Homeostasis model assessment of insulin resistance in non-diabetic heart failure patients: A case-control investigation at tertiary care Hospitals of Karachi

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Abstract: Heart failure is a progressive, chronic disorder. Insulin resistance (IR) has been more and more involved as a preliminary metabolic perturbance predisposing to hyperglycemia, hyperlipidemia and atherosclerosis with others heart diseases. To investigate the relation of insulin resistance (IR) in non-diabetic heart failure patients this case-control study was carried out to ascertain the presence of IR with the aid of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) in non-diabetic heart failure patients (N_DH_F patients) compared with healthy controls. The sample size was calculated for both, cases (N_DH_F patients) and control (healthy subjects), which was initially consisted of 113 respondents each. The study consisted of two phase duration. In Phase I, N_DH_F patients were approached initially; only 80 patients with N_DH_F completed the study procedure. In Phase II, 80 healthy subjects were targeted and matched. Fasting blood glucose level (FBGL) and serum insulin was estimated. 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. Data was analyzed on SPSS version 16. Mean values with ± standard deviation (SD) of insulin (10.2±4.36) and HOMA-IR (2.52±1.15) were significantly ($p<0.05$) higher in N_DH_F patients as compared to control subject (6.4±3.39, 1.45±0.80). Average insulin to glucose ratio was 0.10±0.044 in N_DH_F patients which was significantly ($p<0.0001$) lowered in controls i.e., 0.073±0.039. Marginal and matrix plot analysis revealed that a higher patients count have had the HOMA-IR values <1.5 units while opposite scenario was observed in control group. Regression analyses of HOMA-IR with FBGL (as independent indicator) also authenticate the similar pattern. The present study concludes that insulin resistance (decreased insulin sensitivity) is a characteristic finding in Pakistani population of heart failure as compared to matched healthy controls.

Keywords: Heart failure, Congestive Heart Failure, Insulin resistance, HOMA-IR.

INTRODUCTION

The term 'heart failure', generally referred as a chronic congestive condition or syndrome mainly linked with the cardiac dysfunction (Dokainish *et al.,* 2017). Idiosyncratic establishment of signs and symptoms preliminary reflects the inability of heart to maintain or pump sufficient or required quantity of blood towards the various organs or tissues or cellular levels of the body (Hogg *et al.,* 2004). Researchers' focused on clinically linked scenario of heart failure described that this longstanding health issue has direct connectivity with unhealthy life style, poor or miserable physical health condition, obesity and other health issues (Chia *et al.,* 2018; Mosterd & Hoes, 2007).

The gradual onset of heart failure also has its straight association with pulmonary symptoms like shortness of breath and weakness in respiratory mechanism results due to constrained blood pumping activity (Rutten *et al.,* 2006). Literature established that heart failure was declared as a prime reason (among other of the epidemiological scenario) for the increment of mortality and morbidities burden rates in both urban as well as rural areas population of the entire world so far (Gamble *et al.,* 2011). However, the prevalence of heart failure was also measured and found more engaged with age-adjusted factor i.e., four (04) to eight (08) folds more among those have age range of 50 years, or above, as compared to others (Gottlieb *et al.,* 2004). Analyzing the main cause of heart failure for understanding the biochemical basis / mechanism includes the role of hypertension, obesity, smoking, diabetes with or without dyslipidemia profile, coronary artery disease (CAD), and other heart diseases (Bui *et al.,* 2011; Mosterd & Hoes, 2007).

