DOI: 10.7860/JCDR/2023/62899.17808

Original Article

Biochemistry Section

Association of Cardiac Autonomic Function Derangement with Obesity and Glycated Haemoglobin: A Cross-sectional Study

PIYUSH BANSAL[1], PRERNA PANJETA[2], PRAVEEN PRASHANT[3], KOMAL[4]

ABSTRACT

Introduction: Hyperglycaemia (as assessed by Glycated haemoglobin (HbA1c)) and obesity lead to the production of advanced glycation end products in blood, which are responsible for damage to the microvasculature, slowly leading to cardiac autonomic dysfunction. Thus, chronic prediabetic hyperglycaemia, as measured by HbA1c may affect cardiac autonomic function in different ranges of obesity (overweight and obese).

Aim: To study the association of cardiac autonomic dysfunction with Body Mass Index (BMI) and HbA1c.

Materials and Methods: The cross-sectional study was conducted at BPS Government Medical College, Sonepat, Haryana, India, from June to December 2019. This study included age and sex-matched 50 healthy, 50 overweight, and 50 obese subjects aged 18-50 years. Serum HbA1c, lipid profile and cardiac autonomic function tests for the parasympathetic system (Resting heart rate, Expiration-inspiration difference on deep breathing, Heart rate response to standing/30:15 stand ratio, Valsalva ratio) and sympathetic system {postural hypotension/fall in Systolic Blood Pressure (SBP) and change in Diastolic Blood Pressure (DBP) on sustained hand grip test} were performed. Chi-square test and Mann-Whitney test were used for statistical analysis.

Results: The prevalence of sympathetic autonomic dysfunction was highest in the obese group (36% in males n=25, and 32% in females, n=25) followed by overweight group (12% in males, n=25 and 12% in females, n=25). The prevalence of parasympathetic autonomic dysfunction was highest in the obese group (40% in males, n=25 and 32% in females, n=25), followed by the overweight group (24% in males, n=25 and 16% in females, n=25). Further, HbA1c was highest in obese males (6.27±1.54) and females (5.94±0.45), followed by overweight males (5.89±0.92) and females (5.46±1.84). Males and females with autonomic dysfunction had significantly higher HbA1c (Males 6.4±0.42 and Females 6.2±0.38) than those without it (Males 5.4±0.86 and Females 5.2±0.75) in the obese and overweight groups taken together.

Conclusion: The prevalence of parasympathetic and sympathetic dysfunction is incrementally increased with higher obesity (BMI) and HbA1c. Overweight and obese subjects with cardiac autonomic dysfunction had higher HbA1c and worse lipid profiles than overweight and obese subjects without autonomic dysfunction.

Keywords: Body mass index, Parasympathetic, Sympathetic

INTRODUCTION

Obesity is the modern-day worldwide pandemic extending across all geographical, racial, religious, and economic divides. Adipocytes secrete cytokines and free fatty acids, which are responsible for insulin resistance and subsequent hyperglycaemia [1]. Chronic hyperglycaemia, as reflected by HbA1c levels, gradually increases over the years from the prediabetic range (HbA1c 5.7-6.4%) to the diabetic range (HbA1c ≥6.5%). Prediabetic hyperglycaemia or episodes of hyperglycaemia lead to the production of advanced glycation end products in blood. These advanced glycation end products causes microvascular damage, peripheral neuropathy, autonomic dysfunction, nephropathy, and retinopathy [1-3]. HbA1c levels reflect chronic hyperglycaemia and advanced glycation end-product levels [2,3].

Cardiac autonomic function testing helps measure the grade of autonomic neuropathy and dysfunction. Parasympathetic tests include: Resting heart rate, Expiration-inspiration (E-I) difference on deep breathing, Heart rate response to standing (30:15 stand ratio), Valsalva ratio [4,5]. Sympathetic tests include: Postural hypotension/fall in SBP and change in DBP on sustained hand grip/isometric exercise test [6,7].

Prevalence of parasympathetic dysfunction was 25%, and the prevalence of sympathetic dysfunction was 6% in patients with hyperglycaemia in impaired glucose tolerance (prediabetic) range from the Finnish Diabetes Prevention Study cohort [8]. Putz Z et al., demonstrated that the mean 24-hours SBP and DBP were significantly higher in 75 people with prediabetic hyperglycaemia compared to a control group of 40 individuals [9]. Lu Y et al., described that cardiac autonomic neuropathy was associated with metabolic syndrome and hyperglycaemia [10]. Ziegler D et al., described prevalence of cardiac autonomic dysfunction was increased not only in individuals with diabetes but also in those with hyperglycaemia in the prediabetic range [11]. Garg R et al., observed in 30 obese subjects aged 21-40 years, that the results of heart rate response to standing (30:15 ratio), valsalva ratio, heart rate response to deep breathing, isometric handgrip exercise test and cold pressor test were significantly lower in obese subjects as compared to control subjects. They noted that latent autonomic neuropathy may be present in otherwise healthy obese individuals [12]. In studies by Dimova R et al., and Balcioğlu AS et al., cardiac autonomic neuropathy was found in a significantly higher number of prediabetics, and HbA1c was related to sural sensory neuropathy. Their results demonstrated a high prevalence of autonomic and sensory nerve dysfunction in the early stages of hyperglycaemia [13,14]. Multiple studies have shown that obese people are less responsive to blood pressure changes in posture [15]. Monterio G et al., also showed in obese people that there was a decrease in blood pressure response to the isometric handgrip exercise test, reflecting sympathetic dysfunction in contrast to the control group [16]. van Baak MA stated that in obesity, sympathetic activity as measured by isometric hand grip and cold pressor test is reduced, and it may be responsible for the maintenance of obesity [17]. However, Chiheb S et al., in a study on metabolically healthy obese

