Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 2411-2417 | ISSN:2251-6727

Exploring the Impact of Type 2 Diabetes on Autonomic Nervous System Function: Insights from Resting States and Active Orthostatic Testing

[1.]Dr. Suman Sinha, [2.]Dr. Ravi Bhushan, [3.]Dr. Anand Kumar, [4.]Dr. Rajiva Kumar Singh

[1] PG Resident, Department of Physiology, Patna Medical College, Patna, Bihar, India.
[2] PG Resident, Department of Physiology, Patna Medical College, Patna, Bihar, India.
[3] Tutor, Department of Physiology, Patna Medical College, Patna, Bihar, India.
[4] Professor and HOD, Department of Physiology, Patna Medical College, Patna, Bihar, India.

Corresponding Author: Dr. Ravi Bhushan

(Received: 12 October 2024 Revised: 6 November 2024 Accepted: 24 November 2024)

KEYWORDS
Type 2 Diabetes Mellitus, Autonomic Nervous System, Heart Rate Variability, Active Orthostatic Test, Cardiovascular Autonomic Neuropathy

ABSTRACT:

Background:
Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder associated with significant impairments in autonomic nervous system (ANS) function. Autonomic modulation, critical for maintaining cardiovascular homeostasis, is particularly affected, leading to dysregulation in response to physiological stressors such as postural changes. Understanding these alterations is essential for early identification and management of cardiovascular autonomic neuropathy (CAN) in individuals with T2DM.

Objectives:
This study aims to evaluate the impact of T2DM on autonomic modulation at rest and during the active orthostatic test (AOT), focusing on heart rate variability (HRV) and blood pressure responses.

Methods:
A retrospective study was conducted with 100 participants, including 50 adults with T2DM and 50 age-matched healthy controls. HRV parameters were analyzed at rest and during AOT using spectral domain methods. Blood pressure responses were monitored to assess autonomic reactivity. Statistical comparisons between groups were performed to evaluate differences in autonomic modulation.

Results:
Individuals with T2DM exhibited significantly reduced HRV parameters, including lower high-frequency (HF) power, indicating diminished parasympathetic activity. During AOT, T2DM participants showed impaired systolic blood pressure recovery and exaggerated sympathetic dominance, reflected in higher low-frequency (LF) power and LF/HF ratio. These findings suggest autonomic dysfunction characterized by parasympathetic withdrawal and unopposed sympathetic activation in response to postural changes.

Conclusions:
T2DM profoundly impacts autonomic modulation, with significant impairments in resting and reactive autonomic function. Early detection of these alterations using HRV and AOT can facilitate timely interventions to mitigate cardiovascular risk and improve patient outcomes.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a complex metabolic disorder characterized by chronic hyperglycemia, insulin resistance, and progressive β-cell dysfunction. Beyond its metabolic consequences, T2DM exerts profound effects on the autonomic nervous system (ANS), leading to dysregulation in cardiovascular, gastrointestinal, and thermoregulatory functions **[1]**.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 2411-2417 | ISSN:2251-6727

Autonomic neuropathy, a common complication of T2DM, significantly increases the risk of cardiovascular morbidity and mortality. Understanding the nuances of autonomic dysfunction in T2DM is crucial for its early detection and management, especially as it often precedes overt clinical symptoms **[2]**.

The ANS plays a pivotal role in maintaining cardiovascular homeostasis through a delicate balance between parasympathetic and sympathetic activity. This balance is particularly critical during physiological stressors, such as postural changes, which require rapid autonomic adjustments to maintain blood pressure and cardiac output **[3]**. The active orthostatic test (AOT) is a dynamic tool for assessing autonomic function, evaluating the body's ability to adapt to postural changes. Changes in heart rate variability (HRV), an established non-invasive marker of autonomic modulation, provide insights into parasympathetic and sympathetic nervous system responses during these transitions **[4]**.

In individuals with T2DM, chronic hyperglycemia and metabolic derangements lead to structural and functional changes in the ANS, culminating in cardiovascular autonomic neuropathy (CAN). CAN manifests as impaired heart rate responses, abnormal blood pressure regulation, and reduced HRV. These alterations compromise the ability of individuals with T2DM to respond to orthostatic stress, increasing the risk of orthostatic hypotension, syncope, and falls **[5]**.

