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Risk association of fasting insulin resistance index in non-diabetic heart failure patients: A case-control study at Karachi, Pakistan

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Abstract: Present work investigates the risk association of insulin resistance ($I^{Resistance}$) in Non-Diabetic Heart Failure (N^DH^F) patients. Eighty (n=80) N^DH^F patients and same numbers of healthy controls were included to investigate with anthropometric measures, fasting blood glucose level (FBGL), serum insulin (SI), FIRI and β-cells quantification was computed through HOMA-IR. Mean rank assessment of N^DH^F patients showed higher significant (p<0.0001) set of values in FBGL, SI, FIRI and HOMA-IR, when compared with controls. High (p<0.0001 & p<0.05) risk in N^DH^F patients was associated in SI status (OR=8.93-95% CI: 4.1-19.42) and also in HOMA-IR (OR=6.6-95% CI: 3.30-13.19), when compared for Pearson value based probability through Chi Square (χ2 Test) values estimates of probability, respectively. Area under the curve (AUC) of targeted N^DH^F patients showed higher set of estimation (FBGL-AUC =0.667, SI-AUC =0.763, FIRI-AUC=0.780 and HOMA-IR-AUC=0.776). Association of determinants through Pearson's (r) correlation was found significantly (p<0.0001) linked with HOMA-IR and FIRI. Regression coefficient shows that for every additional unit score in FBGL and SI can expect HOMA-IR to increase by an average of 0.883 (for FBGL) and 0.0368 (for SI), respectively. Findings concluded the association of $I^{Resistance}$ with greater risk estimation in N^DH^F patients.

Keywords: Anthropometric measures, heart failure, HOMA-IR, insulin resistance.

INTRODUCTION

Insulin (a peptide hormone) at cellular level promotes energy storage by regulating glucose uptake in many cells of the body so as to enhance the clearance of high glucose magnitude from the circulating blood stream (Menting *et al.,* 2013). Term 'Insulin resistance' ($I^{Resistance}$) is considered as an alleviating condition in which particular cells fail to act in response towards insulin hence, cellular uptake of essential metabolites cannot easily facilitated (Guo, 2014). Around 1990, the idea of $I^{Resistance}$ was commonly reported with the etiology of metabolic syndrome, later it was given different titles like 'syndrome X' and 'the $I^{Resistance}$ syndrome' (Haffner *et al.,* 1992; Reaven, 2005). First time in 1998, World Health Organization included $I^{Resistance}$ as diagnostic criteria for metabolic syndrome (Alberti *et al.,* 1998). With the passage of time the main characteristic of metabolic syndrome has moved entirely away from $I^{Resistance}$ to a collective of metabolic deviation that has better predictive value (Alberti *et al.,* 2006; Alberti *et al.,* 2009; Yamada *et al.,* 2012).

Normally insulin binds precisely to its target receptor (RTk receptor tyrosine kinase) promoting a cascade mechanism with the main output is to uptake glucose molecules from peripheral blood stream (Hubbard *et al.,* 1994; Schäffer, 1994; Lemmon & Schlessinger, 2010). Likewise, GLUT4 (glucose transporter type 4 in striated muscles and adipose tissues) is regulated by insulin secretion (Kanai *et al.,* 1993; Im *et al.,* 2007). Probing the molecular domain of binding of insulin peptide with RTk promotes protein phsophorylation, which in turns sequentially change the behavior of molecules within the cytosol (Goodyear *et al.,* 1995; Lemmon & Schlessinger, 2010). This further establishes the conversion of guanosine triphosphate (GTP) through PKB or AKT (Protein Kinase B), therefore, pre-formed cytosolic GLUT4 vesicles were transferred to the surface of cell membrane with aid of Kinesin motors and microtubules (Kanai *et al.,* 1993; Schäffer, 1994; Goodyear *et al.,* 1995; Shepherd and Kahn, 1999; Schlessinger, 2014). The insulin mediated sensitivity of this signaling pathway is important to understand in diabetes mellitus (DM), as in type 1 DM insulin level is much low hence the signaling is inefficient (Saltiel and Kahn, 2001; Rains & Jain, 2011). However, in type 2 DM, interaction between insulin with RTk is not sensitive which not efficiently triggers the cascade mechanism or any of the steps in signal transduction is faulty, hence not much GLUT4 was available on membrane and peripheral blood glucose magnitude remains high (Schaffer, 1994; Shepherd and Kahn, 1999; Saltiel and Kahn, 2001; Menting *et al.,* 2013).