phenotype, cardiac autonomic dysfunction was not associated with obesity or hyperglycaemia [1].

Valensi P et al., has demonstrated sympathetic insufficiency in obese people. Additionally, it was shown that patients with autonomic dysfunction have increased glucose-induced reduction of lipid oxidation rate in obese persons, which could be due to a decline in parasympathetic activity [18]. Further, the activity of the sympathetic nervous system is a determinant of energy expenditure which affects obesity [19]. This makes cardiac autonomic dysfunction in obesity even more significant as it may lead to a vicious cycle of maintaining obesity. Cardiac autonomic dysfunction in different range of obesity (overweight and obese ranges) has not been described separately in previous studies [15,17]. The study was conducted in 2019 and the advent of the COVID-19 pandemic from year 2020 has further increased the importance of such pre-COVID-19 data related to obesity and its health effects. The aim and objectives of the study were to study association of cardiac autonomic dysfunction with BMI and HbA1c. Comparison of prevalence of cardiac autonomic dysfunction in healthy, overweight and obese adults and comparison of HbA1c levels in subjects with and without cardiac autonomic dysfunction.

MATERIALS AND METHODS

The hospital-based case-control cross-sectional study was conducted at BPS Government Medical College, which caters to the rural population of Khanpur Kalan, Haryana, India, from June to December 2019 in the pre-COVID era. Institutional scientific and ethical clearance was taken vide letter no. BPSGMCW/RC 445/IEC 19 dated 13 May 2019. Informed and voluntary consent was taken from all subjects.

Inclusion criteria: Individuals of age 18-50 years, consenting voluntarily (volunteers, doctors, and staff working in the medical college and hospital) were included in the study.

Exclusion criteria: Individuals with pregnancy/lactation, history of stroke or coronary/peripheral artery disease as assessed from medical records or complete clinical history and examination, acute or chronic renal/liver/thyroid disease, history of gout/autoimmune diseases, hormonal disorders, Diabetes Mellitus and use of drugs affecting testosterone/estradiol/thyroid/metabolism were excluded from the study.

Sample size: A sample size of 150 as was decided for the study-50 healthy, 50 overweight, and 50 obese subjects with each group having 25 males and 25 females. Relevant clinical history and physical examination including measurement of BMI, weight in kg/square of height in meter were performed in all subjects to meet inclusion and exclusion criteria. The healthy BMI range was defined as 18.5-24.9 kg/m^2, overweight as BMI 25-29.9 kg/m^2, and obesity as BMI ≥30 kg/m^2 for the purpose of this study [1,2].

Cardiac autonomic function tests were done in the central research lab with the help of the Cardiac Autonomic Function System (CANS) 504^R instrument. The laboratory environment was kept quiet, the temperature between 30-35ºC, and the lighting subdued. Subjects were asked to empty their bladder before the tests. The tests did not involve intravascular instrumentation or administration of drugs at any stage. Tests were carried out after 10 minutes of adaptation to the lab environment [7,20]. Cardiac autonomic function tests include assessment of parasympathetic function by measurement of:

1. **Resting heart rate:** normal is 60 to 100 beats per minute [4].
2. **Heart rate response to standing (30:15 stand ratio):** performed during the initial phase of adaptation to orthostasis i.e. immediately upon standing (first 45s), and the ratio is calculated as a quotient of the maximal (around 30th heart beat) to minimal (near 15th heart beat) RR interval in this period in the Electrocardiogram (ECG) recorded. Value less than 1.04 is abnormal [5,20].
3. **Expiratory-Inspiratory difference (E-I difference)/heart rate response to deep breathing:** Heart rate was recorded first during normal breathing (at rest) and then during deep breathing (6/minutes, with five seconds of inhalation and five seconds of exhalation per breath). ECG was recorded and difference between the average of the largest accelerations during inspiration and the average of the largest decelerations during expiration was calculated. Value < 15 beats per minute is abnormal [5,20].
4. **The valsalva ratio:** Subjects were instructed to exhale into a mouthpiece connected to a mercury manometer and to maintain the expiratory pressure of 40 mmHg for 15 seconds. A clamp is placed on the nose and it is suddenly released after 15 seconds. ECG is recorded during the resting period and during the subsequent 40 heart beats after releasing the clamp. The ratio was calculated between the maximum R-R interval (after the release of strain) and the minimum R-R interval (during strain). Value below 1.21 is abnormal [7,20].