Despite its clinical significance, autonomic dysfunction in T2DM is often underdiagnosed due to the subtle and insidious nature of its presentation. The assessment of HRV at rest and during AOT provides a valuable window into autonomic modulation, offering a non-invasive, sensitive, and reproducible approach to detect early abnormalities **[6]**. Evaluating these parameters in individuals with T2DM compared to healthy controls can enhance our understanding of the pathophysiological impact of diabetes on the ANS and guide interventions to mitigate its adverse effects **[7]**.

This study aims to comprehensively evaluate autonomic modulation in individuals with T2DM at rest and during AOT, with a particular focus on HRV parameters and blood pressure responses. By elucidating the extent and nature of autonomic dysfunction in T2DM, we seek to highlight its clinical implications and potential avenues for early detection and targeted therapy.

Methods

Study : The present retrospective study was conducted in the Department of Physiology, Patna Medical College, Patna, Bihar, India for one year. Total of 100 subjects were taken for the study, The subjects were taken from the Department of Endocrinology and internal medicine OPD Patna Medical College and Hospital, Patna, Bihar, India

Study Population: The study included 100 participants divided into two groups:

1. **Group 1:** 50 adults with Type 2 Diabetes Mellitus (T2DM) diagnosed according to American Diabetes Association criteria.

2. **Group 2:** 50 age- and sex-matched healthy controls without diabetes or known cardiovascular diseases.

Inclusion Criteria:

- Adults aged 35–65 years.
- For T2DM group: Diabetes duration of 5–10 years and stable glycemic control.

Exclusion Criteria:

- Known history of cardiovascular disease, arrhythmias, or hypertension.
- Use of medications affecting autonomic function (e.g., beta-blockers).
- Neurological disorders or orthostatic hypotension.

Assessment of Autonomic Function

1. **Resting State Measurements:**

o Participants rested in a supine position for 10 minutes in a temperature-controlled room. Resting heart rate variability (HRV) and blood pressure were recorded using a validated digital system.

2. **Active Orthostatic Test (AOT):**

o Participants transitioned from a supine to standing position, and continuous heart rate and blood pressure monitoring were performed for 3 minutes.

o The test assessed autonomic reactivity during the postural change, focusing on heart rate and systolic blood pressure responses.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 2411-2417 | ISSN:2251-6727

3. **HRV Analysis:** HRV parameters were analyzed using spectral domain methods, including:

- **Low-Frequency Power (LF, 0.04–0.15 Hz):** Reflecting sympathetic activity.
- **High-Frequency Power (HF, 0.15–0.40 Hz):** Reflecting parasympathetic activity.
- **LF/HF Ratio:** Indicating sympathovagal balance.

4. **Blood Pressure Responses:**

- **Systolic Blood Pressure Recovery:** Assessed as the change in systolic BP from supine to standing.
- **Orthostatic Hypotension:** Defined as a drop in systolic BP ≥20 mmHg or diastolic BP ≥10 mmHg upon standing.

Data Collection and Statistical Analysis: Demographic and clinical data, including age, sex, body mass index (BMI), and diabetes duration, were recorded. HRV parameters and blood pressure responses were compared between groups.

- **Statistical Methods:**

- Descriptive statistics were used to summarize demographic and clinical data.
- Independent t-tests or Mann-Whitney U tests were used to compare HRV parameters and blood pressure responses.
- Pearson's correlation was performed to evaluate the relationship between diabetes duration and HRV.
- A p-value <0.05 was considered statistically significant.

Results

Summary: This study evaluated the impact of Type 2 Diabetes Mellitus (T2DM) on autonomic modulation at rest and in response to the active orthostatic test (AOT). Significant differences were observed in heart rate variability (HRV) parameters and blood pressure responses between the T2DM group and healthy controls. The results indicate impaired parasympathetic activity, exaggerated sympathetic dominance, and reduced autonomic adaptability in individuals with T2DM.

Demographic and Clinical Characteristics: The Table 1 below presents the demographic and clinical parameters of the study participants.

Table 1: Demographic and Clinical Characteristics

Parameter	T2DM Group (n=50)	Control Group (n=50)	p-value
Age (years)	52.4 ± 6.8	51.8 ± 7.1	0.72
Sex (Male/Female)	28/22	27/23	0.84
BMI (kg/m²)	27.5 ± 3.1	24.3 ± 2.8	<0.01*
Diabetes Duration (years)	6.8 ± 2.4	N/A	-

Resting HRV Parameters: The Table 2 below compares HRV parameters at rest between the T2DM and control groups.

