97)00005-6.
9. Valensi P, Pariès J, Attali JR. Cardiac autonomic neuropathy in diabetic patients: influence of diabetes duration, obesity, and microangiopathic complications--the French multicenter study. Metabolism. 2003;52(7):815-20. doi: 10.1016/s0026-0495(03)00095-7.
10. Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, Shearman DJ. Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. Eur J Nucl Med. 1991;18(4):229-34. doi: 10.1007/bf00186645.
11. Jones KL, Russo A, Stevens JE, Wishart JM, Berry MK, Horowitz M. Predictors of delayed gastric emptying in diabetes. Diabetes Care. 2001;24(7):1264-9. doi: 10.2337/diacare.24.7.1264.
12. Hill SR, Fayyad AM, Jones GR. Diabetes mellitus and female lower urinary tract symptoms: a review. Neurourol Urodyn. 2008;27(5):362-7. doi: 10.1002/nau.20533.
13. Kaiser AB, Zhang N, van der Pluijm W. Global prevalence of type 2 diabetes over the next ten years (2018-2028). Diabetes. 2018;67(Suppl 1):202-LB. doi: 10.2337/db18-202-LB.
14. Balcıoğlu AS, Müderrisoğlu H. Diabetes and cardiac autonomic neuropathy: clinical manifestations, cardiovascular consequences, diagnosis and treatment. World J Diabetes. 2015;6(1):80-91. doi: 10.4239/wjd.v6.i1.80.
15. Campbell RW, Gardiner P, Amos PA, Chadwick D, Jordan RS. Measurement of the QT interval. Eur Heart J. 1985;6(Suppl_D):81-3. doi: 10.1093/eurheartj/6.suppl_D.81.
16. Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med. 1993;328(23):1676-85. doi: 10.1056/nejm199306103282306.
17. Cheshire WP. Clinical classification of orthostatic hypotensions. Clin Auton Res. 2017;27(3):133-5. doi: 10.1007/s10286-017-0414-x.
18. Oguejiofor O, Odenigbo U, Oguejiofor C. Screening for peripheral neuropathy in diabetic patients: the benefits of the United Kingdom screening test–UKST-(a clinical scoring system). Trop J Med Res. 2008;12(1):45-9. doi: 10.4314/tjmr.v12i1.30491.
19. Mann DL, Zipes DP, Libby P, Bonow RO. Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. Elsevier Health Sciences; 2014.
20. Ko GT, Chan WB, Chan JC, Tsang LW, Cockram CS. Gastrointestinal symptoms in Chinese patients with Type 2 diabetes mellitus. Diabet Med. 1999;16(8):670-4. doi: 10.1046/j.1464-5491.1999.00135.x.
21. Papatheodoridis GV, Karamanolis DG. Prevalence and impact of upper and lower gastrointestinal symptoms in the Greek urban general population. Scand J Gastroenterol. 2005;40(4):412-21. doi: 10.1080/00365520510012271.
22. Ewing DJ, Campbell IW, Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. Ann Intern Med. 1980;92(2 Pt 2):308-11. doi: 10.7326/0003-4819-92-2-308.
23. Mjörnheim AC, Finizia C, Blohmé G, Attvall S, Lundell L, Ruth M. Gastrointestinal symptoms in type 1 diabetic patients, as compared to a general population. A questionnaire-based study. Digestion. 2003;68(2-3):102-8. doi: 10.1159/000074523.
24. Krishnan B, Babu S, Walker J, Walker AB, Pappachan JM. Gastrointestinal complications of diabetes mellitus. World J Diabetes. 2013;4(3):51-63. doi: 10.4239/wjd.v4.i3.51.
25. Quan C, Talley NJ, Jones MP, Spies J, Horowitz M. Gain and loss of gastrointestinal symptoms in diabetes mellitus: associations with psychiatric disease, glycemic control, and autonomic neuropathy over 2 years of follow-up. Am J Gastroenterol. 2008;103(8):2023-30. doi: 10.1111/j.1572-0241.2008.01943.x.
26. Clouse RE, Lustman PJ. Gastrointestinal symptoms in diabetic patients: lack of association with neuropathy. Am J Gastroenterol. 1989;84(8):868-72.
27. Agréus L, Svärdsudd K, Nyrén O, Tibblin G. The epidemiology of abdominal symptoms: prevalence and demographic characteristics in a Swedish adult population. A report from the Abdominal Symptom Study. Scand J Gastroenterol. 1994;29(2):102-9. doi: 10.3109/00365529409090447.