The incidence of heart failure approaches between the ranges of 5 to 10 patients per 1000 individuals, annually (Mosterd & Hoes, 2007). American College of Cardiology / American Heart Association (ACC / AHA) emphasized that the heart failure is preventable by proper and timely controlling or managing the blood pressure (both systolic and diastolic), diabetes mellitus and also the asymptomatic structural and functional cardiovascular abnormalities (Mosterd & Hoes, 2007; Lam, 2015). The vulnerability of heart failure was considered and mentioned by ACC / AHA as a prominent stage when the

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person have main disease status of any or combination like hypertension, diabetes mellitus, and CAD (Mosterd & Hoes, 2007). Similarly, most researchers elaborated that two prime contributing factor for the progression of heart failure were reported, which includes hypertension and diabetes mellitus (Azmi *et al.,* 2017). In addition to this, these two contributing determinants or factors progress side by side, either by genetic or environmental triggers (Konzem *et al.,* 2002; Azmi *et al.,* 2017). The envisaged factor for this worsening was reported as unmanaged diabetes mellitus, specifically type 2 diabetes mellitus, which not only links with metabolic deviation due to relative or absolute deficiency of insulin, producing least cellular energy in terms of ATP (adenosine triphosphate), NADH (nicotinamide adenine dinucleotide phosphate), and others, with relevance to cellular energy demands (Abou-Seif & Youssef 2004). These biochemical abnormalities also enhances the generation of ROS (Reactive Oxygen Species) and RNR (Reactive Nitrogenous Radicals) at cellular levels which ultimately leads to the orientation of many chronic metabolic irregularities (Abou-Seif &Youssef, 2004; Zhang & Shah, 2008), which commonly and collectively may set the basis of heart failure (Zhang & Shah, 2008).

Previous studies indicated that elevated insulin and atherogenesis has direct association (Iguchi *et al.,* 2013), however, few studies stated the link between insulin resistances with cardiovascular disease (CVD mainly coronary plaque vulnerability). Nowadays, homeostasis model of insulin resistance (HOMA-IR) has been used as a clinical indicator for the assessment and interpretation of the strength of pancreas in term of insulin quantification and β-cells' physiology (Gayoso-Diz *et al.,* 2013). Moreover, HOMA-IR is also recognized as gold standard method for interpretation of insulin resistance (Shashaj *et al.,* 2016). Up till now, in Pakistan, the specific categorization of HOMA-IR in non-diabetic heart failure patient was not reported. Therefore, present study was designed to investigate the HOMA-IR in non-diabetic heart failure patient of Karachi. In near future, comparative as well as detailed country wide assessment / experimentation on similar set objectives with relation to anthropometric markers will be perform to strengthens and authenticate the present outcomes.

MATERIALS AND METHODS

Study site and population

This case control study was carried out at Institute of Basic Medical Sciences (IBMS), 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. The sample size was calculated for both, cases (N_DH_F patients) and control (healthy subjects), which was initially consisted of 113 respondents each. It was calculated from *Rao Soft online calculator* for sample size calculation by setting the margin of error at 5%, confidence level at 95%, population size at 20000 and response distribution at 8%. Prior to this, informed consent was also taken from each subject.

Institutional ethical approval

Prior to the conduction of research and collection of samples, permissions were taken from both the hospitals. Institutional Ethical Research approval was also taken from the Institutional Research Committee of Dow University of Health Sciences, Karachi in 2012 (Reference letter number: IRB-296/DUHS-11).

Study protocol

The study was consisted of two phase duration. In Phase I, only N_DH_F patients were approached through non-probability, purposive sampling technique. Total of 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 (fig. 1).

In Phase II, 80 healthy subjects were targeted, in order to equate the targeted sample population of cases. Healthy controls were selected on the basis of their last five (05) years record with full assurance that they have neither diabetes nor heart diseases (fig. 1).

Exclusion and inclusion criteria

Patients were included on the basis of either sex recently diagnosed with heart failure. 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 125mg/dl or 7.0mmol/l as defined by the ADA (American Diabetes Association) criteria were left out from the study.

Following N_DH_F patients were excluded from the study:

- Patients below 40 years
- Pregnant women.
- Women who are on oral contraceptives pills
- Patients having any other medical condition.