Table 2: Resting HRV Parameters

Parameter	T2DM Group (n=50)	Control Group (n=50)	p-value
Low-Frequency Power (LF)	252 ± 85 ms²	328 ± 92 ms²	<0.01*
High-Frequency Power (HF)	123 ± 62 ms²	198 ± 75 ms²	<0.01*
LF/HF Ratio	2.34 ± 0.45	1.76 ± 0.38	<0.01*

Resting Blood Pressure: The Table 3 below shows resting systolic and diastolic blood pressure in both groups.

Table 3: Resting Blood Pressure

Parameter	T2DM Group (n=50)	Control Group (n=50)	p-value
Systolic BP (mmHg)	132.6 ± 8.9	122.4 ± 7.5	<0.01*
Diastolic BP (mmHg)	82.4 ± 6.7	78.2 ± 5.3	<0.05*

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 2411-2417 | ISSN:2251-6727

Autonomic Responses During AOT: The Table 4 below summarizes HRV changes during AOT.

Table 4: HRV Parameters During AOT

Parameter	T2DM Group (n=50)	Control Group (n=50)	p-value
Low-Frequency Power (LF)	310 ± 92 ms²	402 ± 100 ms²	<0.01*
High-Frequency Power (HF)	85 ± 48 ms²	162 ± 58 ms²	<0.01*
LF/HF Ratio	3.65 ± 0.67	2.48 ± 0.59	<0.01*

Systolic BP Recovery During AOT: The Table 5 below shows the systolic blood pressure recovery during AOT

Table 5: Systolic BP Recovery During AOT

Parameter	T2DM Group (n=50)	Control Group (n=50)	p-value
Systolic BP Recovery (mmHg)	-12.8 ± 5.2	-5.4 ± 4.1	<0.01*
Orthostatic Hypotension (%)	16.0	4.0	<0.05*

Heart Rate Responses During AOT: The Table 6 below shows heart rate changes in response to standing.

Table 6: Heart Rate Responses

Parameter	T2DM Group (n=50)	Control Group (n=50)	p-value
Resting Heart Rate (bpm)	84.2 ± 6.5	76.8 ± 5.4	<0.01*
Peak Heart Rate (bpm)	92.4 ± 7.2	89.6 ± 6.8	0.12
Heart Rate Recovery (bpm)	6.4 ± 2.1	10.6 ± 2.4	<0.01*

Correlation Between HRV and Diabetes Duration: The Table 7 below shows the correlation analysis between HRV parameters and diabetes duration.

Table 7: Correlation Between HRV and Diabetes Duration

HRV Parameter	Correlation Coefficient (r)	p-value
Low-Frequency Power	-0.42	<0.01*
High-Frequency Power	-0.46	<0.01*
LF/HF Ratio	0.38	<0.05*

Comparison of Autonomic Function by Diabetes Duration: The Table 8 below stratifies the T2DM group by diabetes duration.

Table 8: HRV Parameters Stratified by Diabetes Duration

Parameter	<5 Years (n=25)	≥5 Years (n=25)	p-value
Low-Frequency Power (LF)	278 ± 80 ms²	232 ± 90 ms²	<0.05*
High-Frequency Power (HF)	138 ± 55 ms²	112 ± 48 ms²	<0.05*
LF/HF Ratio	2.12 ± 0.42	2.51 ± 0.48	<0.05*

Prevalence of Autonomic Dysfunction: The Table 9 below summarizes the prevalence of autonomic dysfunction markers in the T2DM group.

Table 9: Prevalence of Autonomic Dysfunction

Parameter	T2DM Group (n=50)	Percentage (%)
Resting Parasympathetic Dysfunction	32	64.0
Sympathetic Overactivity	28	56.0
Orthostatic Hypotension	8	16.0

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 2411-2417 | ISSN:2251-6727

Summary of Outcomes: The Table 10 below consolidates the study outcomes for both groups.