Parasympathetic dysfunction was defined as abnormal result on abnormal heart rate response to standing (30:15 stand ratio) test or abnormal result on both E-I difference and Valsalva ratio tests [20].

Sympathetic function tests included:

1. **Postural hypotension/fall in SBP:** After baseline recording of SBP and heart rate in the supine position, the subject was asked to stand for atleast 120 seconds. Blood pressure and heart rate were recorded immediately and 120 seconds after the standing position. Difference between the baseline supine and the minimal blood pressure after standing up was taken. More than 20 mmHg decline in SBP is abnormal [7,20].
2. **Change in DBP on sustained hand grip/isometric exercise test:** After recording basal blood pressure, subjects were asked to perform an isometric handgrip exercise. Subjects were instructed to hold the handgrip spring dynamometer in the dominant hand to have a full grip. The handles of the dynamometer were compressed by the subject with maximum effort for a few seconds. The entire process was carried out three times, with breaks in between to prevent fatigue. The mean of the three readings was referred to as maximal isometric tension (T max). Then, the subjects were instructed to perform an isometric handgrip exercise at 30% of T max for two minutes. During the test, blood pressure was recorded from the non exercising arm. Five minutes after completion of the exercise blood pressure was again recorded. Difference between the highest diastolic pressure during the examination and the average diastolic pressure at rest was taken. It should normally be higher than 10 mmHg [6,20].

Sympathetic dysfunction was defined as abnormal result on both of the above tests of cardiac sympathetic function [20]. Presence of either of parasympathetic or sympathetic dysfunction was defined as presence of cardiac autonomic dysfunction in a subject [20].

SBP and DBP were measured during cardiac autonomic function testing using CANS 504^R instrument. Normal SBP and DBP were taken as <120 mmHg and <80 mm Hg, respectively [20].

HbA1c and lipid profile were done in all subjects enrolled in fasting blood samples. These tests were performed on the Roche Modular P800^R biochemistry autoanalyser. Appropriate quality control was carried out for all investigations. HbA1c was measured using National Glycohaemoglobin Standardisation Program standardised

assay using the immune-inhibition method-based commercial kits on Roche Modular P800^R autoanalyser [21]. Reference range of HbA1c was taken as: Normal < 5.7%, Prediabetic 5.7-6.4%, Diabetic ≥6.5%. Lipid profile included total cholesterol (cholesterol esterase and cholesterol oxidase method, normal <200 mg/dL), Low Density Lipoprotein (LDL) cholesterol (calculated by Friedwald formula, normal <130 mg/dL), High Density Lipoprotein (LDL) Cholesterol (magnesium sulphate/PEG-Cholesterol esterase method, normal 40-60 mg/dL), and Triglycerides (glycerol oxidase-lipase method, normal <150 mg/dL) [22].

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) version 20.0 was used for various statistical analyses. A comparison of data between groups was made using the Mann-Whitney test for quantitative data and the Chi-square test for qualitative data. A p-value <0.05 was considered to be statistically significant.

RESULTS

The results of BMI, HbA1c, parasympathetic function tests, and sympathetic function tests in healthy, overweight, and obese subjects are summarised in [Table/Fig-1]. Age distribution was similar in the three groups. Amongst parasympathetic function tests, obese males had maximum decline in E-I Difference (15.79±3.61), 30:15 stand Ratio (0.98±0.04) and Valsalva Ratio (1.31±0.17) compared to healthy counterparts. Parasympathetic dysfunction was present in 40% (10/25) of obese males and 32% (8/25) of obese females compared to 24% (6/25) of overweight males and 16% (4/250) of overweight females. Amongst sympathetic function tests, maximum fall in SBP was seen in obese males (16.43±5.65) and obese females (15.48±5.27). Decline in DBP change on sustained hand grip was noted most in obese males (5.9±2.1) and obese females (6.3±2.9) followed by overweight females (8.7±2.5) compared to healthy counterparts. Sympathetic dysfunction was present in 36% (9/25) of obese males and 32% (8/25) of obese females compared to 12% (3/25) of overweight males and 12% (3/25) of overweight females. Amongst the 50 obese and overweight males 16 had cardiac autonomic dysfunction. Amongst the 50 obese and overweight females 12 had cardiac autonomic dysfunction. The comparison of overweight and obese subjects with and without cardiac autonomic dysfunction is summarised in [Table/Fig-2]. HbA1c, total-cholesterol, LDL-cholesterol and triglyceride levels were significantly higher in the former group in both male and female subjects. HbA1c levels were maximum in obese and overweight males with cardiac autonomic dysfunction (6.4±0.42%).