Determination of Blood and Serological Markers and HOMA-IR

For fasting blood glucose, 5ml of blood sample were drawn and collected in the grey top bottle containing EDTA. The specimens were centrifuged at a rate of 3500 rotation/min for 5-7 minutes to get clear serum samples. For fasting insulin, whole blood was collected in gel/SST clot activator tube with yellow top and allowed to clot for

25-30 minutes. Once the formation of complete clot had taken place, centrifugation of the specimens were done at a rate of 3500 rotation/min for 5-7 minutes to get clear serum of the samples. FBGL and Serum fasting insulin was estimated using ARCHITECT 1000 analyzer from Abbott Medical Diagnostics. 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)

STATISTICAL ANALYSIS

The data were analyzed on SPSS version 16. Values were represented with mean with standard deviation (SD). Minitab version 17 statistical software for Windows version 7 professional was used to for the detailed marginal and matrix analysis of serum insulin (as independent factor) with HOMA-IR (as dependent variable). Online *GraphPad* Software, Quick Calcs Online Calculator for scientist was also used for Regression analysis of fasting blood glucose level (as independent factor) with HOMA-IR (as dependent variable). Differences were considered significant with $p \leq 0.05$.

RESULTS

Study subjects

In N_DH_F patients group, Out of 80 patients, the gender wise distribution of patients showed that 53 (66.3%) were males and 27 (33.8%) were females. With reference to the age wise distribution, N_DH_F patients group, 17 patients (21.3%) were from 40 to 49 years, 28 patients (35%) were from 50 to 59 years, 26 patients (32.5%) were from 60 to 69 years, and only 9 patients (11.3%) were from 70 or more years age group (table 1).

In control group, out of 80 health subjects, 53 (66.3%) were males and 27 (33.8%). With reference to the age wise distribution, the two age groups i.e., 40-49 and 50-59 years were similar as compared with control (N_DH_F patients) group, however, 27 patients (33.8%) were from 60 to 69 years, and only 8 patients (10%) were from 70 or more years' age group. There was no significant difference (p=0.831) found in the mean age of cases (57.6±9.55) and the controls (57.9±10.43) (table 1).

Fasting blood glucose, serum insulin and HOMA-IR

Mean fasting blood glucose level of N_DH_F patients (98.8± 11.73) showed significant (p≤0.001) increase as compared with the normal healthy control group (88.6±17.24). Mean serum insulin level of N_DH_F patient was 10.2 ±4.36, which was significantly (p≤0.001) high when compared with the normal healthy control group (6.4±3.39) (table 2).

Mean HOMA-IR values was computed for both groups, specifically in N_DH_F patients very significantly (p≤0.001) high levels were observed i.e., 2.52 ±1.15, as compared to control healthy subjects i.e., 1.45±0.80 (table 2).

Glucose to insulin & insulin to glucose ratio analysis

Mean values for Glucose: Insulin ratio values was computed for both study groups, in case of N_DH_F patients least significant (p≤0.0695) association were observed i.e., 13.16±10.19, as compared to control healthy subjects i.e., 28.22±72.89 (table 2). However, mean values for Insulin: Glucose ratio values was also computed for both study groups, in case of N_DH_F patients very significantly (p≤0.0001) high association were observed i.e., 0.10±0.044, as compared to control healthy subjects i.e., 0.073±0.039 (table 2).

Marginal and matrix analysis of serum insulin with HOMA-IR

In order to understand the every single patient and healthy subject level of serum insulin and its direct impact on HOMA-IR values marginal plot and matrix analysis was also performed for both study groups. In marginal plot analysis, serum insulin was set as an independent biochemical marker whereas HOMA-IR was used as dependent marker. The patient to patient analysis showed that maximum number of N_DH_F patients have serum insulin range higher from 10mIU/L. With reference to this, higher HOMA-IR values were also exists in the range of 2 to 5 units of HOMAR-IR (fig. 2: A-I & A-II). Box-pots of these two markers also confirmed this pattern of variation. Verification for these changes was also evident from the healthy subject's controls levels. From individual to individual level validation, marginal plot analysis showed that maximum number of healthy subjects has serum insulin range lower or in between 10mIU/L. With reference to this, higher HOMA-IR values of controls were also exists in the range of 0.5 to 2 units of HOMAR-IR (fig. 2: A-III & A-IV). Box-pots of these two markers of controls also authenticate this change with relation to N_DH_F patients.