In Asian countries like Pakistan the progressive increase in type 2 DM is big upcoming challenge (Basit *et al.,* 2018). DM linked complications mainly initiated with the chronic status of hyperglycemia due to the impaired

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utilization of glucose, which leads to accelerated lipolysis that results in hyperlipidemia or diabetic dyslipidemia (Parhofer, 2015), which ultimately associated with micro- and macro vascular complications related to cardiovascular disease (CVD) (Fowler, 2008; Wing *et al.,* 2011), neuropathy, retinopathy and nephropathy (Olsen *et al.,* 2000). $I^{Resistance}$ has been recognized as a predictive cause of risk for a count of chronic ailments such as diabetes and CVD (Mcfarlane *et al.,* 2001; Patel *et al.,* 2016). The role of $I^{Resistance}$ has also been established as the foremost leading cause towards the development of dyslipidemic symptoms like high triglycerides and LDL-cholesterol, decrease HDL-cholesterol levels and central adiposity which collectively have been tagged as metabolic syndrome (Alberti *et al.,* 2006; Al-Rubeaan *et al.,* 2016). Of which CVD is the most prevalent than other chronic complications (Katon *et al.,* 2004), and it has been estimated previously that high magnitude of complications resulting from type II $D_{mellitus}$ were related to CVD (Gaede *et al.,* 2003). Studies reported that raised levels of insulin are considered as a factor to fasten the progress of atherosclerosis and other coronary artery diseases which results in uplifting the burden of mortalities and co-morbidities (Hydrie *et al.,* 2012; Iguchi *et al.,* 2013). Therefore, the aim of the present work was to investigate the risk association of $I^{Resistance}$ in Non-Diabetic Heart Failure (N^DH^F) patients and compared them with healthy matched control at Karachi, Pakistan.

MATERIALS AND METHODS

Present work was conducted at Institute of Basic Medical Sciences (IBMS), Dow University of Health Sciences (DUHS), Karachi in collaboration with the Cardiology Departments of the two tertiary care hospitals in Karachi; *Dr. Ruth K. M. Pfau*, Civil Hospital and Dow University Hospital. Initially sample size was calculated for both, N^DH^F cases and healthy control was 113 individual (Ahsan *et al.,* 2018). Study's protocol was approved by the Institutional Review Board of DUHS, Karachi (Reference letter number: IRB-296/DUHS-11). Schematic sequence of processes involved in this study is mentioned in fig. 1.

Prior to the start of research and samples collection, permission were also taken from both of the above mentioned tertiary care hospitals. The study was further divided into two (02) steps. In first step, N^DH^F patients were approached through non-probability, purposive sampling technique. Total number of eighty (n=80) patients with N^DH^F completed the study procedures, however, 14 N^DH^F patients regretted their availability and 19 patients were associated with other ailments, therefore, they were excluded from study inclusion. In second step, healthy matched control (n=80) were targeted. Selection of healthy controls were done on the basis of their past record of last five (05) years to insured that that they have neither any type of diabetes nor heart diseases.

Those N^DH^F patients were included who fulfilled Framingham criteria with echocardiography evidence of cardiac dysfunction and belong to different classes of New York Heart Association (NYHA) classification of heart failure (Roger *et al.,* 2011; Fonarow, 2008). They had chronic heart failure of ≥4 months' duration and those patients with a prior diagnosis of diabetes or patients having a fasting plasma glucose more than 125 mg/dl or 7.0 mmol/l as defined by the ADA (American Diabetes Association) criteria were left out from the study (Bakris *et al.,* 2016) (fig. 1). Patients below 40 years, pregnant women, women who were on oral contraceptives pills and patients having any other medical condition were excluded. In fasting state, 5ml of blood sample were drawn from the subjects of both groups. FBGL and SI was estimated using ARCHITECT 1000 analyzer from Abbott Medical Diagnostics (Azmi *et al.,* 2019). Mathematical model to quantify β-cell function and insulin resistance was also computed through Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) in both groups (Matthews *et al.,* 1985). Fasting insulin resistance index was estimated according to the index already mentioned by Azmi and Qureshi, 2016.