Variables	Males			Females		
	Healthy (controls) (n=25)	Overweight (n=25)	Obese (n=25)	Healthy (n=25)	Overweight (n=25)	Obese (n=25)
Age (years)	29.26±6.52	31.0±8.24 p=0.344	34.67±9.14 p=0.093	30.15±7.33	28.92±7.52 p=0.357	35.42±9.68 p=0.063
BMI (kg/m^2)	21.71±1.78	28.17±1.08 p<0.001	33.36±1.29 p<0.001	20.83±1.84	27.17±1.15 p<0.001	34.55±2.15 p<0.001
Systolic Blood Pressure (SBP) (mmHg)	112.80±11.67	126.37±7.88 p<0.001	138.35±18.79 p<0.001	110.64±12.84	128.64±15.47 p<0.001	136.47±19.76 p<0.001
Diastolic Blood Pressure (DBP) (mmHg)	74.65±5.7	81.71±9.76 p<0.001	85.66±12.23 p<0.001	72.27±6.5 p<0.001	80.45±9.65 p<0.001	86.51±8.41 p<0.001
HbA1c and lipid profile						
HbA1c (%)	5.05±1.65	5.89±0.92 p=0.026	6.27±1.54 p=0.007	4.91±0.65	5.46±1.84 p<0.001	5.94±0.45 p<0.001
Total Cholesterol (mg/dL)	163.4±37.34	185.45±27.5 p=0.021	210.4±52.1 p<0.001	156.4±34.3	172.4±32.4 0.093	199.34±47.4 p<0.001
LDL Cholesterol (mg/dL)	93.6±17.8	132.61±30.8 p<0.001	141.5±36.1 p<0.001	89.7±17.5	123.45±29.3 p<0.001	136.7±28.7 p<0.001
Triglycerides (mg/dL)	139.6±41.9	177.0±55.3 p=0.008	193.0±55.7 p<0.001	117.3±39.6	168.2±41.1 p<0.001	189.4±52.4 p<0.001
Parasympathetic function tests						
Resting HR	74.5±13.1	82.7±11.2 p=0.020	89.7±12.4 p<0.001	71.3±10.2	80.6±9.6 p<0.001	90.4±10.3 p<0.001
E-I difference	26.73±5.03	23.36±5.58 p=0.025	15.79±3.61 p<0.001	25.69±4.86	23.10±6.02 p=0.098	18.12±3.35 p<0.001
30:15 stand ratio	1.21±0.19	1.16±0.11 p=0.260	0.98±0.04 p<0.001	1.19±0.18	1.12±0.09 p=0.087	1.02±0.05 p<0.001
Valsalva ratio	1.72±0.26	1.63±0.26 p=0.227	1.31±0.17 p<0.001	1.69±0.24	1.51±0.28 p=0.018	1.29±0.11 p<0.001
Parasympathetic dysfunction (%)	0%	24% (6/25) p<0.001	40% (10/25) p<0.001	0%	16% (4/25) p<0.001	32% (8/25) p<0.001
Sympathetic function tests						
Fall in SBP (postural hypotension)	3.56±1.78	7.44±3.55 p<0.001	16.43±5.65 p<0.001	2.55±1.22	8.83±4.12 p<0.001	15.48±5.27 p<0.001
Change in DBP on sustained hand grip	9.1±2.8	7.6±4.4 p=0.156	5.9±2.1 p<0.001	10.6±2.7	8.7±2.5 p=0.012	6.3±2.9 p<0.001
Sympathetic dysfunction (%)	0%	12% (3/25) p<0.001	36% (9/25) p<0.001	0%	12% (3/25) p<0.001	32% (8/25) p<0.001

[Table/Fig-1]: Demographic, BMI, biochemical variables, parasympathetic and sympathetic function tests in enrolled subjects (p-values of comparison with controls are given with each parameter, p <0.05=significant*).
*Mann-Whitney U test used for quantitative data and Chi-square test used for qualitative data

Variables	Males			Females		
	Without autonomic dysfunction (n=34)	With autonomic dysfunction (n=16)	p-value	Without autonomic dysfunction (n=38)	With autonomic dysfunction (n=12)	p-value
HbA1c (%)	5.4±0.86	6.4±0.42	<0.001	5.2±0.75	6.2±0.38	<0.001
Total Chol	175.7±27.3	241.4±32.3	<0.001	163.6±35.2	225.6±30.6	<0.001
LDL Chol	127.6±46	149.5±38.21	0.093	115.7±28.4	145.6±36.8	0.004
Triglycerides	170.9±51.2	205.4±41.1	0.024	159.19±39.22	201.3±45.83	0.002

[Table/Fig-2]: Comparison of HbA1c and lipid profile in subjects with and without autonomic dysfunction in overweight and obese subjects (p<0.05=significant*).
*Mann-Whiteny U test