Regression analysis of fasting blood glucose with HOMA-IR

The coefficient of regression was computed in both groups by setting the FBG level as independent variable (X) and HOMA-IR values as dependent variable (Y). In N_DH_F patients, Best-fit values of slope were obtained as 0.049±0.0096 (95% Confidence Intervals = 0.029-0.068), with HOMA-IR (Y-intercept) -2.33±0.96, X-intercept was 47.48 and 1/slope was 20.37. Assessing the regression equation through Goodness of fit, R-square value was 0.2494 which represents the percent of the variance in the values of Y (HOMA-IR) that can be explained by knowing the value of X (FBG). F-value was 25.92, p-value was <0.0001 which indicated that deviation from horizontal was significant. However, comparison from

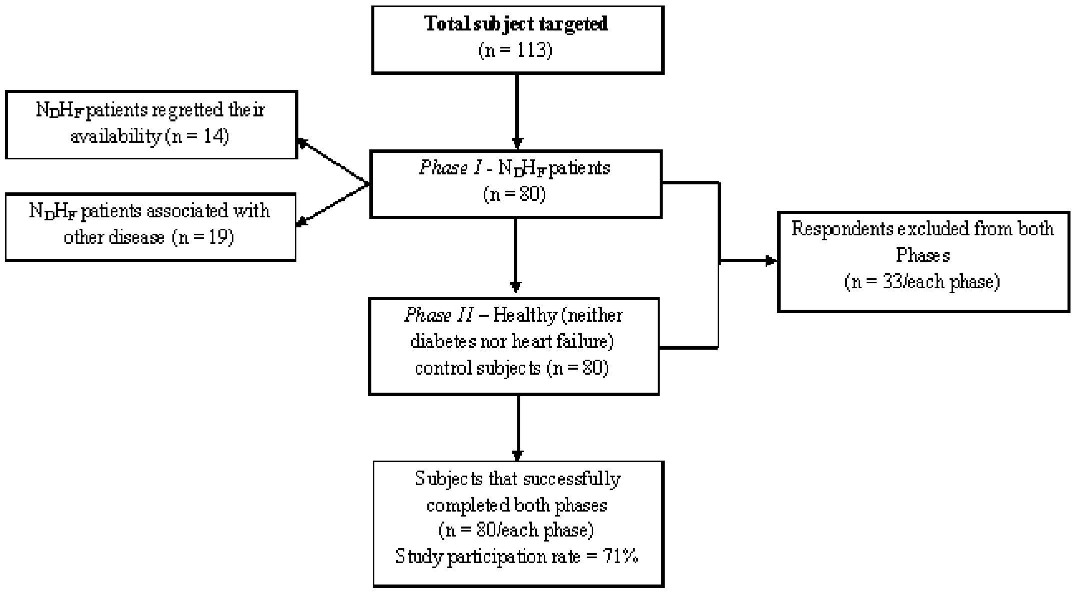

Fig. 1: Subjects' Enrollment.

Table 1: Gender and age distribution of 80 Patients with Non-diabetic Chronic Heart Failure (Cases) and 80 Healthy Subjects (Controls)

	Cases (N_DH_F patients) (n=80)	Control (n=80)	P-value
Gender			
Male	53 (66.3%)	53 (66.3%)	1.000
Female	27 (33.8%)	27 (33.8%)	
Age in years			
40-49	17 (21.3%)	17 (21.3%)	0.994
50-59	28 (35.0%)	28 (35.0%)	
60-69	26 (32.5%)	27 (33.8%)	
70 & above	9 (11.3%)	8 (10.0%)	
Mean ± S.D.	57.6 ± 9.55	57.9 ± 10.43	0.831

