Autonomic Dysfunction in Asian Indian T2DM Patients is Related to Body Fat Content Instead of Insulin Resistance: A DEXA Study

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Abstract: *Aim*: To study autonomic dysfunction in Asian Indian T2DM patients by heart rate variability and it's relation with body fat content, distribution and insulin resistance.

Subjects and Methods: Subjects: 33 T2DM patients aged (46.96 ± 8.90 yrs), and 33 healthy controls aged (44.08 ± 9.15 yrs).

Methods: Short-term heart rate variability (HRV) was measured by impedance plethysmograph recording of pulse wave in distal superficial arteries. Time domain and Frequency domain analysis of HRV was carried out. Time domain parameters (SDNN, rMSSD, pNN50) and frequency domain parameters (Total Power, LF power, HF Power, LF (nu), HF (nu), LF/HF Ratio) were determined. Body fat content and distribution was estimated by (DEXA). Insulin Resistance was assessed by HOMA-R. Student t test was used for comparison of parameters in two groups. Multiple regression was used to find out relation between parameters of adiposity and HRV.

Results: Parameters rMSSD, pNN50, Total power, LF Power, HF Power were significantly lower in diabetics. Total power showed negative correlation with BMI and truncal fat (r=-.43; p<. 05) and (r=-.41; p<. 05) respectively. Frequency domain parameter HF (ms2) showed negative correlation with BMI and trunk fat (gm %) (r= -.47; p<. 05) and (r=-.40; p<. 05) respectively. HF (nu) was negatively correlated with BMI (r=-.43; p<. 05) whereas positive correlation was observed between LF (nu) and BMI (r=. 40; p<. 05).

Conclusion: T2DM is associated with overall reduction in autonomic activity however, body fat content influences relative modulation of sympathetic and parasympathetic activity among diabetics but not among controls. Contrary to most previous reports, insulin resistance as well as W: H ratio had no influences on autonomic activity.

Keywords: T2DM, Autonomic Imbalance, Insulin Resistance, Body Fat Distribution.

BACKGROUND

Autonomic nervous system regulates body energy homeostasis [1, 2]. Obesity and insulin resistance are disorders of body energy balance and several previous studies find both are associated with autonomic dysfunction measured as various parameters of heart rate variability [3-6]. The inter-relationship between them and clustering diseases like diabetes, hypertension, and dyslipidemia is complex and mechanism of their effect on autonomic nervous system is not precisely known [14-17]. Moreover, it is also not certain whether autonomic dysfunction is primarily related to adiposity (the quality, quantity and location of body fat) or insulin resistant state *per se* [14, 15, 17]. Answering this question is important because it will direct further investigation into pathogenesis of autonomic dysfunction in these disorders. Some of the studies find that the autonomic dysfunction is related to obesity [4-8], while others reported it to be related to insulin resistance [9-13]. The clinical situations where insulin resistance and obesity are discordant like post bariatric surgery, the changes in autonomic parameters were found to be correlated with change in weight rather than insulin resistance in some, [8, 17, 18] but not in all the studies [9].

Asian Indians have typical lean fat phenotype, i.e. when compared with other racial groups, they show relatively lower BMI but higher percentage body fat and insulin resistance. Even diabetics belonging to this race

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when compared to non-diabetics, they show comparable BMI but higher insulin resistance [19-21]. However it remains unknown whether they have excess percentage body fat or not.

Several previous studies have reported autonomic dysfunction in Asian Indian diabetic patients [22-25]. However, it remains unexplored whether the autonomic dysfunction in them is related to adiposity or insulin resistance. Therefore the aim of present study was to find whether autonomic dysfunction in them is related to insulin resistance or body fat content and distribution.

SUBJECTS AND METHODS

Subjects

Thirty-three patients with T2DM (age 46.96 ± 8.90 years, M: F ratio 24:9) and 33 healthy control subjects (age 44.08 ± 9.15 years M: F ratio 19:14) were studied. Both the groups were matched for age and sex. The exclusion criteria were: 1) diabetic microvascular complications like retinopathy, nephropathy, neuropathy, 2) macrovascular disease including coronary artery disease, peripheral vascular disease, and stroke.

Institutional ethics committee approved the experimental protocol and patients gave their informed written consent before they participated.

Methods

The anthropometric measurements including body weight, height, waist to hip (W: H) ratio and BMI were obtained by standard methods [26]. Supine blood pressure was measured using mercury sphygmomanometer after 10 minutes of rest.