For the estimation of odds ratios (OR), cutoff values for anthropometric and clinical markers were identified from relevant studies. The cutoff value for FBGL (5.55 mmol/L) and serum insulin (70 pmol/L) was set according to American Diabetes Association, 2016 (Bakris *et al.,* 2016) and Hydrie *et al.,* 2012, whereas, HOMA-IR (1.7 units) was set according to Yamada *et al.,* 2012. Cutoff value for BMI (25 kg/m^2) was taken through Fawwad *et al.,* 2016.

STATISTICAL ANALYSIS

The data were entered and analyzed on SPSS version 16. Values were represented with mean with standard error mean (SEM). One-way ANOVA, followed through least significant difference (LSD) with Tukey's test was used to compare mean difference between groups. Mann-Whitney U test was performed to analyzed the Nonparametric mean rank comparison between cases and control. Risk was analyzed by using odds ratio (OR) with 95% confidence of intervals (CI) and Phi coefficient was used to find the risk association of variables. Accuracy of markers in N^DH^F cases were also investigated in comparison with healthy matched control values through the area under the ROC-curve (AUC) estimation. Quantitative (Pearson's 'r') and qualitative (Spearman 'R') two-tailed correlation was performed between FIRI and HOMA-IR with anthropometric, biochemical markers. Coefficient for regression analysis with HOMA-IR scores as the dependent variables and anthropometric and biochemical markers were performed in all cases. Results were considered significant when P value $\leq$ 0.05.

