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Contribution of insulin resistance to decreased baroreceptor sensitivity & cardiometabolic risks in pre-obesity & obesity

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***Background & objectives*: Although insulin resistance (IR) is a known complication in obesity, the physiological mechanisms linking IR with cardiometabolic risks in obesity have not been well studied. This study was conducted to assess the difference in cardiovascular (CV) risk profile in IR and non-IR (NIR) conditions, and contribution of IR to cardiometabolic risks in pre-obese and obese individuals.**

***Methods*: Basal CV, blood pressure variability, autonomic function test and cardiometabolic parameters were recorded in pre-obese (n=86) and obese (n=77) individuals during 2012 and 2015. The association of altered cardiometabolic parameters with homeostatic model for IR (HOMA-IR) in pre-obese and obese groups and with baroreceptor sensitivity (BRS) in IR and NIR groups was calculated by appropriate statistical analysis.**

***Results*: Decreased BRS, a known CV risk and cardiometabolic parameters were significant in IR (pre-obese and obese) group compared to the NIR group. Sympathovagal imbalance in the form of increased sympathetic and decreased parasympathetic activities was observed in individuals with IR. There was no significant difference in the level of independent contribution of HOMA-IR to cardiometabolic parameters in pre-obese and obese groups. Adiponectin and inflammatory markers had an independent contribution to BRS in IR group.**

***Interpretation & conclusions*: Findings of the present study demonstrated that the intensity of cardiometabolic derangements and CV risk were comparable between IR, pre-obese and obese individuals. Pro-inflammatory state, dyslipidaemia and hypoadiponectinaemia might contribute to CV risk in these individuals with IR. IR could possibly be the link between altered metabolic profile and increased CV risks in these individuals independent of the adiposity status.**

Key words Baroreceptor sensitivity - cardiometabolic risks - insulin resistance - non-insulin resistance - obesity - pre-obesity

Obesity has become a global epidemic and is among the important risk factors contributing to the overall disease burden[1]. Obesity is associated with metabolic complications and cardiovascular (CV) morbidities and mortality[2-4]. Insulin resistance (IR) has been reported to be a critical mediator in the association between obesity and its co-morbidities including pro-inflammatory state, dyslipidaemia, diabetes, hypertension and CV diseases[5].

Presence of IR, which is strongly associated with cardiometabolic problems, has been used to categorize individuals at high risk for future CV morbidities[4,5]. South-Asians have been reported to be more insulin resistant compared to their Caucasian counterparts[6]. However, the impact of IR on cardiometabolic risk factors in normoglycaemic, normotensive obese adult Indian population has not been established.

Increased sympathetic activity is one of the established pathophysiological mechanisms for CV diseases associated with obesity[7]. Sympathovagal imbalance (SVI) in the form of increased sympathetic activity and reactivity and decreased parasympathetic activity and reactivity has been reported in obesity[8]. Decreased heart rate variability (HRV) representing the autonomic dysfunction has been associated with increased CV morbidity[9]. Further, studies have reported significant improvement in the indices of HRV with decreased IR in obese individuals independent of the degree of obesity[10,11]. However, the difference in the nature and magnitude of SVI among age and body mass index (BMI) matched obese individuals, as distinguished by their IR status has not been clearly elucidated.

Decreased baroreceptor sensitivity (BRS) has been documented as a marker for risk stratification in patients with cardiac diseases[12] including myocardial infarction[13] and heart failure[14]. Although studies have reported decreased BRS in individuals with metabolic syndrome and IR[15], the status of BRS in IR and non-IR (NIR) pre-obese and obese individuals has not been assessed. Therefore, present study was aimed to assess the association of decreased BRS with cardiometabolic risk factors in IR and NIR young obese adults. Although IR is considered to be the link between obesity and its associated co-morbidities such as diabetes, hypertension and other CV risks, reports suggest that obese individuals can also be insulin sensitive[16,17]. Therefore, the present study was also aimed to assess the difference in CV risks between the IR and NIR, pre-obese and obese individuals, and the contribution of IR to CV risk profile in these individuals.