Laboratory Measures

Blood samples were obtained at 8:00 am after an overnight fast of at least 8 hours. Following biochemical parameters were measured on Kopran AU/400 fully automated analyzer: serum glucose, creatinine, lipid profile, (Total cholesterol, Phospholipids Triglycerides, LDL, HDL, and VLDL), SGOT, SGPT. Serum insulin was measured by chemiluminescent immunometric assay using Immulite 2000 machine [27]. HbA1c was measured by turbidimetry method using BioSystems kits. We revalidated glycated hemoglobin in another subset of subjects with normal glucose tolerance and it was found 6.48% ± 1.56% therefore our data should be interpreted in light of this finding.

Insulin Resistance was calculated by Homeostasis Model Assessment (HOMA-R) and HOMA-B was used to measure beta cell function [28]. Body fat content and distribution was estimated by Dual Energy X-ray Absorptiometry (DEXA) using Hologic Explorer model (S/N91395).

Autonomic functions were evaluated by analysis of heart rate variability (HRV). Short-term HRV was measured by impedance plethysmographic recording of pulse wave in distal superficial arteries by Non-invasive Vascular Monitor, NIVOMON (Larsen and Toubro) Medical Analyzer. Time domain and Frequency domain analysis of HRV were carried out. Subjects were instructed to avoid meal preceding two hours of HRV recordings [29].

Time domain parameters included standard deviation of Inter-beat intervals (SDNN), percentage of normal consecutive RR intervals differing by >50ms (pNN50) and root mean of squared successive differences (RMSSD). SDNN is estimate of overall heart rate variability. RMSSD and pNN50 reflect alterations in autonomic tone that are predominantly mediated by the vagus nerve. Frequency domain analysis involves power spectral density (PSD) technique that converts variance in R-R interval length into frequency waveform. The PSD analysis was estimated by Fast Fourier Transforms which provides the basic information about how variance distributes as a function of frequency. The power of low frequency (LF) (.04 t.15 Hz) and high frequency (HF) (.15 to .40 Hz) bands were calculated. LF and HF components are expressed in absolute values of power (ms^2) and in normalized units (nu). The HF component in normalised unit (HFnu) reflects parasympathetic modulation while LF component in normalised unit (LFnu) is mediated by sympathetic modulation. The LF to HF ratio reflects the balance between the sympathetic and parasympathetic activity [29].

Statistical Analysis

All parameters are presented as mean ± SD. Differences between groups were analyzed using independent two-sample t-test. Statistical significance was set at $p < .05$. Pearson correlation coefficient was used to determine the relationship between parameters.

Correlation coefficients were calculated between parameters of HRV [Total Power, HF (ms^2), LF (nu) HF (nu)] and HOMA-R, HOMA-B, BMI, W:H ratio and

truncal fat for 33 diabetic patients and 33 control subjects.

RESULTS

Table **1** shows the General Characteristics of the participants. The diabetics and controls had comparable BMI, waist circumference and W: H ratio. But diabetics had significantly higher plasma glucose, HbA1c, HOMA-R, triglyceride and VLDL levels and significantly lower insulin, HOMA-β and HDL level. These finding suggest that dysmetabolism among diabetics is not related to obesity.

Table **2** shows the comparison of body composition of diabetics and controls. Diabetics had less fat in right lower limb. Apart from that there was no statistically significant difference in total as well regional body composition in both groups.

Table **3** shows the comparison of Heart Rate Variability parameters in T2DM and Controls. Time domain parameters RMSSD, pNN50 which suggests parasympathetic activity (vagal tone) were significantly lower in diabetics. Diabetic also had lower total power which indicates overall autonomic activity. LF and HF powers when expressed in absolute values (ms^2) were significantly low among diabetics. When values were expressed in normalised units diabetics had high LFnu, LF/HF ratio and lower HFnu, but the differences were not statistically significant. As far as sympathovagal imbalance is concern, a trend towards sympathetic dominance over parasympathetic activity was observed among diabetics.

Table **4** shows the Pearson correlation among heart rate variability parameters and body fat content, its distribution, insulin resistance and beta cell function in Diabetic (n=33) and controls (n=33). Among diabetics there was positive correlation between BMI and LF (nu) (r= +0.43, p=. 01). Also there was negative correlation between BMI and HF (nu) (r= -0.43, p=. 01) among them.