Table 2: Fasting Blood Sugar and Serum Insulin details of Cases (N_DH_F patients) and Healthy Subjects (Controls)

Variables	Cases (N_DH_F patients) (n=80)	Controls (n=80)	P-value
	Mean ± S.D.	Mean ± S.D.	
Fasting Blood Sugar (mg/dl)	98.8 ± 11.73	88.6 ± 17.24	*0.001**
Insulin (mIU/L)	10.2 ± 4.36	6.4 ± 3.39	*0.001**
HOMA-IR	2.52 ± 1.15	1.45 ± 0.80	*0.001**
Insulin: Glucose Ratio	0.10±0.044	0.073±0.039	0.0001

control showed that Best-fit values of slope were obtained as 0.0147±0.0049 (95% Confidence Intervals = 0.0048 to 0.024), with HOMA-IR (Y-intercept) 0.1101±0.4588, X-intercept was -7.449 and 1/slope was 67.63. Assessing the regression equation through Goodness of fit, R-square value was 0.1018 which represents the percent of the variance in the values of Y (HOMA-IR) that can be explained by knowing the value of X (FBG). F-value was 8.845; p-value was equivalent to 0.0039 which indicated that deviation from horizontal was also significant. The regression equation for N_DH_F patients computed as HOMA-IR increases with 0.049 units of FBG with a Y (HOMA-IR) intercept value of -2.330. Whereas, in healthy control subjects, the regression equation was computed as HOMA-IR increases 0.01479 units of FBG with a Y (HOMA-IR) intercept value of 0.1101.

DISCUSSION

Implications of insulin resistance in case of type 2 diabetes mellitus (T2DM) were not solely focused simply on impaired carbohydrate metabolism, as its relevance with obesity, hypertension, dyslipidemia, cancer and other autoimmune disorders were also reported (Reader, 2007;

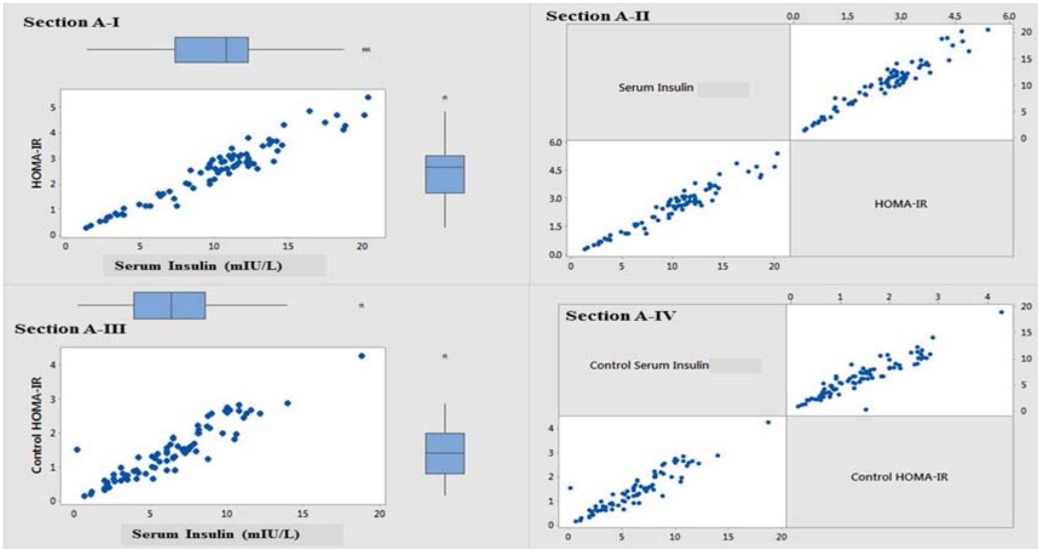

Fig. 2: Matrix and Marginal Analysis of Serum Insulin and HOMA-IR of Cases (N_DH_F patients) versus control subject. Section A-I showed marginal plot analysis of HOMA-IR versus serum insulin (mIU/L) of N_DH_F patients. Section A-II showed matrix plot analysis of HOMA-IR versus serum insulin (mIU/L) of N_DH_F patients. Section A-III showed marginal plot analysis of HOMA-IR versus serum insulin (mIU/L) of controls. Section A-IV showed matrix plot analysis of HOMA-IR versus serum insulin (mIU/L) of controls.

