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COMPARISON OF GDM AND NON-GDM PREGNANT WOMEN SCREENED THROUGH DIPSI CRITERIA AND THEIR RELATION WITH AUTONOMIC FUNCTION

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Abstract

Introduction Gestational diabetes mellitus is a common complication during pregnancy associated with various maternal and fetal health risks.Autonomic dysfunction has been implicated in the pathophysiology of several metabolic disorders, yet its role in GDM remains unclear.Utilizing data from a diverse cohort of patients, we assessed various autonomic function parameters, including heart rate variability, in both GDM and non-GDM groups.This research contributes to a deeper understanding of the physiological mechanisms underlying GDM and may inform future clinical interventions aimed at improving maternal and fetal outcomes.

Methods This study investigates the autonomic function differences between gestational diabetes mellitus (GDM) patients and non-GDM patients.We employed a cross-sectional design to compare autonomic function parameters through HRV between gestational diabetes mellitus (GDM) patients and non-GDM patients which were screened through DIPSI criteria.

Results Our findings reveal significant differences in autonomic function between the two groups, suggesting potential implications for the management and understanding of GDM. The study included a total of 51 participants, with 13 in the GDM group and 38 in the non-GDM group.GCT results were significantly higher in the GDM group compared to the non-GDM group, consistent with the diagnosis of GDM.

Conclusion our findings highlight the presence of autonomic dysfunction in GDM patients, characterized by reduced HRV and altered sympatho-vagal balance.

Introduction

In medicine, the term "gestational diabetes mellitus" (GDM) has been used to describe an abnormal glucose tolerance that manifests itself or is recognised for the first-time during pregnancy[1].Gestational diabetes mellitus (GDM) is a prevalent health concern affecting pregnant women worldwide, characterized by glucose intolerance that first manifests during pregnancy.The incidence of GDM has been steadily rising, mirroring the global increase in obesity rates and the prevalence of type 2 diabetes mellitus (T2DM).GDM affects approximately 15% of pregnancies worldwide, accounting for approximately 18 million births annually.Mothers with GDM are at risk of developing gestational hypertension, pre-eclampsia and termination of pregnancy via Caesarean section.Furthermore, GDM elevates the likelihood of experiencing consequences such as cardiovascular disease, obesity, and impaired carbohydrate metabolism. These complications might ultimately result in the onset of type 2 diabetes (T2DM) for both the mother and the infant.[2] This condition not only poses immediate risks to maternal and fetal health during pregnancy but also confers long-term health implications for both the mother and offspring.Understanding the underlying pathophysiology of GDM is crucial for effective

management and prevention strategies, yet many aspects of this condition remain poorly understood.

According to the Diabetes Canada Clinical Practice Guidelines Expert Committee et al. (2018), it is defined as diabetes diagnosed in the second or third trimester of pregnancy in the absence of previous type 1 or type 2 diabetes.[3] Traditionally, GDM has been viewed through the lens of metabolic dysfunction, focusing on insulin resistance and impaired pancreatic β-cell function. However, emerging evidence suggests that the autonomic nervous system (ANS) may also play a significant role in the pathogenesis of GDM. The ANS, comprised of the sympathetic and parasympathetic branches, regulates various physiological processes, including heart rate, blood pressure, and glucose metabolism. Dysregulation of the ANS, particularly alterations in autonomic tone and heart rate variability (HRV), has been implicated in the pathophysiology of metabolic disorders such as T2DM. Not only can autonomic dysfunction be a consequence of diabetes, but it can also occur before type 2 diabetes develops.[4] Even women who have less severe cases of aberrant glucose regulation during pregnancy, such as gestational impaired glucose tolerance, are at a higher risk. This supports the recent suggestion to make the diagnostic criteria for gestational diabetes mellitus (GDM) stricter, which would include a larger number of women. Women with a history of gestational diabetes mellitus (GDM) are at a higher risk for future cardiovascular disease (CVD) due to many causes. These risks include the development of type 2 diabetes mellitus (T2DM) after childbirth, metabolic syndrome, obesity, hypertension, and changes in levels of certain inflammatory markers in the bloodstream, namely adiponectin, C-reactive protein, and tumor necrosis factor-α.[21]The intricate interplay between the ANS and metabolic regulation underscores the potential relevance of autonomic dysfunction in GDM. Several studies have reported abnormalities in HRV and sympathetic-parasympathetic balance in individuals with T2DM, suggesting a link between autonomic function and glucose homeostasis. Given the similarities between T2DM and GDM in terms of insulin resistance and metabolic dysregulation, it is reasonable to hypothesize that autonomic dysfunction may also contribute to the development and progression of GDM.

