Risk assessment of insulin resistance with anthropometric measures in non-diabetic heart failure patients: A gender based case-control investigation at tertiary care hospitals of Karachi, Pakistan

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Abstract: To assess the risk of anthropometric measures and serum markers of insulin resistance in non-diabetic heart failure (N^DH^F) patients and the difference among male and female subjects. 53 males, 27 females N^DH^F patients were enrolled and 80 healthy subjects were matched as control. Anthropometric measures, fasting blood glucose level (FBGL) and serum insulin (SI) were measured. Insulin's function (β-cells quantification) was computed through Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Significant ($p \leq 0.05$) difference in height was observed in N^DH^F male and female patients, whereas, weight was only significant in females. Higher mean values of FBGL, SI, and HOMA-IR in N^DH^F patients were observed. Highly significant ($p \leq 0.0001$ & $p \leq 0.05$) difference was also found in similar gender based case-control markers like FBGL, SI, and HOMA-IR. Phi coefficient for risk associations showed weak-positive correlation in both genders in FBGL, SI, and HOMA-IR. Anthropometric measures indicated lesser risk in both gender, especially in females' decreased risk in body height and waist circumference was observed. Risk measurement through odds ratios (OR) of FBGL and HOMA-IR in female subjects indicated significantly ($p<0.001$) double risk, whereas, in SI, three fold risks were measured in females as compared to male. Odds of exposure in cases were significantly ($p<0.001$) greater than in controls verified with significant Pearson and Fisher Exact Probability Test (FEPT) values with two-tailed estimates of probability in χ^2 (Chi –Square) estimation test. Findings suggest increased risk of IR in female N^DH^F patients. Increased in FBGL IR and HOMA-IR and BMI were also found as distinguishing findings in N^DH^F cases.

Keywords: Heart failure, insulin resistance, HOMA-IR.

INTRODUCTION

In medical science term 'heart failure' is alluded as a perpetual congestive state or condition leading with the dysfunctioning of cardiac physiological mechanism(s) (Inamdar & Inamdar, 2016; Dokainish *et al*., 2017). The foundational signs and effects mainly relates with the failure of heart to keep pump and uphold the adequate blood magnitude towards the various organs as well as tissues and its flow to the systematic cellular entities of the body (Hogg *et al.,* 2004). Annual heart failure's incidence scopes between average five (05) to ten (10) cases out of 1000 persons (Mosterd & Hoes, 2007), which may be due to longstanding of individual with poor and unhealthy life-style pattern enduring certain other medical problems along with this outcome (Chia *et al.,* 2018). Therefore, literature sources proclaimed heart failure as a foremost reason for the addition of morbidities and mortality load in different developed and developing regions among the globe (Gamble *et al.,* 2011).

Increase in age has straight influence for the development of heart failure and other cardiovascular problems (Gottlieb *et al.,* 2004). As prominent contributing factor different pulmonary conditions especially like breath shortness and others were also directly reported for the restricted blood supply with constrained pumping action of heart (Rutten *et al.,* 2006). Previous researches also indicated that mechanism based onset of heart failure has it connectivity with chronic dyslipidaemia and its associated consequences (Mosterd & Hoes, 2007; Bui *et al.,* 2011).Whereas, the preliminary blend of diseases like obesity, hypertension, diabetes mellitus were also accounted as progressive and direct contributing cause of heart failure (Bui *et al.,* 2011). Beside this, the role of undiagnosed diabetes mellitus or impaired glucose tolerance based hyperglycaemia results in gradual transformation into type 2 diabetes that lead to other severe consequences to body (Inamdar & Inamdar, 2016; Mosterd & Hoes, 2007; Lam, 2015; Azmi *et al.,* 2017). Beside this, role of free radical in cardiac diseases and its worsening appearances related with or without other metabolic disorders have identically established determinants or intensifying factor especially in heart failure patients (Abou-Seif & Youssef, 2004; Zhang & Shah, 2008). Considering the environmental or genetic factors triggers in association with the above characteristics, the envisaged deficiency (either absolute

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or relative) of insulin was never underestimated (Appleton *et al.,* 2013). The biochemical deviation in metabolic processes is mainly revolves around towards the insufficiency of insulin or IR due to post-receptor defect(s) of this peptide with its native molecular receptors (Azmi *et al.,* 2017; Iguchi *et al.,* 2013). This abnormal biochemical action(s) results imbalances in the required cellular energy (ATP adenosine triphosphate, NADH - nicotinamide adenine dinucleotide phosphate and others) needs with subsequent generation of free radicals, which collectively sets the basis of many chronic metabolic disorders (Abou-Seif & Youssef, 2004).