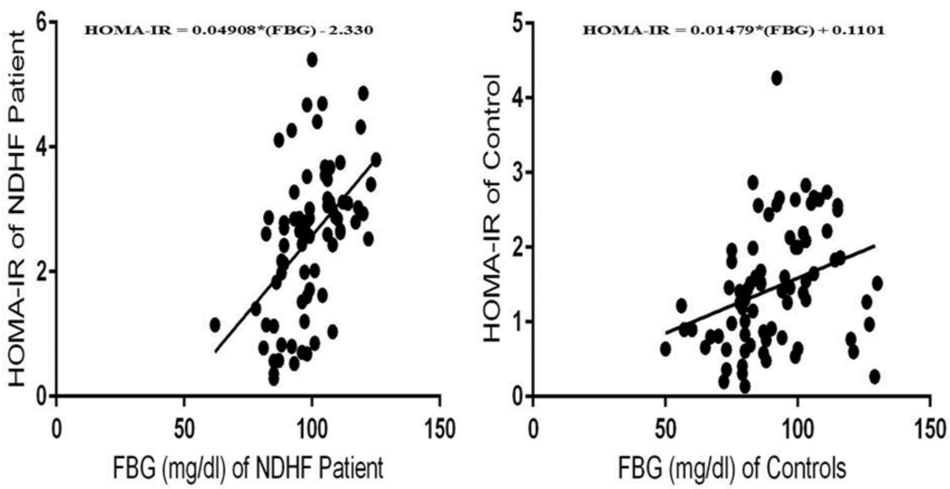

Fig. 3: Regression Analysis of Fasting Blood Glucose level with HOMA-IR of Cases (N_DH_F patients) versus control subject.

Goodwin *et al.,* 2009; Seriolo *et al.,* 2008). Description of metabolic disorders categorically relates its basis on multiple affianced clinical signs and symptoms like abdominal or central obesity and others (Azmi *et al.,* 2017). In addition to impaired and unmanaged glucose metabolism has its escalatory role for the provision of the basis of severe secondary chronic metabolic disorders like T2DM, cardiovascular diseases and others (Azmi *et al.,* 2017). Moreover, in recent decades the prevalence of the above signs, symptoms and disease burden has prominently increased in general population due to sedentary lifestyle pattern (Tremblay *et al.,* 2010). Besides other clinical symptoms heart failure was seen as resultant of unhealthy lifestyle, obesity, hypertension with poor metabolic conditions (Mosterd & Hoes, 2007; Azmi *et al.,* 2017).

According to the metabolically linked risk factors, AHA categorized heart failure at stage A with high risk and no symptoms (Mosterd & Hoes, 2007), so the rationale for this study revolves around this abovementioned concept, therefore, selection or recruitment of cases were done purely with non-diabetic history with heart failure cases. Furthermore, studies also reported that patients with younger age have hardly ever reported with heart failure cases (Gottlieb *et al.,* 2004). So, in this regard, age selections were done from 40 years onwards and mean range of patients' age was 57 to 58 years. The definite association of hypertension and diabetes mellitus was reported in literature and this serves as a basis to investigate some other clinical markers to probe this analysis (Konzem *et al.,* 2002; Azmi *et al.,* 2017).

Findings of this study also focused on the estimation of fasting blood glucose level (FBGL) which was found in normal limits during investigation, in both groups that i.e., cases (N_DH_F patients) and controls. In addition to this, the insulin level of the cases (N_DH_F patients) were found significantly risen when relates with control group. This means that there is no prominent effect of raised insulin level within range to FBGL of N_DH_F patients directly. Therefore, in order to strengthen this finding we need to focus on HOMA-IR as tool to conclude and justified this association (Gayoso-Diz *et al.,* 2013). According to literature sources the cut-off range of HOMA-IR is between 1.85 and 2.07 (Gayoso-Diz *et al.,* 2013; Shashaj *et al.,* 2016).