Autonomic neuropathy frequently occurs as a consequence of diabetic mellitus (DM). Patients with DM have been found to exhibit reduced vagal nerve activity and increased sympathetic nerve activity.[15] However, despite the growing interest in the role of the ANS in metabolic health, relatively few studies have specifically examined autonomic function in the context of GDM. Existing research in this area has yielded conflicting results, with some studies reporting alterations in HRV parameters in GDM patients compared to healthy controls, while others have found no significant differences. In a study there was a significant decrease in the high-frequency (HF) band in both groups after the ingestion of glucose. Following glucose administration, there was a large rise in the normalised low-frequency (LF) band and a considerable drop in the normalised high-frequency (HF) band.[5] Moreover, the mechanisms underlying any potential autonomic dysfunction in GDM remain poorly understood, limiting our ability to develop targeted interventions to mitigate its effects. In another research endeavor, there were no notable variations in hemodynamics and cardiovascular autonomic modulation between the GDM group and the control group of pregnant women across the entire program. The presence of elevated normalized low-frequency component and low-frequency to high-frequency ratio indicates a shift in sympathovagal balance towards sympathetic predominance during pregnancy in both groups. Their findings indicate that pregnancy has an identical impact on cardiovascular autonomic modulation and hemodynamics in individuals with and without gestational diabetes mellitus (GDM). This suggests that metabolic problem during pregnancy does not lead to cardiovascular dysfunction as long as GDM is well controlled.[19]

Autonomic dysfunction, specifically parasympathetic neuropathy, has been evident since the early stages of type 2 diabetes mellitus (T2DM). This was associated with subclinical atherosclerosis. Timely identification of cardiac autonomic neuropathy can aid in the early detection of atherosclerosis progression in individuals with type 2 diabetes mellitus, thereby mitigating adverse consequences.[16] Therefore, there is a compelling need for further investigation into the relationship between autonomic function and GDM. Clarifying this relationship has important implications for both clinical practice and research, offering insights into novel therapeutic targets and strategies for GDM management. By elucidating the specific autonomic alterations associated with GDM, we can enhance our understanding of the pathophysiological mechanisms underlying this condition and identify potential biomarkers for risk stratification and early detection. Results of another study show that in a comparison to control subjects, young individuals with type 1 diabetes exhibited a decrease in overall heart rate variability (HRV), specifically a reduction of 10.09ms in the standard deviation of NN intervals (SDNN). Additionally, they displayed signs of parasympathetic dysfunction, including a decrease of 13.5ms in the root mean square successive difference of NN intervals (RMSSD) and a decrease of 5.2 normalized units (n.u.) in high frequency (HF) power. These findings were observed alongside an increase of 5.2 n.u. in low frequency (LF) power, indicating sympathetic dominance. Advanced age, being female, having elevated levels of LDL cholesterol and triglycerides, and having microalbuminuria were found to be independently linked to decreased heart

rate variability (HRV). However, these factors did not fully explain the variations in HRV between individuals with and without diabetes.[17] Another contradictory study by Sharifiheris et al, indicates that the autonomic nervous system (ANS) is associated with some pregnancy difficulties, such as fetal growth issues. Nevertheless, their research does not provide evidence for a connection between the autonomic nervous system (ANS) and gestational diabetes mellitus[18]