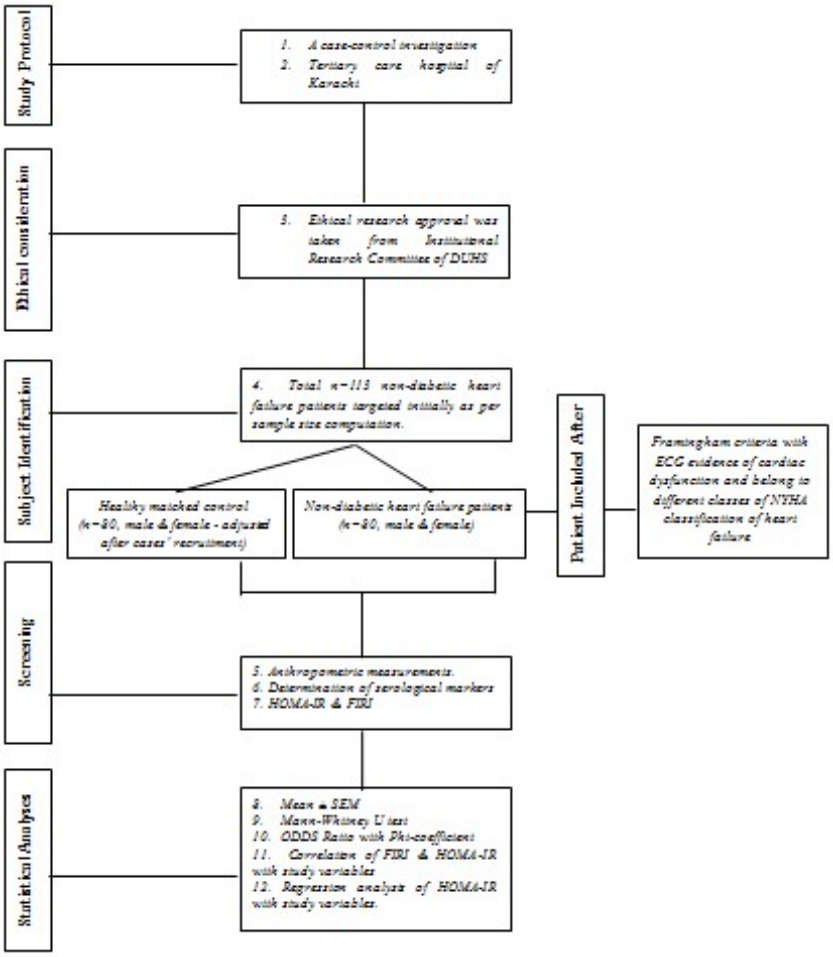


Fig. 1: Flow chart showing sequential process of study completion. Abbreviations used are - DUHS: Dow University of Health Sciences, ECG: echocardiography, NYHA: New York Heart Association, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, FIRI: Fasting insulin resistance index.

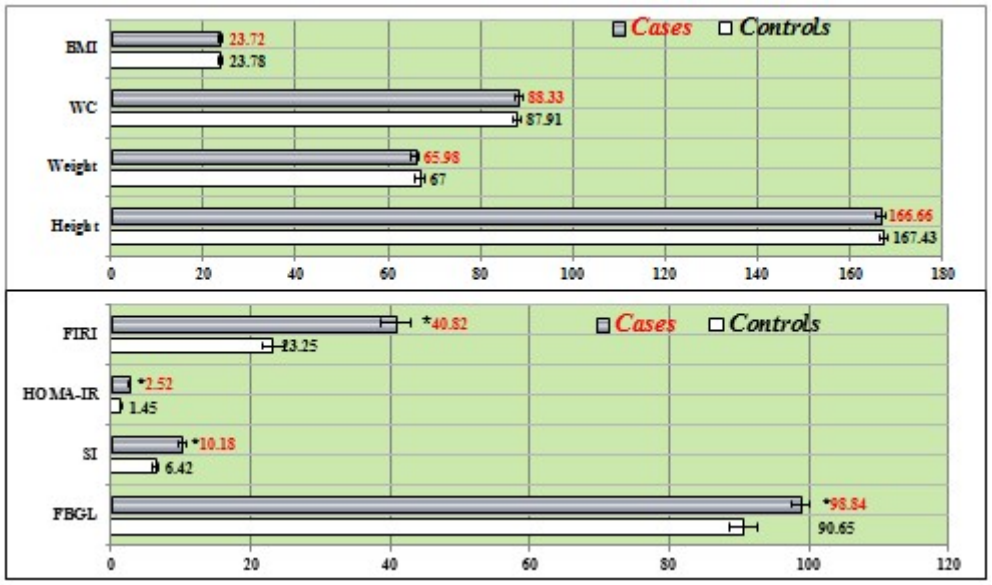


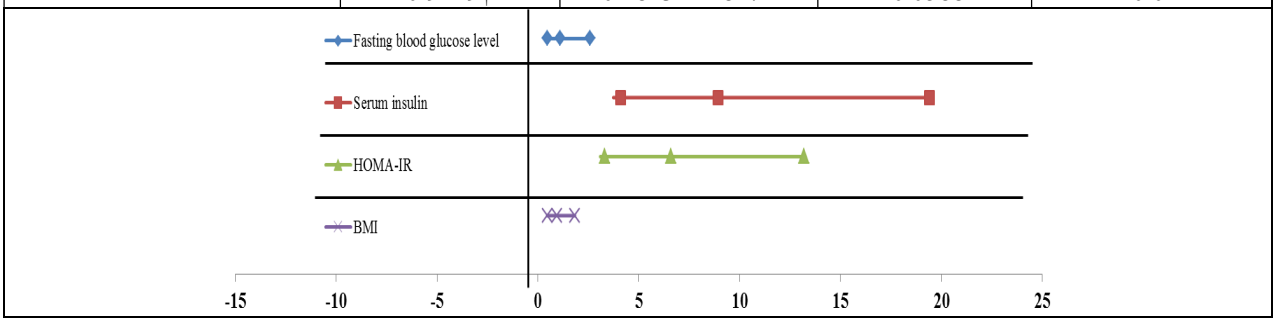
Fig. 2: Respondents' mean representation of anthropometric and biochemical marker of both non-diabetic heart failure cases with healthy matched controls. Sign representation of * showed statistically significant (*p-value* $\leq$ 0.001) mean difference computed through one-way ANOVA LSD and Tukey's test for comparison.