A study published on Japanese population in 2014 showed that increase or elevated levels of HOMA-IR units had a strong impact on the development of T2DM (Morimoto *et al.,* 2014). Interestingly, the T2DM incidence has dramatically increased in Asian population in last few decades (Chen *et al.,* 2012*;* Azmi & Qureshi, 2016). Likewise, HOMA-IR is the robust tool to estimate insulin resistance (IR) as researchers elaborate its importance as with little change or least increment in any individual (Matthews *et al.,* 1985; Gayoso-Diz *et al.,* 2013). HOMA-IR values related with increased risk for T2DM (Morimoto *et al.,* 2014). Importantly in countries like Pakistan, the main cause for the increment of disease burden is due to the lack of preventive strategies as well as lack of cost-effective way of diagnosis (through clinical markers) (Azmi *et al.,* 2017).

Considering HOMA-IR as a premise tool for investigation, our study showed that a significant variation ($P< 0.001$) was observed in N_DH_F patients as compared to control group. In this regard, HOMA-IR values indicated the higher insulin level may be due to decreased insulin compatibility with its target receptors (Azmi & Qureshi, 2016; Li *et al.,* 2017) or this resistance is most probably in N_DH_F patients is due to masking of insulin receptors (Azmi & Qureshi, 2016; Li *et al.,* 2017). Here, the condition of insulinoma should not be neglected which in our case-group might reflects the endogenous hyperinsulinism and concurrent hypoglycemic level (Li *et al.,* 2017). Several studies also recommended the use of serum insulin to blood glucose (SI: FBGL) ratio/ index as a reliable indicator (Li *et al.,* 2017) to understand or validate the HOMA-IR results. These two screening indices i.e., HOMA-IR and SI: FBGL ratio set the clinical significance in quantification of higher insulin levels in N_DH_F patient as compared to control subjects.

Through marginal and matrix plot analysis (fig. 2) the patient to patient (in cases) and person to person (in controls) vulnerability for high serum insulin with HOMA-IR was also analyzed. Findings reveals that higher proportion of N_DH_F patients were engaged or have with higher serum insulin level that is 5 mIU/L and more in patient were observed with HOMA-IR greater than 1.5 units. Contrary to this, the opposite scenario was observed in healthy controls which may set up set as an evident factor for the better insulin utilization in normal individuals.

Studies revealed that DM is well reported risk factor for the generation and development of cardiovascular diseases (Appleton *et al.,* 2013). In addition, HOMA-IR model was also found more predictable when there is increased basal glucose production (especially in fasting as well as random status) (Matthews *et al.,* 1985; Gayoso-Diz *et al.,* 2013; Shashaj *et al.,* 2016). Focusing the direct relationship between blood glucose levels with HOMA-IR assessment in both groups that is cases N_DH_F and healthy control also establish and authenticate our previous findings. Through linear regression analysis (fig. 3) the value corresponding between FBGL with HOMA-IR showed that maximum patient with higher HOMA-IR levels equate with higher FBGL that is 90-120 mg/dL (in fasting state) and through equation HOMA-IR and FBGL has 4% effect on its straight association in N_DH_F patients. Whereas, 1% similar effect was also computed in normal healthy subjects. As in control subject least HOMA-IR range occupied maximum healthy subjects. In present research study, with the aid of HOMA-IR, the biochemically linked factors was established, evident and authenticated that beside the moderate increase in serum insulin in N_DH_F patients, the vulnerability towards IR was not neglected.

CONCLUSION

The present study concludes that insulin resistance (decrease insulin sensitivity) is a common finding in non-diabetic heart failure patients of Pakistani population as compared to matched healthy subjects.

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