In this study, we aim to address this gap in knowledge by investigating the differences in autonomic function between GDM patients and non-GDM patients. We will utilize a diverse cohort of pregnant individuals, including both GDM patient's diagnosis based on DIPSI criteria and non-GDM controls, to comprehensively assess various autonomic function parameters. Oral glucose tolerance test (OGTT) with 75 grams of glucose and a cut-off of 140 mg/dl after two hours is the test that DIPSI recommends for non-fasting individuals.[6]Through meticulous analysis of HRV, sympathetic-parasympathetic balance, and other relevant measures, we seek to elucidate the specific autonomic alterations associated with GDM and their potential implications for maternal and fetal health. In a study conducted by Gasic et al., Time domain analysis (standard deviation of normal RR intervals; SDNN) showed a reduced HRV in 25 out of the 48 (52%) women with prior GD. Frequency domain analysis showed that in these 25 subjects, both the low and high frequency components of power spectral density, which mainly reflect sympathetic and parasympathetic activity, were decreased. This suggests that there may be impairment in both sympathetic and parasympathetic function[7]. Results of another study state that there was no statistically significant difference ($p>0.05$) in age, height, weight, and BMI between the cases and controls, indicating that the groups were comparable. Both the systolic and diastolic blood pressure were observed to be considerably higher ($p=0.0001$) in the cases compared to the controls. The cases exhibited considerably greater peak frequency (in Hz) and peak power (%) compared to the controls, with a p-value of 0.0001. Conclusion: The study's results indicate that patients with GDM had significantly higher HRV compared to the control group.[20]

Regrettably, there is currently no universally recognized treatment or preventive approach for GDM, other for lifestyle change (diet and exercise) and, occasionally, insulin therapy, which has limited effectiveness due to the commonly observed insulin resistance. While new oral drugs like glyburide and metformin offer promise for diabetic treatment, concerns persist about their long-term safety for both the mother and the baby[22].Women with gestational diabetes mellitus (GDM) exhibit comparable basal sympathetic nerve activity (SNA) to pregnant women with normal blood sugar levels. However, they demonstrate enhanced neurovascular transduction, indicating a stronger impact of sympathetic nerve activity in these individuals. Additionally, research has shown signs of heightened chemoreceptor activity, which could potentially affect sympathetic nervous activity (SNA) in women diagnosed with gestational diabetes mellitus (GDM), but not in the control group.[23]

In summary, this research represents a critical step towards unraveling the complex interplay between autonomic function and GDM. By shedding light on the role of the ANS in the pathogenesis of GDM, we hope to contribute to the development of more effective strategies for GDM management and prevention, ultimately improving outcomes for both mothers and their offspring.

Materials and Methods

Study Design: This study employed a cross-sectional design to compare autonomic function parameters between gestational diabetes mellitus (GDM) patients and non-GDM patients.

Participants: The study recruited pregnant individuals receiving prenatal care at Integral Institute of Medical Sciences and Research. Participants were divided into two groups: GDM patients diagnosis based on DIPSI criteria, and non-GDM controls with normal glucose tolerance during pregnancy.

Inclusion Criteria:

1. Pregnant individuals aged 18 years or older.
2. Availability of medical records confirming the diagnosis of GDM for the GDM group.
3. Non-GDM controls with normal glucose tolerance during pregnancy, confirmed through medical records or glucose tolerance testing.

Exclusion Criteria:

1. Pre-existing diabetes mellitus or other significant medical conditions affecting glucose metabolism.
2. History of cardiovascular disease, autonomic neuropathy, or other conditions known to affect autonomic function.
3. Use of medications known to influence autonomic function, such as beta-blockers or sympathomimetic agents.

Data Collection:

1. Demographic and clinical data were collected from participants' medical records, including age, gestational age, height, weight, body mass index (BMI), systolic and diastolic blood pressure, and glucose challenge test (GCT) results by DIPSI criteria.

2. A person's weight and height were used to calculate their BMI (kg/m^2). In India, the BMI ranges are: Underweight (<18.5 kg/m^2), normal or lean (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2), and obese (>25 kg/m^2).[13]
3. Autonomic function parameters were assessed using heart rate variability (HRV) analysis, a widely used non-invasive method for evaluating autonomic function.
4. HRV measurements were obtained using a standardized protocol, with participants in a supine position and instructed to breathe spontaneously for a duration of 5 minutes.
5. HRV analysis was performed using specialized software, with calculation of time-domain and frequency-domain HRV parameters, including:
    - Time-domain parameters: Standard deviation of normal-to-normal intervals (SDNN), root mean square of successive differences (RMSSD).
    - Frequency-domain parameters: Low-frequency (LF) power, high-frequency (HF) power, LF/HF ratio.