Table 1: Comparative analyses of non-diabetic heart failure patients with healthy controls through Mann-Whitney U test

Variables	Groups	Mean Rank	Sum of Rank	*U*	*Z*	*p*
Age	Controls	80.78	6462.50	3177.50	-0.077	0.939
	Cases	80.22	6417.50			
Height	Controls	83.30	6664	2976	-0.766	0.444
	Cases	77.70	6216			
Weight	Controls	81.63	6530.50	3109.50	-0.309	0.757
	Cases	79.37	6349.50			
WC	Controls	79.21	6337	3.097E3	-0.352	0.725
	Cases	81.79	6543			
BMI	Controls	80.59	6447.50	3.192E3	-0.026	0.980
	Cases	80.41	6432.50			
FBGL	Controls	67.11	5368.50	2128.50	-3.658	0.0001
	Cases	93.89	7511.50			
SI	Controls	59.49	4759	1519	-5.737	0.0001
	Cases	101.50	8121			
HOMA-IR	Controls	58.42	4674	1.434E3	-6.027	0.0001
	Cases	102.58	8206			
FIRI	Controls	58.11	4648.50	1408.50	-6.11	0.0001
	Cases	102.89	8231.50			

Table 2: Odds Ratio (95% Confidence Intervals) computation in Non-diabetic heart failure patients with controls

Variables	OR	CI (95%)	Log Odds	Phi coefficient
Fasting blood glucose level	1.0995	0.468 – 2.583	0.0949	+0.02
Serum Insulin	8.9339*	4.1094 – 19.4223	2.1899	+0.47
HOMA-IR	6.6*	3.302 – 13.192	1.8871	+0.44
BMI	0.9429†	0.4813 – 1.8471	-0.0588	-0.01



RESULTS

Comparative analysis of non-diabetic heart failure patients with healthy control

High significant ($p \leq 0.001$) difference were observed between FBGL, SI, HOMA-IR and FIRI values when compared with LSD and tukey's test between cases and control groups (fig. 2). The average value computed through Mann-Whitney test analysis in anthropometric variables almost showed non-significant association. In case of age, height, weight and BMI; the values in control group (mean rank =80.78, 83.30, 81.63, 80.59) exceed those of cases. However, in WC, the case group value (Mean Rank =81.79) exceeded those of control subjects (table 1).

Contrary to this on average, the fasting blood glucose levels FBGL of cases (mean rank = 93.89) significantly ($p \leq 0.0001$) exceeded those of the healthy control, U= 2128.50 & z = -3.658. The serum insulin status in cases on average (mean rank=101.50) also significantly ($p \leq 0.0001$) exceeded those of the healthy control. HOMA-IR and FIRI indices of the case groups (mean rank = 102.58 & 102.89, respectively) significantly ($p \leq 0.0001$) exceeded those of the healthy control which were indicated with almost half of the mean rank values as compared to the case group (table 1).

Table 3: Correlation between HOMA-IR and FIRI with anthropometric, biochemical markers

Cases (N_DH_F patients n = 80) with FIRI	Pearson's r	Spearman R	P-value
Age	-0.07	-	0.538
Body height	-0.104	-	0.359
Body weight	0.419**	-	0.0001
Waist circumference	0.627**	-	0.0001
BMI	0.574**	-	0.0001
FBG	0.503**	-	0.0001
Serum Insulin	0.966**	-	0.0001
Gender	-	0.072	0.525
Cases (N_DH_F patients n = 80) with HOMA-IR	Pearson's r	Spearman R	P-value
Age	-0.067	-	0.556
Body weight	0.417**	-	0.0001
Body height	-0.110	-	0.331
Waist circumference	0.621**	-	0.0001
BMI	0.578**	-	0.0001
FBG	0.499**	-	0.0001
Serum Insulin	0.966**	-	0.0001
Gender	-	0.076	0.502