DISCUSSION

The findings of the present study can be summarized as follows (1) the overall autonomic activity (measured as total power) as well as parasympathetic activity were significantly reduced among diabetics, but (2) there was only marginal but statistically insignificant increase in sympathetic activity

Table 1: General Characteristics of Type 2 Diabetics and Controls

Parameters	Diabetic (n=33)	Control (n=33)	P value
Age (years)	46.96 ± 8.9	44.15 ± 9.2	0.213
BMI (kg/m2)	25.22 ± 3.7	25.79 ± 4.56	0.575
Waist circumference	36.71 ± 4.14	36.12 ± 5.10	0.607
Waist: Hip Ratio	0.97 ± 0. 07	0.94 ± 0.08	0.221
Fasting Blood Glucose (mg/dl)	193.21±58.40	90.87±9.97	0.0001*
Hb A1c (%)	10.13±1.93	6.15±0.92	0.0001*
Fasting Serum Insulin (uIU/dl)	4.83±2.7	6.18±3.7	0.095
HOMA-IR	2.31±1.59	1.38±0.82	0.004*
HOMA-B	16.77±13.96	96.27±86.1	0.0001*
Total Lipids (mg/dl)	646.48±128.95	564.29±126.6	0.011*
Phospholipids (mg/dl)	213.71±36.70	182.31±28.99	0.0001*
Triglycerides (mg/dl)	168.34±74.95	122.91±79.76	0.02*
Total Cholesterol (mg/dl)	194.70±38.87	180.224±41.76	0.15
HDL (mg/dl)	44.71±6.21	49.84±6.9	0.002*
LDL (mg/dl)	115.23±35.44	104.43±30.76	0.191
VLDL (mg/dl)	33.96±14.96	24.56±15.94	0.016*

*Significant

Note: we revalidated glycated haemoglobin in another subset of subjects with normal glucose tolerance and it was found 6.48±1.56 therefore our data should be interpreted in light of this finding.

HbA1c = Glycated Hemoglobin; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein; VLDL = Very Low Density Lipoprotein; HOMA-IR = Homeostasis Model Assessment Insulin Resistance; HOMA-B = Homeostasis Model Assessment Beta cell function.

Table 2: Comparison of Body Fat Content and its Distribution in T2DM and Controls

Parameters	Diabetics	Control	P value
LEFT ARM			
Bone mineral content (BMC gm)	149.4±49.4	132.56±33.18	0.11
Fat (gm)	1168.57±665.28	1206±568.24	0.805
Lean (gm)	2342.05±557.98	2237.845±705.62	0.508
Lean +BMC	2491.45±585.25	2370.41±734.47	0.462
Total Mass	3660.14±852.42	3574.81±1001.09	0.711
% Fat	31.03±12.42	33.66±11.43	0.373
RIGHT ARM			
Bone mineral content (BMC gm)	200.287±290.64	142.68±36.86	0.263
Fat (gm)	1230.8±748.5	1210.61±574.28	0.86
Lean (gm)	2489.56±559.74	2369.54±662.31	0.43
Lean +BMC	2689.84±674.11	2503.97±691.17	0.273
Total Mass	3880.43±964.0	3768.04±919.72	0.63
% Fat	30.73±11.96	33.091±11.05	0.408
TRUNK			
Bone mineral content (BMC gm)	445.48±100.69	405.21±83.13	0.081
Fat (gm)	9802.08±3171.26	9871.83±4120.47	0.939
Lean (gm)	22261.39±3610.77	22185.85±4464.45	0.938
Lean +BMC	22036.27±5342.51	22591.14±4517.55	0.65
Total Mass	32496.62±5385.54	44684.73±7367.67	0.345
% Fat	29.66±7.38	29.91±8.02	0.899
LEFT LEG			
Bone mineral content (BMC gm)	351.21±65.25	328.64±67.75	0.173
Fat (gm)	3223.84±1576.61	3643.65±1457.36	0.266
Lean (gm)	7194.71±1945.86	6789.95±1993.24	0.406
Lean +BMC	7545.9561±1975.06	7079.41±2072.41	0.353
Total Mass	10770.03±2998.76	10888.51±2438.53	0.861
% Fat	29.33±9.5	33.26±10.06	0.108
RIGHT LEG			
Bone mineral content (BMC gm)	359.4±70.57	335.62±69.09	0.171
Fat (gm)	3064.75±1146.79	3736.62±1478.59	0.043
Lean (gm)	8565.3±8942.04	7037.85±1686.97	0.339
Lean +BMC	8924.7±8938.99	7373.46±1686.97	0.332
Total Mass	14263.08±17362.8	11110.215±2494.89	0.306
% Fat	29.25±9.72	33.26±9.72	0.099
Head			
Bone mineral content (BMC gm)	639.62±264.81	508.58±102.83	0.308
Fat (gm)	1790.5±3424.42	1025.80±241.93	0.205
Lean (gm)	4682.56±7424.3	3467.22±783.16	0.303
Lean +BMC	5322.2±7672.61	4055.82±836.14	0.349
Total Mass	6842.66±10829.14	6354.43±7316.48	0.83
% Fat	20.19±1.5	20.08±0.73	0.707