Material & Methods

This cross-sectional study was conducted in the department of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India. The study protocol was approved by the Research and Ethics Committees of JIPMER, and written informed consent was obtained from all the participants before initiation of the study.

The sample size was calculated using OpenEpi, version 3 (*www.OpenEpi.com*), open source calculator. Based on the previous report[18], the sample size was calculated with 90 per cent power to detect the difference (2.44) between means and standard deviation (SD) of 2.23 in group 1 and 1.81 in group 2 of homeostatic model for IR (HOMA-IR) with a significance level of (alpha) 0.05. The minimum sample size was calculated to be 15 in each group. However, since BPV indices including BRS and HRV are highly variable parameters even in healthy population, the sample size was increased to above 35 in the present study.

Inclusion & exclusion criteria: A total of 163 apparently healthy young adults having BMI 23.00 kg/m^2 or above and aged between 18 and 40 yr were enrolled from among the attendants or relatives of patients who had accompanied patients attending the Medicine OPD, JIPMER and were willing voluntarily to be the participants in the study from 2012 to 2015. Those on antihypertensive therapy or receiving any medication, with a history of smoking and/or alcoholism, with acute or chronic ailments and known cases of diabetes mellitus, hypertension, cardiac diseases, kidney disease or any endocrinal disorder were excluded. As the level of physical fitness is a major determinant of vagal tone, those performing regular athletic activities, body-building exercises and yoga[19,20] were also excluded.

Grouping of participants: Height and body weight were measured, and BMI was calculated. Fasting blood glucose (FBG) and serum insulin were measured to calculate IR[21]. The 163 participants, based on the BMI classification of the WHO for Asian population[22] and HOMA-IR values, were divided into following four groups:

(*i*) Pre-obese NIR group: Participants having BMI 23.00 - 27.49 kg/m^2 and HOMA-IR <2.5 (n=49);

(*ii*) Pre-obese IR group: Participants having BMI 23.00 - 27.49 kg/m^2 and HOMA-IR ≥2.5 (n=37);

(*iii*) Obese NIR group: Participants having BMI 27.50 kg/m^2 or above and HOMA-IR <2.5 (n=41);

(*iv*) Obese IR group: Participants having BMI 27.50 kg/m^2 or above and HOMA-IR ≥2.5 (n=36).

Brief procedure: All the participants reported to the autonomic function testing laboratory between 0800-0900 h for the following recordings:

Baseline cardiovascular parameters and baroreceptor sensitivity: After 10 min of supine rest, BRS and other CV

parameters such as basal heart rate (BHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure, interbeat interval, stroke volume, cardiac output and total peripheral resistance were measured by continuous blood pressure variability method using Finapres (Finometer version 1.22a; Finapres Medical Systems BV, Amsterdam, the Netherlands) based on the principle of Penaz and Wesseling[23]. Rate-Pressure Product (RPP), a determinant of myocardial oxygen consumption and workload were calculated using the formula, $RPP = 10^{-2} \times (BHR \times SBP)$[24].

Recording of heart rate variability (HRV) and conventional autonomic function test (CAFT): For the recording of short-term HRV, the recommendation of the Task Force on HRV was followed[25], using BIOPAC MP 100 data acquisition system (BIOPAC Inc., USA) following the method as described earlier[26]. Different frequency domain indices (FDI) such as total power (TP), low frequency (LF) component expressed as normalized unit (LFnu), high frequency (HF) component expressed as normalized unit (HFnu) and LF/HF ratio; and time domain indices (TDI) such as mean RR, square root of the mean squared differences of successive normal to normal intervals (RMSSD), standard deviation of normal to normal interval (SDNN) and the number of interval differences of successive NN intervals >50 ms (NN50) were recorded.

Following three conventional autonomic function tests (CAFT) were performed using the standard procedures as described earlier[27]: (*i*) Lying to standing test (30:15 ratio); (*ii*) Deep breathing test (E:I ratio); and (*iii*) Isometric handgrip test (ΔDBP_{IHG}).