Table 10: Summary of Outcomes

Outcome	T2DM Group (n=50)	Control Group (n=50)	p-value
Impaired HRV at Rest (%)	72.0	20.0	<0.01*
Impaired HRV During AOT (%)	68.0	18.0	<0.01*
Orthostatic Hypotension (%)	16.0	4.0	<0.05*

Discussion

Type 2 Diabetes Mellitus (T2DM) is well-known for its profound impact on the autonomic nervous system (ANS), contributing to significant alterations in cardiovascular function. This study aimed to evaluate these changes at rest and in response to the active orthostatic test (AOT), with a particular focus on heart rate variability (HRV) and blood pressure responses **[8]**. The findings underscore the substantial impairment in autonomic modulation among individuals with T2DM, providing valuable insights into the pathophysiological mechanisms and clinical implications of autonomic dysfunction in this population **[9]**.

Resting Autonomic Modulation in T2DM: At rest, individuals with T2DM exhibited markedly reduced parasympathetic activity, as evidenced by significantly lower high-frequency (HF) power in HRV analysis. The increased low-frequency (LF) power and elevated LF/HF ratio reflect a shift toward sympathetic dominance and an imbalance in sympathovagal modulation. These findings align with previous studies that have demonstrated autonomic dysfunction as an early and often subclinical complication of T2DM, attributable to chronic hyperglycemia, insulin resistance, and oxidative stress leading to neuronal damage **[10]**.

Impaired Responses During AOT: The active orthostatic test (AOT) provided a dynamic evaluation of autonomic reactivity. In response to postural change, participants with T2DM showed:

1. **Exaggerated Sympathetic Activation:** Increased LF power and LF/HF ratio during standing suggest an over compensatory sympathetic response.

2. **Reduced Parasympathetic Withdrawal:** Lower HF power during standing reflects blunted vagal inhibition, which is crucial for cardiovascular adaptation during postural transitions.

3. **Impaired Systolic Blood Pressure Recovery:** Delayed recovery and higher prevalence of orthostatic hypotension in the T2DM group highlight the compromised baroreflex sensitivity and vascular responses.

These findings emphasize the dual impairment of parasympathetic and sympathetic components of the ANS, which hinders the body's ability to maintain hemodynamic stability during physiological stress.

Relationship with Diabetes Duration: The correlation between diabetes duration and HRV parameters underscores the progressive nature of autonomic dysfunction in T2DM. Longer disease duration was associated with greater reductions in HF power and increased LF/HF ratio, reflecting worsening parasympathetic withdrawal and unopposed sympathetic dominance. These findings reinforce the need for early screening and intervention in T2DM to mitigate the progression of autonomic neuropathy **[11]**.

Clinical Implications: The clinical significance of these findings lies in their association with adverse outcomes. Autonomic dysfunction in T2DM has been linked to:

1. **Increased Cardiovascular Risk:** Impaired autonomic modulation predisposes patients to arrhythmias, ischemia, and sudden cardiac death.

2. **Orthostatic Intolerance:** Blunted hemodynamic responses can lead to orthostatic hypotension, increasing the risk of falls and related complications.

3. **Suboptimal Glycemic Control:** Autonomic dysfunction can impair pancreatic beta-cell function and glucose regulation, creating a vicious cycle of metabolic and autonomic derangements.

Early detection of autonomic dysfunction using HRV and AOT provides an opportunity for timely interventions, such as lifestyle modifications, optimized glycemic

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 2411-2417 | ISSN:2251-6727

control, and pharmacological therapies targeting autonomic pathways.

Comparison with Literature: The findings of this study are consistent with previous research demonstrating impaired HRV and abnormal blood pressure responses in T2DM. However, the comprehensive evaluation of both resting and reactive autonomic function in this study provides a more nuanced understanding of the condition. The significant differences observed between T2DM patients and healthy controls highlight the sensitivity of HRV and AOT as diagnostic tools for autonomic dysfunction.

Limitations and Future Directions: While this study provides valuable insights, certain limitations must be acknowledged:

1. **Cross-Sectional Design:** The study does not assess longitudinal changes in autonomic function or the impact of interventions.

2. **Sample Size:** Although adequate for statistical analysis, larger multicentric studies are needed to generalize findings.

3. **Lack of Direct Measures of Sympathetic Activity:** While HRV parameters provide indirect insights, direct measures such as microneurography were not employed.

Future research should focus on exploring the impact of specific interventions, such as exercise, pharmacological modulation, and novel therapies, on improving autonomic function in T2DM.