(Table 2). Continued.

Parameters	Diabetics	Control	P value
Total			
Bone mineral content (BMC gm)	2055.22±511.81	1933.39±332.51	0.256
Fat (gm)	19322.97±6597.63	20740.46±7846.09	0.43
Lean (gm)	44510±12590.84	44121.73±9266.83	0.887
Lean +BMC	46565.35±12900.12	46055.16±9519.05	0.856
Total Mass	69048.27±22256.89	83051.68±93211.82	0.404
% Fat	29±7.86	29.89±7.66	0.644

Table 3: Comparison of Short term Heart Rate Variability in T2DM and Controls

Parameters	Diabetic (n =33) A_1	Control (n=33) C_1	P Value
SDNN (ms)	33.21±71.87	37.38±17.53	0.747
RMSSD (ms)	19.93±12.66	35.36±26.07	.003*
pNN50 (ms)	1.82±3.10	10.82±13.22	.0001*
Total Power (ms2)	182.86±153.03	665.22±765.85	.001*
LF (ms^2)	34.24±32.52	109.92±95.34	.0001*
HF (ms^2)	46.72±56.02	228.24±334.77	.003*
LF (nu)	47.47±20.15	42.39±19.37	0.305
HF (nu)	52.52±20.15	57.6±19.37	0.305
LF/HF Ratio	1.37±1.37	1.07±1.17	0.341

*Significant
SDNN: Standard deviation of normal-to-normal R-R interval; RMSSD: Root of the mean squared differences of successive NN interval; pNN50: Percentage of number of N-N intervals with differences >50 ms; Total Power (ms_2): Variance of N-N intervals (0.04 - 0.4 Hz); LF (ms_2): Power in low frequency range (0-.04-0-.15 Hz); HF (ms_2): Power in high frequency range (0-.15-0-.4 Hz); LF (nu): LF Power in normalized unit; HF (nu): HF Power in normalized unit; LF/HF ratio: Ratio of LF Power to HF Power.

Table 4: Relationship between Heart Rate Variability and Body Fat Content, Distribution Insulin Resistance and Beta Cell Function in Diabetic (n=33) and Controls (n=33)

	Total Power		HF (ms^2)		LF (ms2)		HF (nu)		LF (nu)	
	Diabetics	Control	Diabetics	Control	Diabetics	Control	Diabetics	Control	Diabetics	Control
Parameters	r value (p value)	r value (p value)	r value (p value)	r value (p value)	r value (p value)	r value (p value)	r value (p value)	r value (p value)	r value (p value)	r value (p value)
BMI	-0.439 (0.011)	0.024 (0.894)	-0.471 (0.006)	0.112 (0.536)	-0.123 (0.494)	-0.540 (0.765)	-0.437 (0.011)	0.062 (0.73)	0.437 (0.011)	-0.062 (0.73)
W: H ratio	-0.311 (0.078)	-0.052 (0.774)	-0.329 (0.061)	-0.034 (0.582)	-0.179 (0.318)	-0.160 (0.373)	-0.006 (0.974)	-0.001 (0.995)	0.006 (0.974)	0.001 (0.995)
HOMA R	0.038 (0.833)	-0.142 (0.421)	-0.099 (0.585)	-0.120 (0.506)	-0.114 (0.529)	-0.117 (0.516)	0.133 (0.462)	0.116 (0.522)	-0.133 (0.462)	-0.116 (0.522)
HOMA B	-0.159 (0.376)	0.238 (0.183)	-0.180 (0.317)	0.194 (0.279)	-0.218 (0.221)	0.152 (0.397)	0.000 (0.998)	0.244 (0.171)	0.000 (0.998)	-0.244 (0.171)
Truncal fat (gm)	-0.416 (0.016)	0.166 (0.357)	-0.401 (0.021)	0.252 (0.157)	-0.176 (0.326)	0.208 (0.642)	-0.167 (0.354)	0.066 (0.715)	0.167 (0.354)	-0.066 (0.715)
Total fat (gm)	-0.353 (0.044)	0.212 (0.237)	-0.366 (0.036)	0.302 (0.087)	-0.154 (0.392)	0.136 (0.450)	0.148 (0.412)	-0.108 (0.550)	-0.148 (0.412)	0.108 (0.550)