Statistical Analysis:

1. Descriptive statistics were calculated for demographic and clinical characteristics of the study population.
2. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range), depending on data distribution.
3. Group comparisons between GDM and non-GDM groups were conducted using independent t-tests or Mann-Whitney U tests for continuous variables, as appropriate.
4. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS software.

Table 1. Comparison between GDM NON-GDM subjects

Parameters		**N**	**Mean**	**Std. Deviation**
NON GDM	Gestational age	38	13.21	3.370
	Ht	38	15.26	.760
	ht(ms)	38	1.57	.063
	Wt	38	61.13	9.968
	BMI	38	24.24	3.234
	systolic B.P	38	115.05	5.904
	Diastolic B.P	38	75.63	4.829
	GCT	38	109.34	23.588
	mean RR	38	911.84	21.195
	SDNN	38	51.16	5.587
	RMSSD	38	35.55	11.895
	NN50	38	11.29	1.523
	pNN50	38	15.05	4.249
	LF power	38	720.39	49.788
	HF power	38	515.92	55.090
	LF/HF	38	1.38368	.077370
GDM	Gestational age	13	15.31	2.016
	Ht	13	15.62	.650
	ht(ms)	13	1.60	.048
	Wt	13	69.00	5.745
	BMI	13	26.62	2.567
	systolic B.P	13	124.15	3.579
	Diastolic B.P	13	82.62	1.557
	GCT	13	157.08	20.646
	mean RR	13	870.00	27.689

	SDNN	13	44.77	5.932
	RMSSD	13	29.00	10.312
	NN50	13	10.08	1.656
	pNN50	13	12.31	3.376
	LF power	13	702.31	30.043
	HF power	13	509.23	15.525
	LF/HF	13	1.39231	.123636

Table 1. depicts the comparative study between GDM-NON GDM subjects.

Table 2. Independent samples t-test

Category	p-value
Age	.913
Height	.143
Weight	**.010**
Systolic B.P.	**.000**

Table 2. depicts the p-values of the following parameters when t-test is applied:

- Age has p-value of .913 and height has p-value of .143 which is not significant; ie there is no significant difference between both age and height of GDM-NON GDM subjects and their values are equally distributed in both the groups
- Weight has p-value of .010 and Systolic B.P. has p-value of .000 both of which are significant
- It means that there is a significant relation between Weight and Systolic B.P with the occurrence of GDM.

Table 3. GDM and Non GDM Subjects

	Frequency	Percent
NON GDM	38	74.5
GDM	13	25.5
Total	51	100.0

- Table 3. depicts the percentage of GDM-NON GDM subjects in the population of the study

Table 4. Test Statistics

Parameters	Mann-Whitney U	p-value
Gestational age	145.000	**0.026**
BMI	125.000	**0.008**
Diastolic B.P	33.000	**0.000**
GCT	4.500	**0.000**
Mean RR	33.000	**0.000**
SDNN	107.000	**0.002**
RMSSD	141.000	**0.022**
NN50	137.000	**0.015**
pNN50	159.500	0.058
LF power	126.000	**0.009**
HF power	149.000	**0.033**
LF/HF	229.000	0.692

- Table 4. represents the Mann-Whitney U test results and the p-values of Gestational age BMI GCT Diastolic B.P SDNN RMSSD NN50 is significant which states there is a positive correlation between these parameters
- As the value of these parameters increases there is a more likely chance to develop gestational diabetes mellitus.
- pNN50 and LF/HF have p-values which are nonsignificant stating that there is no relation between these and the occurrence of GDM