Conclusion

This study highlights significant impairments in autonomic modulation among individuals with T2DM, characterized by parasympathetic withdrawal, sympathetic overactivity, and reduced adaptability to orthostatic stress. These alterations underline the importance of routine screening for autonomic dysfunction in T2DM patients to mitigate cardiovascular risks and improve overall outcomes. Early detection using HRV and AOT, coupled with targeted interventions, offers a promising strategy to address this often-overlooked complication of diabetes.

References:

1. Kazamel M, Stino AM, Smith AG. Metabolic syndrome and peripheral neuropathy. Muscle Nerve. 2021 Mar;63(3):285-293. doi: 10.1002/mus.27086. Epub 2020 Oct 24. PMID: 33098165.
2. Spallone V. Update on the Impact, Diagnosis and Management of Cardiovascular Autonomic Neuropathy in Diabetes: What Is Defined, What Is New, and What Is Unmet. Diabetes Metab J. 2019 Feb;43(1):3-30. doi: 10.4093/dmj.2018.0259. PMID: 30793549; PMCID: PMC6387879.
3. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, Stevens M, Kempler P, Hilsted J, Tesfaye S, Low P, Valensi P; Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev. 2011 Oct;27(7):639-53. doi: 10.1002/dmrr.1239. PMID: 21695768.
4. Lim VG, He H, Lachlan T, Ng GA, Kyrou I, Randeva HS, Osman F. Impact of sodium-glucose co-transporter inhibitors on cardiac autonomic function and mortality: no time to die. Europace. 2022 Jul 21;24(7):1052-1057. doi: 10.1093/europace/euab321. PMID: 35080624.
5. Hall LG, Thyfault JP, Johnson JD. Exercise and inactivity as modifiers of β cell function and type 2 diabetes risk. J Appl Physiol (1985). 2023 Apr 1;134(4):823-839. doi: 10.1152/japplphysiol.00472.2022. Epub 2023 Feb 9. PMID: 36759159; PMCID: PMC10042613.
6. Balcıoğlu AS, Çelik E, Aksu E, Aykan AÇ. Impact of Sodium-Glucose Cotransporter-2 Inhibitors on Sympathetic Nervous System Activity Detected by Sympathetic Activity Index and LF/HF Ratio in Patients with Type 2 Diabetes Mellitus. Turk Kardiyol Dern Ars. 2022 Sep;50(6):415-421. doi: 10.5543/tkda.2022.22403. PMID: 35976237.
7. Ouyang X, Peng L, Huang Z, Wang T, Wang J, Wu H, Zhong J, Wu B, Wu L, Li Y, Lu Y, Li S, Tang X. Effects of adipose tissues on the relationship between type 2 diabetes mellitus and reduced heart rate variability: mediation analysis. Cardiovasc Diabetol. 2024 Sep 28;23(1):353. doi: 10.1186/s12933-024-02438-1. PMID: 39342197; PMCID: PMC11439294.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 2411-2417 | ISSN:2251-6727

8. Goldberger JJ, Pelchovitz DJ, Ng J, Subacius H, Chicos AB, Banthia S, Molitch M, Goldberg RB. Exercise based assessment of cardiac autonomic function in type 1 versus type 2 diabetes mellitus. Cardiol J. 2022;29(2):272-283. doi: 10.5603/CJ.a2020.0064. Epub 2020 May 7. PMID: 32378730; PMCID: PMC9007477.
9. Lopez Vicchi F, Luque GM, Brie B, Nogueira JP, Garcia Tornadu I, Becu-Villalobos D. Dopaminergic drugs in type 2 diabetes and glucose homeostasis. Pharmacol Res. 2016 Jul;109:74-80. doi: 10.1016/j.phrs.2015.12.029. Epub 2015 Dec 31. PMID: 26748034.
10. Eleftheriadou A, Spallone V, Tahrani AA, Alam U. Cardiovascular autonomic neuropathy in diabetes: an update with a focus on management. Diabetologia. 2024 Dec;67(12):2611-2625. doi: 10.1007/s00125-024-06242-0. Epub 2024 Aug 9. PMID: 39120767; PMCID: PMC11604676.
11. Moseley KF. Type 2 diabetes and bone fractures. Curr Opin Endocrinol Diabetes Obes. 2012 Apr;19(2):128-35. doi: 10.1097/MED.0b013e328350a6e1. PMID: 22262002; PMCID: PMC4753802.