DISCUSSION

Central obesity causes insulin resistance which in turn leads to hyperglycaemia in prediabetic range. Chronic hyperglycaemia is reflected by HbA1c levels and was seen to be incrementally increased in overweight and obese groups in this study. HbA1c is biomarker of advanced glycation end products, which is responsible for endothelial and microvascular damage. Microvascular damage leads to retinopathy, nephropathy, and neuropathy [3]. In this study, levels of HbA1c were significantly higher in obese and overweight subjects with cardiac autonomic dysfunction than those without it. Prevalence of cardiac autonomic dysfunction, as reflected by various tests of sympathetic and parasympathetic function, was significantly higher in obese than overweight and in both these groups than healthy controls. Total cholesterol, LDL cholesterol, and triglycerides, were also significantly higher in obese and overweight subjects with autonomic dysfunction than in obese and overweight subjects without autonomic dysfunction. Parasympathetic dysfunction was found associated with BMI and triglyceride levels but not with cholesterol or HbA1c by Laitinen T et al., [8]. Higher levels of HbA1c and lipids were found in individuals with cardiac autonomic dysfunction in another study [23]. Dimova R et al., and Balcioğlu AS et al., also did not find associations between lipid levels and autonomic dysfunction in obese subjects [13,14]. van Biljon A et al., also described association of high LDL levels with cardiac autonomic dysfunction [24].

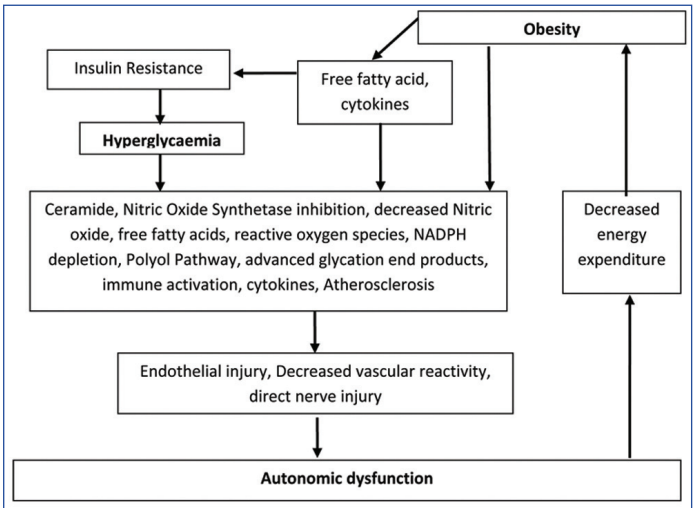
Parasympathetic function tests like E-I difference on deep breathing, 30:15 stand ratio, and Valsalva ratio were significantly deranged in obese males and females than healthy counterparts. Parasympathetic dysfunction reflects decreased baroreflex sensitivity in obese subjects. Baroreceptor resetting may occur in obese individuals due to atherosclerosis that hardens the carotid sinus walls, which reduces vessel wall compliance. Obese people are less responsive to blood pressure changes to posture [15,18]. Sympathetic function test- Fall in SBP/postural hypotension was significantly higher in obese males and females than in healthy counterparts. In other sympathetic function tests, change in DBP on sustained hand grip (isometric exercise) was significantly lower in obese males and females than in healthy subjects. Prevalence of cardiac autonomic dysfunction, as evaluated by deep breathing, valsalva, and standing was found higher in 24 prediabetic individuals compared to 16 healthy controls in a study published by Dimova R et al., [23]. Sushma S et al., assessed cardiac autonomic function by deep breathing test, Valsalva ratio, Orthostatic Heart Rate (OHR), isometric handgrip test, and orthostatic blood pressure in elderly individuals and found significant association for deranged autonomic dysfunction with HbA1c [25]. Increased mean resting heart rate was described in individuals with high HbA1c by Casagrande SS et al., [26]. Findings of present and previous studies are summarised in [Table/Fig-3] [8,9,11-14,16,18,23-26].