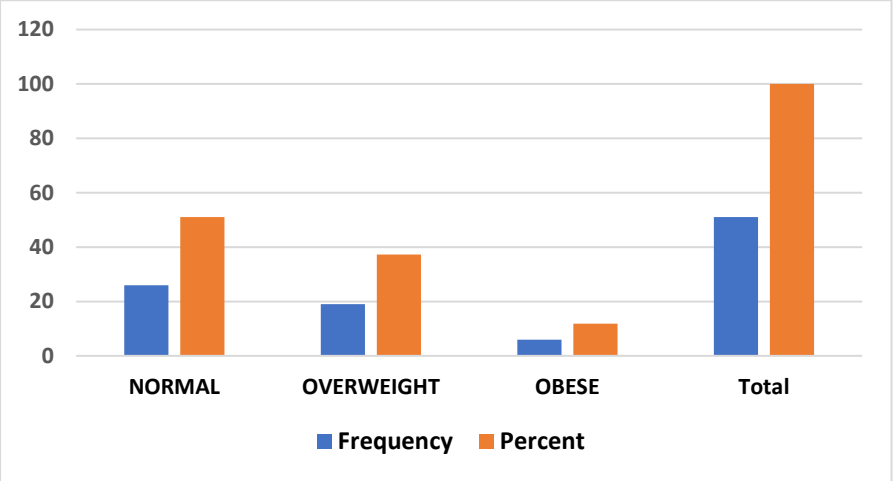

Fig. 1. BMI Category Distribution

Table 5. BMI category distribution

BMI	Frequency	Percent
NORMAL	26	51.0
OVERWEIGHT	19	37.3
OBESE	6	11.8
Total	51	100.0