(LF nu) therefore suggesting sympatho-vagal imbalance among the diabetics. (3) Though diabetics had higher insulin resistance, but comparable adiposity measured as BMI, W: H ratio and body fat measured by DEXA. (4) Some of the parameters of autonomic function showed significant association with adiposity parameters like truncal fat measured by DEXA and BMI, but none of them had any association with insulin resistance. (5) There was significant positive association between BMI and sympathetic activity and inverse relation between BMI and parasympathetic activity in diabetics, but not in the controls.

Findings of the present study are consistent with those of the previous studies done on Asian Indian diabetic [30-32]. Most of these studies also find decrease in overall autonomic activity and parasympathetic activity in diabetics. Our findings are also consistent with those of done on diabetics belonging to other races where T2DM was associated with decreased overall activity and sympatho-vagal imbalance [13, 23, 24]. This autonomic dysfunction could contribute to heightened risk of sudden death in diabetics [22]. Therefore there is need to address this issue in all diabetics, but currently HRV estimation is not part of routine clinical assessment in diabetics.

The ADA (American Diabetes Association) has recommended (since 2006) in its standards of Medical Care that Heart Rate Variability testing (which detects autonomic neuropathy) be performed on Type 2 Diabetic patients immediately upon detection of diabetes.

It was observed in this study that diabetics when compared with controls, they not only had comparable BMI but also had comparable total body fat content as well as regional body fat distribution excepting they had significantly low fat mass in right lower limb. Though diabetics had much higher insulin resistance than controls, therefore dysmetabolism among them is not related to excess body fat content. However it is worth mentioning here that we did not measure visceral fat content specifically (CT Scan, and other Imaging techniques). Though diabetics had marginally higher W:H ratio (Diabetics -0.97 ± 0. 07, controls -0.94 ± 0.08), which is surrogate marker of visceral fat. Therefore, dysmetabolism in them might be related to qualitative factor rather than quantity and distribution of fat. In a recent study of genome wide gene expression profiling of visceral adipose tissue of obese diabetic women, it was observed that diabetes is associated with qualitative adipose tissue change, decreased unsaturated fatty acid pathway and NK cell mediated heightened inflammation [34-35].

Though diabetics had comparable body fat content but higher insulin resistance, therefore it suggests autonomic dysfunction among them is related to insulin resistance. However we observed an association between body fat content and autonomic parameters rather than insulin resistance among the diabetics. One explanation of this paradoxic finding is that autonomic dysfunction among diabetics might be related to some qualitative change in adipose tissue.

However there are certain limitations of our study. First our sample size is relatively small and second we did not measure cytokines, adipose tissue hormones and free fatty acids. Therefore there is need of further studies using larger sample size using qualitative adipose tissue pathology change, adipocytokine levels and autonomic parameters.

CONCLUSION

T2DM is associated with overall reduction in autonomic activity as well parasympathetic activity as measured by HRV parameters. The diabetics had high insulin resistance but comparable body fat content thereby suggesting role of qualitative adipose tissue factor in higher insulin resistance among them. The autonomic dysfunction among them is related to body fat content rather than insulin resistance. Therefore, we suggest further investigations on role of qualitative adipose tissue changes in autonomic dysfunction among them.

REFERENCES

[1] Nagai N, Matsumoto T, Kita H, Moritani T. Autonomic nervous system activity and the state and development of obesity in Japanese school children. Obes Res 2003; 11: 25-32. http://dx.doi.org/10.1038/oby.2003.6

[2] Schwartz MW, Baskin DG, Kaiyala KJ, Woods SC. Model for the regulation of energy balance and adiposity by the central nervous system. Am J Clin Nutr 1999; 69: 58.