S. No.	Author's name and publication year	Place of study	Sample size	Parameters compared	Conclusion
1	Laitinen T et al., 2011[8]	Kuopio, Finland	268 non diabetic individuals with impaired glucose tolerance	Cardiovascular autonomic neuropathy using deep-breathing and active orthostatic tests, HbA1c, lipids, BMI	Prevalence of parasympathetic dysfunction was 25% and prevalence of sympathetic dysfunction was 6%. Subjects with parasympathetic dysfunction had higher triglycerides. Parasympathetic dysfunction was not significantly associated with HbA1c.
2	Putz Z et al., 2013 [9]	Budapest, Hungary	75 people with impaired glucose tolerance and 40 healthy volunteers	Heart rate, heart rate variability, cardiovascular autonomic neuropathy, BMI	Mean 24-h SBP and DBP was significantly higher in the group with impaired glucose tolerance.
4	Garg R et al., 2013 [12]	Ghaziabad, India	30 obese and 30 healthy	Parasympathetic and sympathetic function tests in healthy vs obese (BMI >30)	Obesity is associated with both sympathetic and parasympathetic nervous system dysfunction.
5	Ziegler D et al., 2015 [11]	Düsseldorf, Germany	565 individuals of normal glucose tolerance, 559 had prediabetes , and 78 newly detected diabetes mellitus	Cardiac autonomic function and heart rate variability	Prevalence of cardiac autonomic neural dysfunction was increased not only in individuals with diabetes, but also in prediabetes .
6	Dimova R et al., 2021 [23]	Sofia, Bulgaria	16 with normal glucose tolerance and 24 with prediabetes	Glucose, lipids, and HbA1c, cardiac autonomic function by deep breathing, valsalva, and standing	Significant decline in cardiac autonomic function in prediabetes in comparison with NGT.
7	Balcioğlu AS et al., 2016 [14]	Antalya, Turkey	80 non diabetic patients with metabolic syndrome and 70 control subjects	Heart rate variability and heart rate turbulence as measure of cardiac autonomic function, metabolic syndrome, fasting plasma glucose	Only fasting plasma glucose level was an independent determinant of all heart rate variability and heart rate turbulence.
8	Monterio G et al., 2012 [16]	Mangalore, India	50 subjects	ECG recording was done during normal breathing, deep breathing and cold pressor conditions and heart rate variability	Subjects with a normal BMI showed a better heart rate variability response to cold pressor test, indicating a better parasympathetic activity as compared to obese subjects.
9	Valensi P et al., 1999 [18]	Bondy, France	63 obese patients, and 35 healthy control subjects	Heart rate variations during three standardised tests: deep-breathing, lying-to-standing and valsalva. Isometric contraction (handgrip) for 5 min	36 of 63 obese had abnormal parasympathetic function. Age matched obese patients with cardiac parasympathetic dysfunction had higher BMI.
10	Dimova R et al., 2017 [13]	Sofia, Bulgaria	130 with normal glucose tolerance, 227 with prediabetes and 121 with diabetes type 2	HbA1c, serum lipids, cardiac autonomic function using standard clinical tests	Cardiac autonomic neuropathy was found in 12.3% of normal glucose tolerance, 19.8% of prediabetes and 32.2% of type 2 diabetics.
11	van Biljon A et al., 2019 [24]	Zululand, South Africa	34 South African children	Heart rate variability, lipid profile, blood pressure, blood glucose	High low density lipoprotein cholesterol levels with cardiac autonomic dysfunction.
12	Sushma S et al., 2021 [25]	Bengaluru, India	141 elderly patients	Autonomic function tests such as deep breathing test, valsalva ratio, Orthostatic Heart Rate (OHR), isometric handgrip test, and orthostatic blood pressure	73.8% of patients had autonomic dysfunction. HbA1c, diabetes and hypertension were significantly associated with autonomic dysfunction.
13	Casagrande SS et al., 2020 [26]	Florida, USA	8562 adults	HbA1c, resting heart rate, fasting plasma glucose	Mean heart rate increased with increasing HbA1c level.

14	Present study, Bansal P et al., 2023	Sonepat, India	50 obese, 50 overweight and 50 heathy subjects	Cardiac autonomic function tests, HbA1c, BMI, lipid profile	Prevalence of parasympathetic and sympathetic dysfunction was incrementally increased with higher obesity (BMI) and HbA1c. Overweight and obese subjects with cardiac autonomic dysfunction had higher HbA1c and worse lipid profile than overweight and obese subjects without autonomic dysfunction.

[Table/Fig-3]: Summary of similar studies [8,9,11-14,16,18,23-26].

Obesity leads to decreased activity of the sympathetic nervous system and a lower increase in peripheral resistance to manoeuvres like isometric hand grip exercise which activate the sympathetic system [17,18]. van Baak MA further stated that sympathetic reactivity to isometric handgrip exercise is reduced in obesity. Reduced sympathetic reactivity may be responsible for the maintenance of the obese state by decreasing energy expenditure [17]. Valensi P et al., also demonstrated sympathetic insufficiency in obese people. Further, it was shown that glucose induced inhibition of the lipid oxidation rate in obese people is greater in patients with cardiac autonomic dysfunction, which could be due to a decrease in parasympathetic activity [18]. The possible mechanisms interlinking obesity, hyperglycaemia, and cardiac autonomic dysfunction described in the literature are summarised in [Table/Fig-4] [27-29].



[Table/Fig-4]: Possible mechanisms of autonomic neuropathy due to obesity and hyperglycaemia and their interplay [27-29].

HbA1c is produced non enzymatically from haemoglobin as a glycation product due to prolonged hyperglycaemia. Increased HbA1c is a direct marker of neuronal, endothelial, and microvascular damage due to advanced glycation end-product formation [30]. Stino AM and Smith AG also showed that HbA1c, and increased resting heart rate are the strongest independent predictors of cardiac autonomic dysfunction [30]. Similarly, in the study by Lu Y et al., resting heart rate, HbA1c, diabetes, and hypertension were the strongest predictors of cardiac autonomic dysfunction [10]. Further obesity is known to be associated with hypertension due to multiple factors like adipose tissue-derived angiotensinogen, obstructive sleep apnoea, subclinical inflammation, and high dietary fat and carbohydrate content acutely stimulating peripheral $\alpha 1$ and β-adrenergic receptors [27,28]. In this study also, obese and overweight subjects had higher SBP and DBP than their healthy counterparts.