** Correlation is significant at the 0.01 level (test of significance was computed with 2-tailed)

Table 4: Coefficient results for regression analysis with HOMA-IR scores as the dependent variables and differentiated scores of respondents i.e., gender, age, BMI, FBG and serum insulin as independent (predictor) variables, in cases. The obtained regression results equates for Cases group are HOMA-IR = 2.99 - 0.0081 Age; HOMA-IR = - 3.52 + 0.255 BMI; HOMA-IR = - 2.33 + 0.883 FBG; HOMA-IR = - 0.0790 + 0.0368 Serum Insulin.

Predictor	Coefficient	Standard deviation of coefficient	T	P
Cases (N_DH_F patients n = 80)				
Constant	2.9855	0.7965	3.75	0.0001
Age	-0.00807	0.01365	-0.59	0.556
Constant	-3.5164	0.9704	-3.62	0.001
BMI	0.25452	s0.04067	6.26	0.0001
Constant	-2.3303	0.9595	-2.43	0.017
FBG	0.8835	0.1735	5.09	0.0001
Constant	-0.07902	0.08575	-0.92	0.360
Serum Insulin	0.036770	0.001116	32.95	0.0001

Assessment of risk Association in non-diabetic heart failure patients with healthy control

Association of risk of insulin resistance was indicated very high in case of serum insulin assessment (OR =8.93, 95%CI: 4.1-19.4) in N^DH^F patients as compared to the matched healthy controls. This scenario was relatively low in case of fasting blood glucose (FBGL) levels (OR= 1.099, 95%CI: 0.4-2.5). However, the values of risk estimation in HOMA-IR was elevated (OR=6.6, 95%CI: 3.3-13.9) as compared with matched healthy controls (table 2).

The AUC estimation of serum insulin, HOMA- IR and FIRI showed higher values in N^DH^F patients compared to controls. This means that targeted N^DH^F patients exhibited more elevated higher values of FBGL, serum insulin, HOMA-IR and FIRI as compared to healthy matched controls (fig. 3).

Correlation between HOMA-IR with anthropometric and biochemical markers

The Pearson (r) correlation of body weight, WC, BMI, FBGL, serum insulin showed significantly ($p \leq 0.0001$) moderate to strong positive correlation with FIRI (table 3). Similarly, the Pearson (r) relation of body weight, waist circumference, BMI, FBGL showed moderately ($p \leq 0.0001$) positive correlation whereas serum insulin showed significantly ($p \leq 0.0001$) strong positive correlation with HOMA-IR (table 3).

Regression analysis of HOMA-IR with anthropometric and biochemical markers

The regression coefficient was estimated by setting the HOMA-IR as dependent variable and other inclusive variables as independent factors in N^DH^F patients. To probe the role of HOMA-IR with age, the regression coefficient reveals that for every additional unit score in