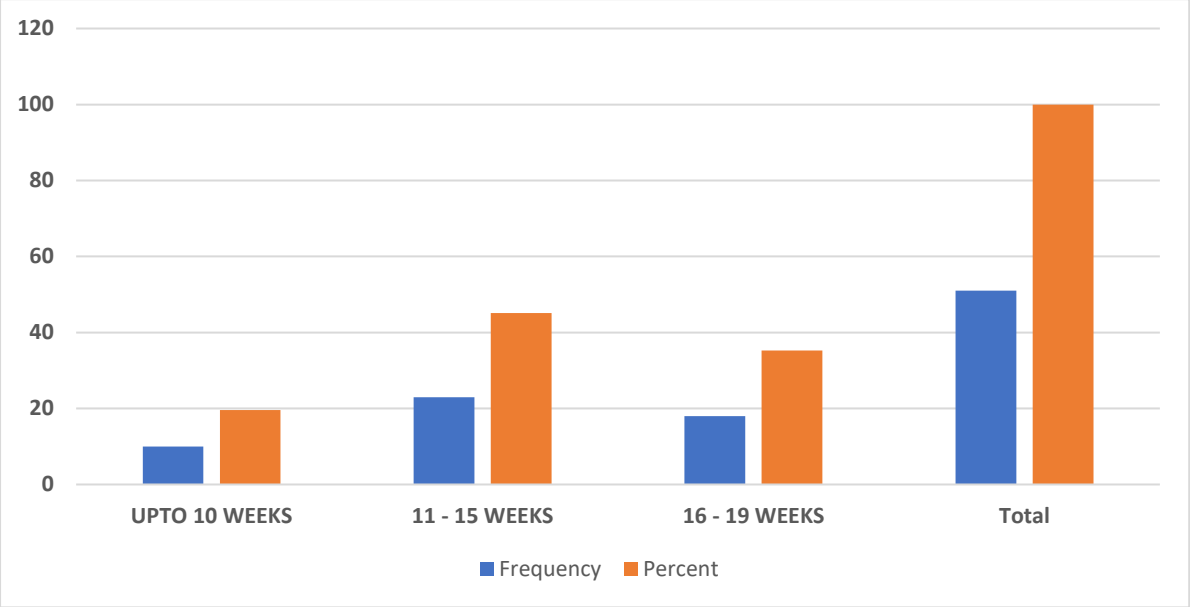

Fig. 2. Gestational Age Distribution

Table 6. Gestational Age distribution

Gestational Age	Frequency	Percent
UPTO 10 WEEKS	10	19.6

11 - 15 WEEKS	23	45.1
16 - 19 WEEKS	18	35.3
Total	51	100.0

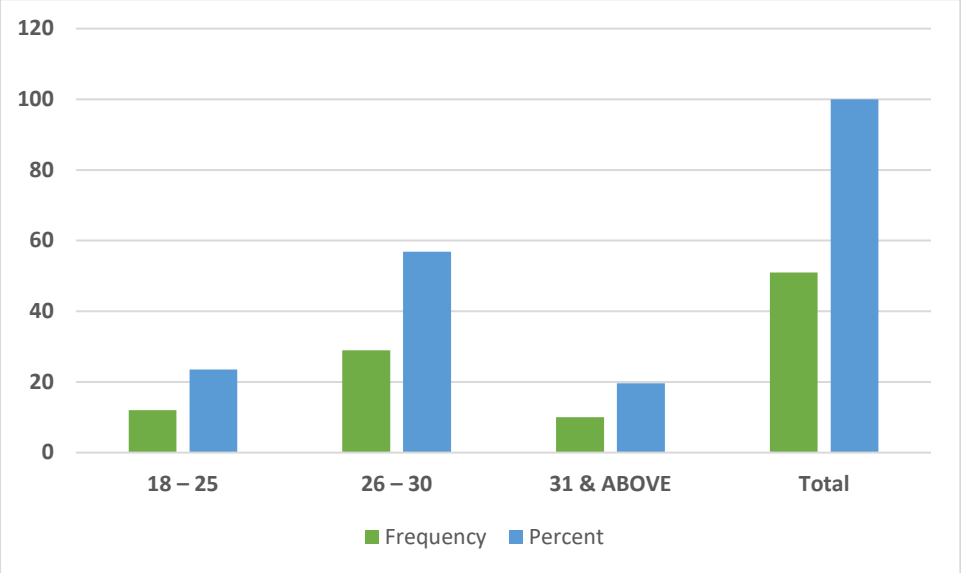

Fig. 3. Age Distribution

Table 7. Age Distribution

Age	Frequency	Percent
18 – 25	12	23.5
26 – 30	29	56.9
31 & ABOVE	10	19.6
Total	51	100.0

Ethical Considerations:

1. This study is approved by the Institutional Ethics Committee of Integral Institute of Medical Sciences and Research.
2. Informed consent was obtained from all participants prior to enrollment in the study, with assurances of confidentiality and voluntary participation.
3. Measures were taken to ensure the privacy and confidentiality of participants' medical information throughout the study.

Limitations:

1. The cross-sectional design limits causal inference and may be subject to selection bias.
2. The sample size is limited, potentially affecting the generalizability of study findings.
3. Confounding variables, such as medication use or comorbidities, may influence study outcomes despite attempts to control for these factors.
4. HRV analysis may be influenced by various factors, including respiratory rate, physical activity, and psychological state, which were not systematically controlled in this study.

Results

Demographic and Clinical Characteristics:

- The study included a total of 51 participants, with 13 in the GDM group and 38 in the non-GDM group.
- There were no significant differences between the two groups in terms of age, and height ($p > 0.05$).

- There were significant differences between the two groups in terms of weight and systolic blood pressure ($p < 0.05$).
- GCT results were significantly higher in the GDM group compared to the non-GDM group, consistent with the diagnosis of GDM.

Autonomic Function Parameters:

- Table 1 presents the results of HRV analysis, including time-domain and frequency-domain parameters between GDM-NON GDM subject
- GDM patients exhibited significantly lower SDNN and RMSSD compared to non-GDM controls, indicative of reduced overall HRV and parasympathetic activity.
- Table 4. represents the Mann-Whitney U test results and the p-values of Gestational age BMI, GCT, Diastolic B.P, SDNN, RMSSD, NN50 is significant which states there is a positive correlation between these parameters
- As the value of these parameters increases there is a more likely chance to develop gestational diabetes mellitus
- pNN50 and LF/HF have p-values which are nonsignificant stating that there is no relation between these and the occurrence of GDM
- Frequency-domain analysis revealed a significantly lower HF power and a higher LF/HF ratio in the GDM group compared to the non-GDM group, suggesting decreased parasympathetic activity and increased sympathetic dominance in GDM patients.