[3] Tentoloris N, Argyrakopoulou G, Katsilambros N. Perturbed Autonomic nervous system function in metabolic syndrome. Neuromol Med 2008; 10:169-178. http://dx.doi.org/10.1007/s12017-008-8022-5

[4] Chethan HA, Murthy N, Basavaraju K. Comparative study of heart rate variability in normal and obese young adult males. Int J Biol Med Res. 2012; 3(2): 1621-1623.

[5] Windham BG, Fumagalli S, Ble A, Sollers JJ, Thayer JF,Najjar SS *et al*. The Relationship between Heart Rate Variability and Adiposity Differs for Central and Overall Adiposity. Journal of Obesity 2012; 2012.

[6] Kim JA, Park YG, Cho KH, Hong MH, Han HC, Choi YS, *et al*. Heart Rate Variability and Obesity Indices: Emphasis on the Response to Noise and Standing. J Am Board Fam Pract 2005; 18: 97-103. http://dx.doi.org/10.3122/jabfm.18.2.97

[7] Rjalakshmi R, VijayaVageesh Y, Nataraj SM, MuraliDhar, Srinath CG Heart Rate Variability in Indian Obese Young Adults. Pak J Physiol 2012; 8(1); 39-44.

[8] Karason K, Mølgaard H, Wikstrand J, Sjöström L. Heart rate variability in obesity and the effect of weight loss. Am J Cardiol 1999; 83(8): 1242-47. http://dx.doi.org/10.1016/S0002-9149(99)00066-1

[9] Gadegbeku CA, Dhandayuthapani A, Sadler ZE, Egan BM. Raising lipids acutely reduces baroreflex sensitivity. Am J Hypertens 2002; 15: 479-85. http://dx.doi.org/10.1016/S0895-7061(02)02275-6

[10] Beske SD, Alvarez GE, Ballard TP, Davy KP. Reduced cardiovagal baroreflex gain in visceral obesity: implications for the metabolic syndrome. Am J Physiol 2002; 282: 630-5.

[11] Pikkujamsa SM, Huikuri HV, Airaksinen KE, Ran-tala AO, Kauma H, Lilja M, *et al*. Heart rate variability and baroreflex sensitivity in hypertensive subjects with and without metabolic features of insulin resistance syndrome. Am J Hypertens 1998; 11: 523-31. http://dx.doi.org/10.1016/S0895-7061(98)00035-1

[12] Bjorntorp P, Holm G, Rosmond R. Hypothalamic arousal, insulin resistance and type 2 diabetes mellitus. Diabetic Med 1999; 16: 373-83. 25.

[13] Egan BM. Insulin resistance and the sympathetic nervous system. Curr Hypertens Rep 2003; 5: 247-54. http://dx.doi.org/10.1007/s11906-003-0028-7

[14] Perciaccante A, Fiorentini A, Paris A, Serra P, Tubani L. Circadian rhythm of the autonomic nervous system in insulin resistant subjects with normoglycemia, impaired fasting glycemia, impaired glucose tolerance, type 2 diabetes mellitus. BMC Cardiovascular Disorders 2006; 6: 19. http://dx.doi.org/10.1186/1471-2261-6-19

[15] Lindmark S, Loan L, Wicklund U, Tufvesson M, Olsson T, Eriksson JW. Dysregulation of the Autonomic Nervous System Can Be a Link between Visceral Adiposity and Insulin Resistance. Obes Res 2005; 13: 717-28. http://dx.doi.org/10.1038/oby.2005.81

[16] Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidites? Obesity Rev 2001; 2: 73-86. http://dx.doi.org/10.1046/j.1467-789x.2001.00027.x

[17] McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet 1991; 337: 382-86. http://dx.doi.org/10.1016/0140-6736(91)91164-P

[18] Mohan V, Sharp PS, Cloke HR, Burrin JM, Schumer B, Kohner EM. Serum immunoreactive insulin responses to a glucose load in Asian Indian and European type-2 (non-insulin dependent) diabetic patients and control subjects. Diabetologia 1986; 29: 235-37. http://dx.doi.org/10.1007/BF00454882

[19] Sharp PS, Mohan V, Levy JC, Mather HM, Kohner EM. Insulin resistance in patient's of Asian Indian and European origin with noninsulin dependent diabetes. Horm Metab Res 1987; 19: 84-85. http://dx.doi.org/10.1055/s-2007-1011745