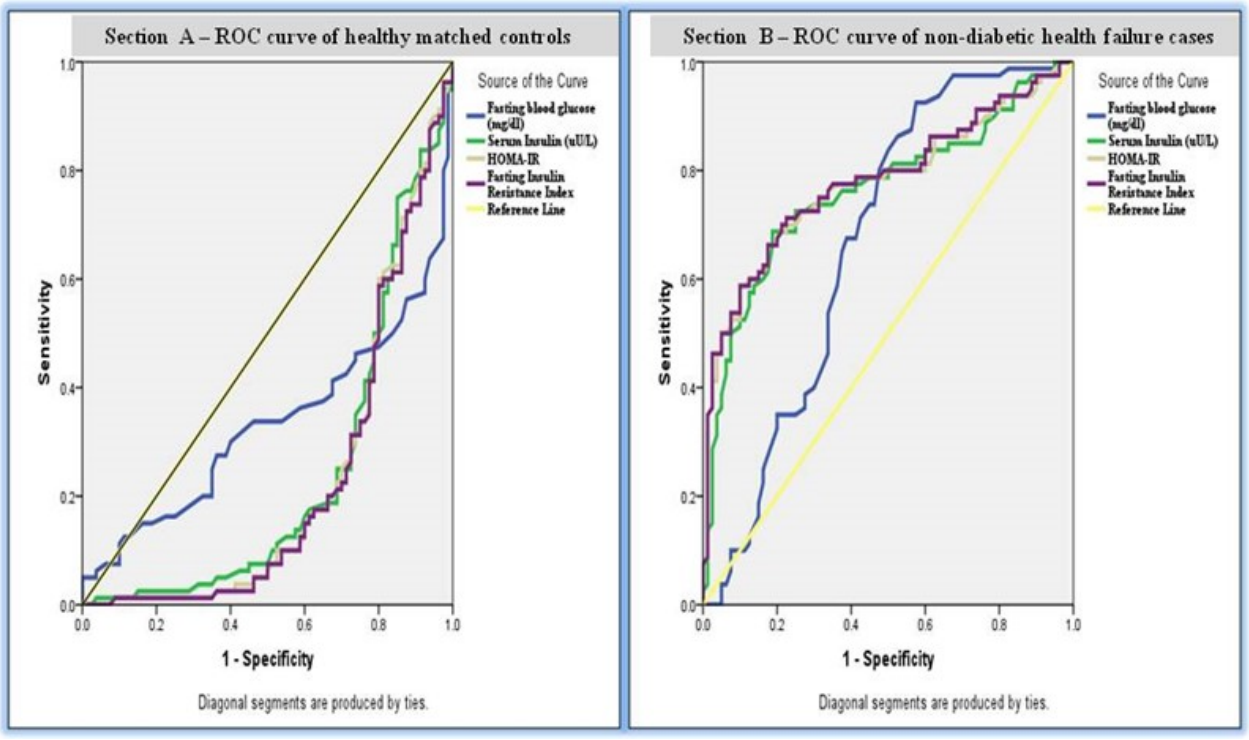


Fig. 3: Estimation of area under ROC-curve (AUC) for healthy matched control and non-diabetic heart failure cases.

age can expect HOMA-IR value to decrease by an average of 0.0081 units (table 4).

In case of BMI, the regression coefficient to relate BMI indicated that for every additional unit score in BMI can expect HOMA-IR to increase by an average of 0.225 units.

Similarly, in case of FBGL and serum insulin, the regression coefficient to relate both independent variable indicated that for every additional unit score in FBGL and serum insulin can expect HOMA-IR to increase by an average of 0.883 (for FBGL) and 0.0368 (for serum insulin), respectively (table 4).

DISCUSSION

Impaired insulin action is linked with altered biochemical processes which simultaneously influence the increased in risk of cardiovascular disease incidence (Mosterd & Hoes, 2007; Chia *et al.,* 2018; Iguchi *et al.,* 2013; Rader, 2007). Manifestations of $I^{Resistance}$ encompass beyond dysfunctional carbohydrate metabolism, further including connections with obesity, hypertension, impaired lipid metabolism, certain malignancies and immunological disorders (Rader, 2007; Goodwin *et al.,* 2009; Seriolo *et al.,* 2008). Role of obesity (abdominal or central) has been previously reported to be linked with metabolic disorders and serves as one of the foundational components of metabolic disorder (Azmi *et al.,* 2017). Further to this, appearance of these clinical signs and associated metabolic ailments has been on the rise. Physical inactivity is thought to have been playing elemental role in worsening of the situation (Tremblay *et al.,* 2010). In this regard, the worse role of sedentary life-style mainly starts with obesity and progress largely with $I^{Resistance}$ which gradually transformed with CVDs (Azmi *et al.,* 2017).