Limitation(s)

The study was limited by minimum sample size as well as inability to study heart rate variability and heart rate turbulence as added test of cardiac autonomic function due to limitations of resources.

CONCLUSION(S)

The prevalence of parasympathetic dysfunction was incrementally increased with higher obesity. The prevalence of sympathetic dysfunction was also increased in obese individuals. Overweight and obese subjects with cardiac autonomic dysfunction had higher HbA1c than overweight and obese subjects without autonomic dysfunction. Based on the findings of this study, a larger sample size study that also examines heart rate variability, heart rate turbulence as well as fasting insulin and serum advanced glycation end products could be very beneficial in understanding the impact of obesity on cardiac autonomic function across the complete range of BMI.

REFERENCES

[1] Chiheb S, Cosson E, Banu I, Hamo-Tchatchouang E, Cussac-Pillegand C, Nguyen MT, et al. Are obese individuals with no feature of metabolic syndrome but increased waist circumference really healthy? A cross sectional study. Exp Clin Endocrinol Diabetes. 2016;124(7):410-16. Doi: 10.1055/s-0035-1569264.
[2] Bilha SC, Branisteanu D, Buzduga C, Constantinescu D, Cianga P, Anisie E, et al. Body composition and circulating estradiol are the main bone density predictors in healthy young and middle-aged men. J Endocrinol Invest. 2018;41(8):995-1003. Doi: 10.1007/s40618-018-0826-z.
[3] Irani M, Merhi Z. Role of vitamin D in ovarian physiology and its implication in reproduction: A systematic review. Fertil Steril. 2014;102:460-68. Doi: 10.1016/j.fertnstert.2014.04.046.
[4] Page MM, Watkins PJ. The heart in diabetes: Autonomic neuropathy and cardiomyopathy. Clin Endocrinol Metabol. 1977;6:377-88. Doi: 10.1016/s0300-595x(77)80043-1.
[5] Berntson GG, Bigger JT, Eckberg DL, Grossman P, Kaufmann PG, Malik M, et al. Heart rate variability: Origins, methods, and interpretive caveats. B Psychophysiology. 1997;34:623-48. Doi: 10.1111/j.1469-8986.1997.tb02140.x.
[6] Ewing DJ, Irwing JB, Kerr F, Wildsmith JAW, Clarke RF. Cardiovascular response to sustained handgrip in normal subjects and in patients with diabetes mellitus: A test of autonomic function. Clin Sci Mol Med. 1974;46:295-306. Doi: 10.1042/cs0460295.
[7] Ewing DJ. Analysis of heart rate variability and other non invasive tests with special reference to diabetic mellitus. In: Bannister R, Mathias CJ, editors. Autonomic failure. A textbook of clinical disorders of the autonomic nervous system. 3rd edition. New York: Oxford University Press; 1992. Pp.312-33.
[8] Laitinen T, Lindström J, Eriksson J, Ilanne-Parikka P, Aunola S, Keinänen-Kiukaanniemi S, et al. Cardiovascular autonomic dysfunction is associated with central obesity in persons with impaired glucose tolerance. Diabet Med. 2011;28(6):699-704. Doi: 10.1111/j.1464-5491.2011.03278.x.
[9] Putz Z, Németh N, Istenes I, Martos T, Gandhi RA, Körei AE, et al. Autonomic dysfunction and circadian blood pressure variations in people with impaired glucose tolerance. Diabet Med. 2013;30(3):358-62. Doi: 10.1111/dme.12111.
[10] Lu Y, Tang ZH, Zeng F, Li Y, Zhou L. The association and predictive value analysis of metabolic syndrome combined with resting heart rate on cardiovascular autonomic neuropathy in the general Chinese population. Diabetol Metab Syndr. 2013;17(1):73. Doi: 10.1186/1758-5996-5-73.
[11] Ziegler D, Voss A, Rathmann W, Strom A, Perz S, Roden M, et al. Increased prevalence of cardiac autonomic dysfunction at different degrees of glucose intolerance in the general population: The KORA S4 survey. Diabetologia. 2015;585:1118-28. Doi: 10.1007/s00125-015-3534-7.
[12] Garg R, Malhotra V, Goel N, Dhar U, Tripathi Y. A study of autonomic function tests in obese people. IJMRHS. 2013;2:750-55. Doi: 10.5958/j.2319-5886.2.4.120.
[13] Dimova R, Tankova T, Guergueltcheva V, Tournev I, Chakarova N, Grozeva G, et al. Risk factors for autonomic and somatic nerve dysfunction in different stages of glucose tolerance. J Diabetes Complications. 2017;31:537-543. Doi: 10.1016/j.jdiacomp.2016.11.002.
[14] Balcioğlu AS, Akinci S, Çiçek D, Eldem HO, Çoner A, Bal UA, et al. Which is responsible for cardiac autonomic dysfunction in non diabetic patients with metabolic syndrome: Prediabetes or the syndrome itself? Diabetes Metab Syndr. 2016;10(1):S13-20. Doi: 10.1016/j.dsx.2015.09.001.
[15] Emdin M, Gastaldelli A, Muscelli E, Macerata A, Natali A, Camastra S, et al. Hyperinsulinemia and autonomic nervous system dysfunction in obesity: Effect of weight loss. Circulation. 2001;103:513-19. Doi: 10.1161/01.cir.103.4.513.
[16] Monteiro G, Chathoth V, Kishan K. Cardiac autonomic response during a cold pressor test in normal and overweight adults. IJBAR. 2012;3(6):514-16.
[17] van Baak MA. The peripheral sympathetic nervous system in human obesity. Obes Rev. 2001;2:03-14. Doi: 10.1046/j.1467-789x.2001.00010.x.