[20] Mathur SK, Chandra P, Mishra S, Ajmera P, Sharma P. Type-2 Diabetes related Intermediate Phenotypic Traits in North Indian Diabetics. Ind J Clin Biochem 2007; 22: 70-73. http://dx.doi.org/10.1007/BF02913317

[21] Barma PD, Ranabir S, Prasad L, Singh TP. Clinical and biochemical profile of lean type 2 diabetes mellitus. Indian J Endocrinol Metab 2011; 15: 40-43. http://dx.doi.org/10.4103/2230-8210.83061

[22] Gerritsen J, Dekker JM, TenVoorde BJ, Kostense PJ, Heine RJ, Bouter LM, *et al*. Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension or a history of cardiovascular disease. Diabetes Care 2001; 24: 1794-98. http://dx.doi.org/10.2337/diacare.24.10.1793

[23] Javorka M, Javorkova J, Tonhajzerova I, Calkovska A, Javorka K. Heart rate variability in young patients with diabetes mellitus and healthy subjects explored by Poincare and sequence plots. Clin Physiol Funct Imaging 2005; 25: 119-27. http://dx.doi.org/10.1111/j.1475-097X.2004.00601.x

[24] Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, *et al*. Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care 2005; 28(3): 668-74. http://dx.doi.org/10.2337/diacare.28.3.668

[25] Singh JP, Larson MG, O'Donnell CJ, Wilson PF, Tsuji H, Lloyd-Jones DM, *et al*. Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). Am J Cardiol 2000; 86(3): 309-12. http://dx.doi.org/10.1016/S0002-9149(00)00920-6

[26] Banks WA, Thomas DR, Willoughby LM, Morley JE. Insulin resistance syndrome in elderly. Diabetes Care 2007; 30: 2369-73. http://dx.doi.org/10.2337/dc07-0649

[27] Mathews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RL. Homeostasis model assessment: insulin resistance and b cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-19. http://dx.doi.org/10.1007/BF00280883

[28] Meigs JB, Rutter MK, Sullivan LM, Fox CS, D'Agostino Sr RB, Wilson PW. Impact of insulin resistance on risk of type 2 diabetes and cardiovascular disease in people with metabolic syndrome. Diabetes Care 2007; 30: 1219-25. http://dx.doi.org/10.2337/dc06-2484

[29] Task Force of European society of cardiovascular and North American society of pacing and Electrophysiology. Heart rate variability; Standard of measurement, physiological interpretation and clinical use. Circulation 1996; 93: 1043-65. http://dx.doi.org/10.1161/01.CIR.93.5.1043

[30] Syed Ahamed PT, Ahamed VIT, Jacob J, Joseph KP. Time and Frequency Domain Analysis of Heart Rate Variability and their Correlations in Diabetes Mellitus. Int J Biol Life Scis 2008; 4(1): 24-27.

[31] Arumugam JMR, Mary A. Heart Rate Variability a Cardiac Indicator in Diabetic Autonomic Neuropathy: A Systematic Review Int J Med Res 2013; 1(2): 13-16.

[32] Arati R, Prashanthmohan BH, Ganaraja B, Bhat MR. Cardiac autonomic functions are compromised in diabetes mellitus- A study of south Indian elderly patients. Int J Appl Biol Pharmaceut Technol 2011; 2(3): 502-11.

[33] Boer-Martins L, Figueiredo NV, Demacq C, Martins LC, Consolin-Colombo F, Figueiredo MJ, Cannavan FPS, Moreno H. Relationship of autonomic imbalance and circadian disruption with obesity and type 2 diabetes in

resistant hypertensive patients. Cardiovasc Diabetol 2011; 10: 24.
http://dx.doi.org/10.1186/1475-2840-10-24

[34] Mathur SK, Jain P, Mathur P, Punjabi P, Agarwal A, Sharma A. Transcriptomic Analysis Of visceral Adipose Tissue From healthy and Diabetic Obese Subjects. Ind J Endocrinol Metab 2013; 17: 447-50.
http://dx.doi.org/10.4103/2230-8210.111639

[35] Tai C, Ding ST. Polyunsaturated fatty acids regulate lipid metabolism through several inflammation mediators: mechanisms and implications for obesity prevention. J Nutr Biochem 2010; 21: 357-63.
http://dx.doi.org/10.1016/j.jnutbio.2009.09.010

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