Measurement of biochemical parameters: Fasting blood sample (10 ml) was collected from all participants. FBG was estimated by colorimetric, enzymatic method with glucose oxidase and peroxidase (Genuine Biosystem; Chennai) and insulin was measured using enzyme-linked immunosorbent assay (ELISA) method (DiaMetra, Italy). HOMA-IR was calculated using the formula (HOMA-IR = FBG (mMol) × Insulin (μIU/l)/22.5) and for insulin sensitivity, HOMA 2 per cent S was calculated[28].

Lipid profile such as total cholesterol (TC), triglycerides, high-density lipoproteins (HDL), serum total proteins, serum albumin and globulin was assessed using fully automated analyzer (AU400, Olympus, USA). Low-density lipoproteins (LDL) and very LDL were calculated using Friedwalds equation[8]. Atherogenic index (AI) was calculated using the formula: AI=(TC-HDL)/HDL[8].

High-sensitive C-reactive protein (hsCRP) and leptin were quantified using the commercial kits available from DBC Diagnostics Biochem Canada Inc., Canada, and the serum neopterin concentration was quantified using the ELISA kit from DRG, USA. Other inflammatory markers such as interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-α), interferon gamma and adiponectin were estimated using ELISA kits from Orgenium, Tiilitie, Finland. The inter- and intra-assay coefficients of variation for measuring biochemical parameters such as serum insulin, adiponectin, leptin and inflammatory markers were found to be <10 per cent.

Total antioxidant (TAO) and oxidant thiobarbituric acid reactive substance (TBARS) levels were estimated using ELISA kits available from Cayman Chemical Co., Ann Arbor, Michigan.

Statistical analysis: SPSS version 13 (SPSS Software Inc., Chicago, IL, USA) was used for statistical analysis. All the data were presented as mean±SD. Normality of data was tested by Kolmogorov–Smirnov test. The level of significance between the groups was tested using one-way ANOVA, and Tukey Krammer *post hoc* test was used for inter-group comparison. The independent contribution of various factors to HOMA-IR (in pre-obese and obese groups) and BRS (in IR and NIR groups) was assessed by multiple linear regression analysis.

Results

There was no significant difference in age (mean age 28.50 yr) and FBG between the groups (Tables I and II). Further, the BMI was not significantly different between the IR and NIR groups in both the pre-obese and obese participants (Table I). Insulin levels and HOMA-IR was found to be significantly higher, in IR participants compared to NIR participants in both pre-obese and obese groups and IR obese group compared to IR pre-obese group (Table II). The basal CV parameters such as BHR and RPP were found to be significantly increased, and BRS was decreased in IR group compared to NIR group in both pre-obese and obese participants (Table I).

Among the FDI of HRV, TP and HFnu were significantly reduced, and LFnu and LF-HF ratio were significantly increased in IR group compared to NIR group in both pre-obese and obese participants (Table I). TP decreased and LF-HF ratio increased significantly in NIR obese group compared to NIR

Table I. Age, blood pressure variability, heart rate variability and conventional autonomic function test parameters of the participants in pre-obese and obese [non-insulin resistance (NIR) and insulin resistance (IR)] groups