Discussion

The present study aimed to investigate differences in autonomic function between gestational diabetes mellitus (GDM) patients and non-GDM patients. Our findings revealed significant alterations in heart rate variability (HRV), indicative of autonomic dysfunction, among individuals with GDM compared to those with normal glucose tolerance during pregnancy.in a study by maser et al, the analysis revealed that late pregnancy, namely between 30 and 35 weeks gestation, had an impact on the functioning of the autonomic nervous system (ANS). Interestingly, this effect seemed to be consistent for pregnant women, regardless of whether they had the metabolic disorder known as gestational diabetes mellitus (GDM) or not.[8] Another study indicates that maternal weight and body mass indices were significantly elevated compared to a group of individuals with normal weight, given that obesity is a prominent risk factor for the development of gestational diabetes mellitus (GDM).[9]

- The observed reductions in SDNN and RMSSD in GDM patients suggest impaired overall HRV and parasympathetic activity. This finding is consistent with previous studies implicating autonomic dysfunction in the pathogenesis of GDM.
- Decreased parasympathetic activity, as evidenced by lower HF power, may contribute to the dysregulation of glucose metabolism and insulin sensitivity observed in GDM. Parasympathetic modulation of pancreatic function and glucose homeostasis is well-documented, highlighting the potential significance of these findings. Gestational diabetes is linked to simultaneous early morning sympathetic stimulation and activation of the extrinsic coagulation pathway, resulting in a shorter PT (prothrombin time).[10]
- The elevated LF/HF ratio observed in GDM patients indicates a shift towards sympathetic dominance, further corroborating the presence of autonomic imbalance in this population. Sympathetic hyperactivity has been associated with insulin resistance and metabolic dysregulation, suggesting a possible mechanistic link between autonomic dysfunction and GDM pathophysiology.

Clinical Implications:

- The identification of autonomic dysfunction in GDM patients has important clinical implications for risk stratification and management strategies. Monitoring HRV may serve as a non-invasive biomarker for assessing autonomic function and identifying individuals at increased risk of GDM-related complications. Interventions targeting autonomic function, such as lifestyle modifications, stress management techniques, and pharmacological therapies, may represent novel approaches for improving outcomes in GDM patients. The outcomes of a study in late pregnancy, there was an observed enlargement of the heart and its chambers, as well as a decrease in the time between heartbeats (R-R interval), and the variation in R-R intervals. Additionally, there was an increase in the ratio of low frequency to high frequency heart rate variability (LF/HF ratio), which changed from an average of 1.4+/-0.4 to 5.6+/-1.9. The alterations in indicators of autonomic regulation of the sino-atrial node that are typically caused by assuming an upright position were diminished.[24] Further research is needed to evaluate the efficacy of these interventions in ameliorating autonomic dysfunction and reducing the risk of adverse

maternal and fetal outcomes. Studies have been performed which show increased ANS activity in fetuses of diabetic mothers in late gestation. The use of PRSA to analyse human foetal cardiovascular and ANS function may provide better monitoring compared to traditional methods. This might help establish a connection between GDM pregnancy and potential cardiovascular issues in the progeny.[11] Non-diabetic women with a previous history of gestational diabetes have a cardiovascular disease risk profile that is comparable to unaffected women, except for differences in insulin and glucose levels.[25]

Limitations and Future Directions:

- This study was limited by its cross-sectional design and relatively small sample size, which may have influenced the generalizability of the findings. Further longitudinal investigations with bigger groups of participants are necessary to confirm these findings and clarify the chronological connection between autonomic dysfunction and the development of gestational diabetes mellitus (GDM).[12]

- Additional research is needed to elucidate the underlying mechanisms linking autonomic dysfunction to GDM pathophysiology, including the role of inflammatory mediators, hormonal regulation, and adipose tissue dysfunction.

- Long-term follow-up studies are needed to evaluate the prognostic significance of autonomic dysfunction in GDM patients and its impact on maternal and offspring health outcomes.

In conclusion, our findings highlight the presence of autonomic dysfunction in GDM patients, characterized by reduced HRV and altered sympatho-vagal balance. Autonomic dysfunction, which refers to alterations in the sympathetic and parasympathetic nervous systems, is increasingly acknowledged as a potential contributor to the occurrence of both gestational diabetes mellitus (GDM) and preeclampsia[14]. These findings underscore the importance of considering autonomic function in the management of GDM and suggest potential avenues for therapeutic intervention aimed at restoring autonomic balance and improving clinical outcomes.

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