Scientifically, term 'heart failure' represents persistent congestive state or syndrome, chiefly linked with dysfuctioning of heart's biochemical physiology (Ahsan *et al.,* 2018). The American College of Cardiology (ACC) / American Heart Association (AHA) further describes the stages of heart failure in which Stage A population are generally asymptomatic and include diabetic and hypertensive patients (who do not have developed structural defect yet) (Mosterd & Hoes, 2007). This stage population is always supposed to be on a very high risk of acquiring symptomatic heart failure (Mosterd & Hoes, 2007). Therefore, the aim of current study was to study risk association of $I^{Resistance}$ in $N^{D}H^{F}$ in population of Karachi, Pakistan.

The first part of our findings relates with non-significant probability estimation of anthropometric parameters including age, weight, height and others of cases and controls was conducted to predict their relationship with disease outcomes. There was no significant difference observed in cases and control in terms of age, height,

weight and others (table 1 & fig. 2). This was one of the important finding of present investigation as there was no characteristic difference in cases and controls. Hence, through this effort strong emphasis on anthropometric measures is not properly linked as an absolute indicator in above mentioned, screening of biochemical markers are needed for investigation and classification of patients. Therefore, employed biomarkers in our study including, FBGL, SI, HOMA-IR and FIRI were found to be significantly increased in cases as compared to control (table 1 & fig. 2). Researches previously addressed the preliminary relation of FBGL as it is undoubtedly a central factor and are a key regulator of serum insulin level as well as implied for diagnostic relation of metabolic syndrome (Abou-Seif & Youssef, 2004). Earlier reports have proposed substantial role of $I^{Resistance}$ in development of metabolic disorder(s) and consequential increased incidence of cardiovascular pathology eventually becoming elemental in heart failure (Appleton *et al*., 2013; Iguchi *et al.,* 2013; Rader, 2007). Multifaceted association of $I^{Resistance}$ and metabolic disorder in relationship with HOMA-IR and their causation in the disease development have been well reported (Appleton *et al.,* 2013; Gayoso-Diz *et al.,* 2013; Ahsan *et al.,* 2018; Rader, 2007). In this regard, relation of HOMA-IR has already been reported to be associated with development of Type II diabetes mellitus (Morimoto *et al.,* 2014). The chronic status of diabetes mellitus has been well reported to be crucial in development of cardiovascular diseases and relevant metabolic syndrome (Appleton *et al.,* 2013). Increased HOMA-IR values in N^DH^F are thought to be linked with impaired interaction of insulin with its receptors through least expression of glucose transporters (in various body tissues) and more and more availability of glucose residues in blood stream (Azmi & Qureshi, 2016; Li *et al.,* 2017).

High risk involvement specifically indicated a very strong association of $I^{Resistance}$ with SI level and HOMA-IR in N^DH^F cases as compared to healthy controls (table 2). Contrary to this, a relatively weak association of N^DH^F cases was observed in relation with FBGL. These findings set another important aspect as disease progress (in term of heart failure) with elevated prior magnitude of SI, HOMA-IR and FIRI but remain not much influential for raising the FBGL status. Hence, from our investigation it has been connected as risk association of $I^{Resistance}$ in N^DH^F cases were more relied on SI and its indices as compared with FBGL.

A moderately positive correlation of FIRI and HOMA-IR were observed with weight, waist circumference, BMI, FBGL and strongly positive correlation SI level. A study in 2017 conducted on Taiwanese middle aged and elderly subjects reported that BMI and WC was significant forecaster of $I^{Resistance}$ than total body fat percentage (Cheng *et al.,* 2017). Hence, present findings (table 3) in our study are consistent with the above reported findings. Similarly through regression analysis it was established that HOMA-IR increments of 0.883 and 0.368 units can be expected from each unit increase in FBGL and serum insulin level (table 4). Previous researches emphasized the importance of HOMA-IR as an important predictor for the estimation of risk of CVD specifically in person with type 2 diabetes mellitus (Ref). Therefore, role of $I^{Resistance}$ steadily contribute towards the more devastating complication like persistent appearance of metabolic syndrome, heart failure, etc (Azmi *et al.,* 2019).

CONCLUSION

Present findings strengthen the concept that higher values of $I^{Resistance}$ (FIRI, HOMA-IR) poses greater risk of heart failure in non-diabetics patients.

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