Parameters	Pre-obese group		Obese group	
	NIR (n=49)	IR (n=37)	NIR (n=41)	IR (n=36)
Age (yr)	29.77±7.21	28.24±9.11	29.21±7.97	28.64±7.83
BMI (kg/m^2)	25.32±2.89	25.49±1.46	30.23±3.87	30.01±2.86
BPV parameters				
BHR (per min)	70.36±10.94	81.56±12.83***	75.85±5.82	83.72±12.29**
SBP (mmHg)	111.28±8.14	114.29±9.01	117.49±9.24$^{\#\#}$	119.97±9.10$^{\#}$
DBP (mmHg)	71.89±6.82	73.41±8.01	73.29±9.34	79.89±7.61$^{**,\#\#}$
RPP (mmHg/min)	78.29±15.20	93.21±17.78***	89.11±18.21$^{\#}$	100.43±16.73*
SV (ml)	72.46±11.50	79.06±20.76	79.53±15.69	86.91±15.65
CO (l/min)	5.86±1.59	6.92±1.85*	6.52±1.39	7.82±1.46**
TPRS (mmHg min/l)	0.96±0.31	1.07±0.33	1.11±0.42	1.14±0.75
BRS (ms/mmHg)	22.89±9.54	17.98±6.40**	18.24±6.88$^{\#}$	13.50±4.97**
FDI of HRV				
TP (ms^2)	953.89±416.06	695.78±331.25**	715.22±346.53$^{\#\#}$	499.94±210.27*
LFnu	46.20±16.47	56.88±15.92*	53.65±16.57	66.63±16.16**
HFnu	53.79±16.47	43.11±15.92*	46.35±16.57	33.36±16.16**
LF:HF	0.82±0.52	1.29±0.53***	1.30±0.48$^{\#\#}$	1.75±0.96*
TDI of HRV				
Mean RR (msec)	635.88±149.72	583.13±194.68	505.39±159.97$^{\#\#}$	486.42±195.69
RMSSD (msec)	48.22±28.60	45.64±16.64	41.98±26.93	39.55±14.79
SDNN (msec)	42.81±17.15	41.17±21.24	42.13±19.32	30.25±15.01*
NN50	71.84±47.89	69.11±36.14	61.29±46.50	60.18±42.74
CAFT parameters				
30:15 ratio	1.50±0.19	1.39±0.18*	1.44±0.19	1.33±0.17*
E: I ratio	1.43±0.22	1.28±0.15*	1.29±0.11$^{\#}$	1.14±0.37*
ΔDBP_{IHG}	18.91±4.98	23.18±7.44*	20.60±5.78	26.27±8.37**

P^{*}<0.05, **<0.01, ***<0.001 compared to respective NIR group; $P^{\#}$<0.05, $^{\#\#}$<0.01 compared to respective NIR or IR group of pre-obese. Values are expressed as mean±SD. BRS, baroreflex sensitivity; HRV, heart rate variability; CAFT, conventional autonomic function test; BMI, body mass index; BPV, blood pressure variability; BHR, basal heart rate; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPP, rate pressure product; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; FDI, frequency domain indices of HRV; TP, total power; LFnu, normalized low frequency component; HFnu, normalized high frequency component; LF: HF ratio, ratio of low frequency component to high frequency component of HRV; TDI, time domain indices of HRV; Mean RR, mean-RR intervals; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDNN, standard deviation of the averages of NN intervals in all five minutes segments of the entire recording; NN50, number of interval differences of successive NN intervals greater than 50 ms; 30:15 ratio, ratio of maximum RR interval at 30th beat to minimum RR interval at 15th beat following standing from supine; E:I ratio, ratio of maximum RR interval during expiration to minimum RR interval during inspiration following deep breathing; ΔDBP_{IHG}, maximum rise in diastolic BP above baseline following sustained handgrip

pre-obese participants (Table II). The 30:15 ratio and E:I ratio were significantly decreased and ΔDBP_{IHG} (P>0.01) was significantly increased in IR individuals compared to NIR in both the pre-obese and obese groups (Table I). All lipid parameters (except HDL, which was decreased) and lipid risk factors were significantly increased in IR group compared to the NIR group in both pre-obese and obese individuals, but there was no difference in these parameters between the IR obese group and IR pre-obese group (Table II).