[18] Valensi P, Bich Ngoc PT, Idriss S, Paries J, Cazes P, Lormeauet B, et al. Haemodynamic response to an isometric exercise test in obese patients. Influence of autonomic dysfunction. Int J of Obesity. 1999;23:543-49. Doi: 10.1038/sj.ijo.0800873.
[19] Bray GA. Autonomic and endocrine balance in the regulation of energy balance. Fed Proc. 1986;45:1404-10.
[20] Zygmunt A, Stanczyk J. Methods of evaluation of autonomic nervous system function. Arch Med Sci. 2010;6:11-18. Doi: 10.5114/aoms.2010.13500.
[21] Halwachs-Baumann G, Katzensteiner S, Schnedl W, Purstner P, Pieber T, Wilders-Truschnig M. Comparative evaluation of three assay systems for automated determination of hemoglobin A1c. Clin Chem. 1997;43:511-17.
[22] Fukuyama N, Homma K, Wakana N, Kudo K, Suyama A, Ohazama H, et al. Validation of the Friedewald equation for evaluation of plasma LDL-cholesterol. J Clin Biochem Nutr. 2008;43:01-05. Doi: 10.3164/jcbn.2008036.
[23] Dimova R, Chakarova N, Grozeva G, Tankova T. The relationship between endogenous secretory RAGE and cardiac autonomic function in prediabetes. Int J Clin Pract. 2021;75:e14769. Doi:10.1111/ijcp.14769.
[24] van Biljon A, McKune AJ, DuBose KD, Kolanisi U, Semple SJ. Cardiac autonomic function and its association with cardiometabolic disease risk factors in Black South African children. Auton Neurosci. 2019;219:01-04. Doi: 10.1016/j.autneu.2019.03.002.
[25] Sushma S, Rao MY, Aslam SM. Assessment of functions of the autonomic nervous system in the elderly with different comorbid factors. J Neurosci Rural Pract. 2021;12:80-87. Doi: 10.1055/s-0040-1718854.
[26] Casagrande SS, Cowie CC, Sosenko JM, Mizokami-Stout K, Boulton AJM, Pop-Busui R. The association between heart rate and glycemic status in the national health and nutrition examination surveys. J Clin Endocrinol Metab. 2020;105:e858-70. Doi: 10.1210/clinem/dgaa055.
[27] Narkiewicz K. Obesity and hypertension-the issue is more complex than we thought. Nephrology Dialysis Transplantation. 2006;2:264-67. Doi: https://Doi.org/10.1093/ndt/gfi290.
[28] Jiang SZ, Lu W, Zong XF, Ruan HY, Liu Y. Obesity and hypertension. Exp Ther Med. 2016;12(4):2395-99. Doi: 10.3892/etm.2016.3667.
[29] Borne PVD, Hausberg M, Hoffman RP, Mark AL, Anderson EA. Hyperinsulinaemia produces cardiac vagal withdrawal and nonuniform sympathetic activation in normal subjects. Am J Physiol Regul Integr Comp Physiol. 1999;276:178-83. Doi: 10.1152/ajpregu.1999.276.1.R178.
[30] Stino AM, Smith AG. Peripheral neuropathy in prediabetes and the metabolic syndrome. J Diabetes Investig. 2017;8:646-55. Doi: 10.1111/jdi.12650.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Biochemistry, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, Haryana, India.
2. Associate Professor, Department of Biochemistry, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, Haryana, India.
3. Senior Resident/Demonstrator, Department of Biochemistry, Pt. B.D. Sharma, PGIMS, Rohtak, Haryana, India.
4. Undergraduate Student, Department of HCMS, BPS Government Medical College for Women, Khanpur Kalan, Sonepat, Haryana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Praveen Prashant,
44/11J, Medical Campus, PGIMS, Rohtak-124001, Haryana, India.
E-mail: praveenprashant12@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jan 17, 2023
- Manual Googling: Mar 22, 2023
- iThenticate Software: Apr 14, 2023 (13%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 14, 2023**
Date of Peer Review: **Feb 08, 2023**
Date of Acceptance: **Apr 20, 2023**
Date of Publishing: **May 01, 2023**