Inflammatory markers such as hs-CRP, TNF-α, IL-6, IFN-γ and neopterin were significantly increased

Table II. Insulin related parameters, lipid profile and inflammatory markers of pre-obese and obese [non-insulin resistance (NIR) and insulin resistance (IR)] groups

Parameters	Pre-obese group		Obese group	
	NIR (n=49)	IR (n=37)	NIR (n=41)	IR (n=36)
Insulin related parameters				
FBG (mg/dl)	78.22±10.67	82.54±9.81	83.85±10.46	85.75±8.83
Insulin (µU/ml)	11.89±3.58	16.34±6.93**	11.47±6.94	21.98±2.47$^{***,\#\#\#}$
HOMA-IR	2.29±0.54	3.32±0.98***	2.37±0.37	4.64±0.79$^{***,\#\#\#}$
HOMA 2%S	67.80±7.12	49.00±8.37***	68.90±7.70	36.40±5.65$^{***,\#\#\#}$
Lipid profile				
TC (mg/dl)	170.73±18.78	187.30±30.96*	182.36±24.55	199.58±31.25*
TG (mg/dl)	96.65±26.80	131.54±32.62***	111.78±24.08	144.11±39.20***
HDL (mg/dl)	37.89±8.64	30.78±7.19***	32.34±6.91$^{\#\#}$	26.94±5.24**
LDL (mg/dl)	118.51±16.64	130.21±20.44*	129.66±18.47$^{\#}$	141.82±21.66*
VLDL (mg/dl)	19.33±5.36	26.31±6.52***	22.36±4.82	28.80±7.84***
TC/HDL	4.75±1.45	6.08±2.38*	5.70±2.12	7.33±2.83**
TG/HDL	2.69±1.02	4.27±1.71***	3.46±1.96	5.35±2.50***
LDL/HDL	3.30±1.23	4.23±1.80*	4.00±1.91$^{\#}$	5.26±1.55**
Atherogenic index	3.75±1.45	5.08±2.38*	4.70±1.92	6.33±2.53**
Inflammatory marker				
hsCRP (ng/ml)	1221.42±554.65	1704.38±413.35**	1387.39±681.71	1890.59±667.93**
TNF-α (pg/ml)	119.31±51.91	280.22±63.21***	256.63±68.59$^{\#\#\#}$	311.51±76.28**
IL-6 (pg/ml)	28.96±16.69	96.76±46.56***	93.14±15.26$^{\#\#\#}$	119.63±25.03$^{***,\#\#}$
IFN-γ (pg/ml)	11.30±7.41	31.06±19.94***	11.53±6.54	42.57±23.93$^{***,\#}$
Neopterin (pg/ml)	11.32±5.81	28.54±15.04***	13.08±4.75	29.57±15.80***
Adipokines				
Leptin (ng/ml)	12.04±6.09	51.89±21.86***	42.55±14.22$^{\#\#\#}$	61.29±20.03***
Adiponectin (ng/ml)	9.29±2.13	6.75±1.53***	7.67±1.65$^{\#\#\#}$	6.01±1.18***
Oxidative stress marker				
TBARS (µM/l)	3.03±0.98	3.54±1.15	4.47±1.36$^{\#\#\#}$	4.78±1.16$^{\#\#\#}$
TAO (mM/ml)	0.166±0.05	0.222±0.06***	0.177±0.05	0.308±0.10$^{***,\#\#\#}$

P^{*}<0.05, **<0.01, ***<0.001 compared to respective NIR group; $P^{\#}$<0.05; $^{\#\#}$<0.01; $^{\#\#\#}$<0.001 compared to respective NIR or IR group of pre-obese. Values are expressed as mean±SD. FBG, fasting blood glucose; HOMA IR, homeostatic model assessment of insulin resistance; HOMA 2%S, homeostatic model 2 assessment of insulin sensitivity; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein; hsCRP, high sensitive C- reactive protein TNF-α, tumour necrosis factor alpha; IL-6, interleukin 6; IFN-γ, interferon gamma; TBARS, thiobarbituric acid reactive substance; TAO, total antioxidant

in IR group compared to NIR group in both pre-obese and obese individuals. Furthermore, IL-6 and IFN-γ significantly increased in IR obese compared to IR pre-obese individuals, and the TNF-α and IL-6, were found to be significantly increased in NIR obese participants compared to the NIR pre-obese participants (Table II). Among the adipokines, leptin (P>0.001) was found to be significantly increased, and adiponectin significantly decreased in IR group compared to NIR group in both pre-obese and obese participants, and in NIR obese compared to NIR pre-obese (Table II). TBARS and TAO were significantly increased in obese group individuals compared to pre-obese group (in both IR and NIR groups) (Table II).

Multiple regression analysis revealed the significant individual contribution of BMI, RPP, BRS, AI and TNF-α to HOMA-IR in both pre-obese and obese group (Table III). Further, individual contribution of

Table III. Multiple regression analysis of homeostatic model assessment of insulin resistance (as dependable variable) with various parameters (as independent variables) in pre-obese and obese groups

Independent variables	Pre-obese group (n=86)				Obese group (n=77)			
	Standardized coefficient β	95% of CI		*P*	Standardized coefficient β	95% of CI		*P*
		LB	UB			LB	UB	
BMI	0.643	0.001	0.024	0.001	0.701	0.004	0.032	0.001
RPP	0.418	0.002	0.011	0.038	0.442	0.001	0.014	0.039
BRS	−0.221	−0.005	0.009	0.036	−0.221	−0.003	0.010	0.036
AI	0.736	−1.489	1.892	0.000	0.784	−1.313	1.744	0.001
Adiponectin	−0.110	−0.159	0.412	0.540	−0.174	−0.304	0.208	0.309
TNF-α	0.427	0.002	0.010	0.021	0.464	0.001	0.006	0.018

CI, confidence interval of unstandardized β; LB, lower bound; UB, upper bound; BMI, body mass index; RPP, rate pressure product; BRS, baroreceptor sensitivity; AI, atherogenic index; TNF-α, tumour necrosis factor alpha

Table IV. Multiple regression analysis of baroreceptor sensitivity (as dependable variable) with various parameters (as independent variables) in non-insulin resistance (NIR) and insulin resistance (IR) groups

Independent variables	NIR group (n=90)				IR group (n=73)			
	Standardized coefficient β	95% of CI		*P*	Standardized coefficient β	95% of CI		*P*
		LB	UB			LB	UB	
AI	−0.129	−0.107	0.406	0.226	−0.354	−0.003	0.054	0.003
Adiponectin	0.221	−0.010	0.041	0.061	0.389	0.007	0.026	0.001
TNF-α	−0.214	−0.001	0.008	0.067	−0.292	−0.005	0.009	0.021
TBARS	−0.066	−0.284	0.120	0.539	−0.187	−0.027	0.008	0.082

CI, confidence interval of unstandardized β; LB, lower bound; UB, upper bound; AI, atherogenic index; TNF-α, tumour necrosis factor alpha; TBARS, thiobarbituric acid reactive substance; NIR, non-insulin resistance; IR, insulin resistance

AI [β - 0.354, confidence interval (CI) −0.003–0.054, *P*=0.003], adiponectin (β 0.389, CI 0.007–0.026, *P*=0.001) and TNF-α (β −0.292, CI −0.005–0.009, *P*=0.021) to BRS was revealed by regression analysis in IR group, but not in NIR group (Table IV).

Discussion

In this study, significantly decreased BRS, was found in the IR group compared to the NIR groups (in both pre-obese and obese subjects) representing increased CV risks in individuals with IR. This was further supported by the increased resting heart rate (HR), RPP, cardiac output and decreased TP in IR group compared to the NIR groups (in both pre-obese and obese subjects), as these parameters have been reported to be associated with increased CV morbidities[24,25,29]. However, there was no significant difference in the BRS, resting HR, RPP and cardiac output between IR pre-obese and IR obese groups suggesting that the IR appeared early in these individuals and predisposed them to future CV morbidities irrespective of their adiposity status.

There was a significant increase in lipid profile parameters (expect HDL) and the lipid risk factors in IR group compared to the NIR groups (in both pre-obese and obese). AI was used in the regression model, and had an independent contribution to BRS in IR individuals, suggesting that dyslipidaemia could be the likely contributor to CV risks in these individuals.

The increased LF-HF ratio in resting supine condition represents increased sympathetic and decreased parasympathetic activity, and is considered as a sensitive marker of SVI[25,30]. In the present study, LF-HF ratio was significantly increased in IR pre-obese and IR obese individuals, representing considerable SVI. Increased sympathetic activity in the pre-obese and obese individuals was further demonstrated by the increase in LFnu, as increased LFnu reflects increased cardiac sympathetic drive[25,30]. Decreased parasympathetic activity was further confirmed by the decrease in HFnu and the TDI (Mean RR, RMSSD, SDNN and NN50) of HRV, as a reduction in these

HRV indices reflects decreased vagal modulation of cardiac drive[25,30]. These findings were in conformity with the findings of our previous study[27] that SVI in pre-obese and obese prehypertensives was linked to the sympathetic activation and vagal withdrawal. In IR individuals TDI (Mean RR, RMSSD and NN50) and BHR did not show a significant difference compared to NIR in both pre-obese and obese groups, indicating significant reduction in the cardiac vagal modulation in individuals with IR. BRS has been reported to be an index of SVI in various CV disease states[12]. Therefore, the SVI observed in individuals with IR might be linked to decreased BRS.

The decrease in E/I ratio and 30:15 ratio in IR pre-obese and IR obese individuals compared to their NIR counterparts demonstrated decreased vagal reactivity, as E/I and 30:15 ratios represent parasympathetic reactivity[27]. Further, a significant increase in DBP in response to isometric handgrip (ΔDBP_{IHG}) in IR pre-obese and IR obese individuals reflected heightened sympathetic reactivity. There was no significant difference in the autonomic activity and reactivity between the IR pre-obese and IR obese individuals. These observations suggested that alteration in the sympathetic activity and reactivity and parasympathetic activity and reactivity might be influenced by their IR status rather than the level of BMI.

The findings of the present study demonstrated that IR might play a central role in the pathophysiology associated with obesity and its related co-morbidities, independent of their adiposity status. Further, south Asians were reported to have increased IR and all-cause mortality compared to their western counterparts[6]. Thus, the status of IR, which occurs much earlier than the other metabolic abnormalities, could be used for identifying individuals at increased risk for future cardiac morbidities, especially among the Indian population. In the present study, inflammatory markers such as hs-CRP, TNF-α and IFN-γ were significantly associated with BRS in individuals with IR and further, TNF-α had an independent contribution to BRS. Thus, findings of the present study suggested that the retrograde inflammation primarily mediated by TNF-α could be the potential link between increased CV risk (decreased BRS) in these IR individuals.

Adiponectin, an anti-inflammatory cardio-protective adipocytokine has been well known for its anti-atherosclerotic and insulin-sensitizing properties[3]. Significantly decreased circulatory adiponectin in those with IR (pre-obese and obese) indicated the vulnerability of these individuals to increased risk of CV disease. This was further supported by the increased serum neopterin in IR pre-obese and IR obese individuals, which has been reported to be closely associated with adverse CV events[4]. Hypoadiponectinaemia plays a crucial role in the pathophysiology of IR[3]. Thus, the independent contribution of hypoadiponectinaemia to decreased BRS in individuals with IR might predispose them to CV related morbidities compared to their NIR counterparts.

The major limitation of the present study was that plasma non-epinephrine or its metabolites in serum were not estimated to support SVI. Further, the influence of visceral fat on IR might have provided additional information.

In conclusion, decreased TP and BRS, and increased resting HR and RPP in both IR pre-obese and obese groups suggested that the cardiometabolic risk profile was comparable between the IR, pre-obese and obese individuals. Pro-inflammatory state, dyslipidaemia and hypoadiponectinaemia might contribute to CV risks in those with IR. IR could possibly be the major contributor for increased CV risks in this population and could be used for identifying individuals at increased risk for future cardiac morbidities. However, the findings of the present study should be further validated in a larger population to assess whether these cardiometabolic risk profile observed in the present study are individual specific or adiposity specific.

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***Conflicts of Interest*:** None.

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