Studies reported that lower insulin sensitivity and increase resistance pattern was correlated with the indication of upsurge in atherogenesis rate in patients with metabolically linked morbidities and mortalities (Iguchi *et al.,* 2013; Vardeny *et al.,* 2013). Specifically in last few decades, this resistance pattern of insulin has well elaborately studied with the aid of a combinational index referred as "homeostasis model of insulin resistance (HOMA-IR)" to clearly depict the biochemical influence of insulin on human body (Gayoso-Diz *et al.,* 2013). Therefore the purpose of this study is to compare insulin resistance (IR) in non-diabetic heart failure (N^DH^F) patients (cases) with healthy controls on gender basis. Further, to comparatively assess the risk of anthropometric measures and serum markers of IR among N^DH^F cases and healthy controls.

MATERIALS AND METHODS

This study was carried out 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. 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 *RaoSoft 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% (Ahsan *et al.*, 2018). Prior to this, informed consent was also taken from each subject. Study's protocol was approved by the Institutional Review Board of DUHS, Karachi (Reference letter number: IRB-296/DUHS-11). Earlier to the conduction of research and collection of samples, permissions were also taken from both the mentioned hospitals.

The study was comprised of two (02) stages. In stage-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. In stage-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.

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 $\geq$ 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. Patients below 40 years, pregnant women, women who were on oral contraceptives pills and patients having any other medical condition were excluded. For the estimation of odds ratios (OR), cutoff values for all eight 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 and Hydrie *et al.,* 2012, whereas, HOMA-IR (1.7 units) was set according to Yamada *et al.,* 2012. Cutoff value for age (50 years) was set according to Mosterd and Hoes, 2007. Body weight (60 kg), height (170 cm), waist circumference (male - 88.90 cm: female - 78.74cm) and BMI ($25kg/m^2$) the cutoff value were taken through Riaz *et al.,* 2012; Nadeem *et al.,* 2013; Fawwad *et al.,* 2016, respectively.

In fasting state, 5 ml of blood sample was drawn from the subjects of both groups. FBGL and SI was estimated using ARCHITECT 1000 analyzer from Abbott Medical Diagnostics (Ahsan *et al.,* 2018). 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).

The data were entered and analyzed on SPSS version 16. Values were represented with mean with standard error mean (SEM). Online *Graph Pad* Software, Quick Calcs Online Calculator for scientist was used to compute the probability values through independent sample t-test significance. 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. Results were considered significant when P value $\leq$0.05.

RESULTS

Present work includes the same numbers (53 males, 27 females) of cases i.e., N^DH^F patients with reference to

Table 1: Comparative analysis of anthropometric measures, biochemical markers and index for insulin resistance

Variable	Control versus Cases (n = 53)		p -value (Male to Male-Case-Control)	Control versus Cases (n = 80)		p -value (Female to Female - Case-Control)
	Male (Control)	Male (Cases)		Female (Control)	Female (Cases)	
Age (years)	57.6±1.45	57.43±1.32	0.9311	58.56±1.99	57.89±1.84	0.8057
Body height (cm)	169.04±1.06	172.32±0.5	0.0061	164.30±1.75	155.56±0.56	0.0001
Body weight (kg)	67.96±1.36	69.32±0.99	0.4207	65.11±1.70	59.41±1.22	0.0088
WC (cm)	88.23±0.96	89.64±0.89	0.2839	87.30±1.12	85.74±1.31	0.3696
BMI (kg/m^2)	23.66±0.4	23.26±0.36	0.4590	24±0.5	24.61±0.47	0.3781
FBGL (mmol/l)	4.9±0.05	5.47±0.09	0.0001	4.85±0.06	5.54±0.11	0.0001
SI (pmol/l)	44.45±3.24	69.24±4.29	0.0001	44.78±4.49	73.58±5.52	0.0002
HOMA-IR	1.44±0.11	2.45±0.16	0.0001	1.47±0.15	2.66±0.22	0.0001

Values in each column represent mean ±SEM. p - value was computed by using independent sample t-test.

Table 2: Risk measurement through Odds ratios (OR) and 95% confidence intervals (CI) in non-diabetic heart failure patients

Variables	Male (n=53)		Female (n=27)	
	OR	95% CI	OR	95% CI
Age	1.2146	0.511-2.89	0.8313	0.25-2.74
Body height	1.276	0.323-5.0405	1.3506	0.46-3.96
Body weight	0.9157	0.4023-2.0845	0.64	0.098-4.17
WC	0.9273	0.433-1.986	0.6087	0.15-2.46
BMI	0.823	0.3466-1.956	1.1688	0.39-3.49
FBGL (mmol/l)	9.3137*†	2.56-33.95	20.8*†	2.46-176.2
SI (pmol/l)	6.8889*†	2.7966-16.97	18.18*†	3.55-92.99
HOMA-IR	5.4167*†	2.36-12.48	10*†	2.86-34.93

Sign representation of * and † represents statistically significance (*p-value* $\leq$ 0.001) when compared for Pearson value based probability estimates through Chi –Square (χ2 Test) and Fisher Exact Probability Test (FEPT) values with two-tailed estimates of probability, respectively.

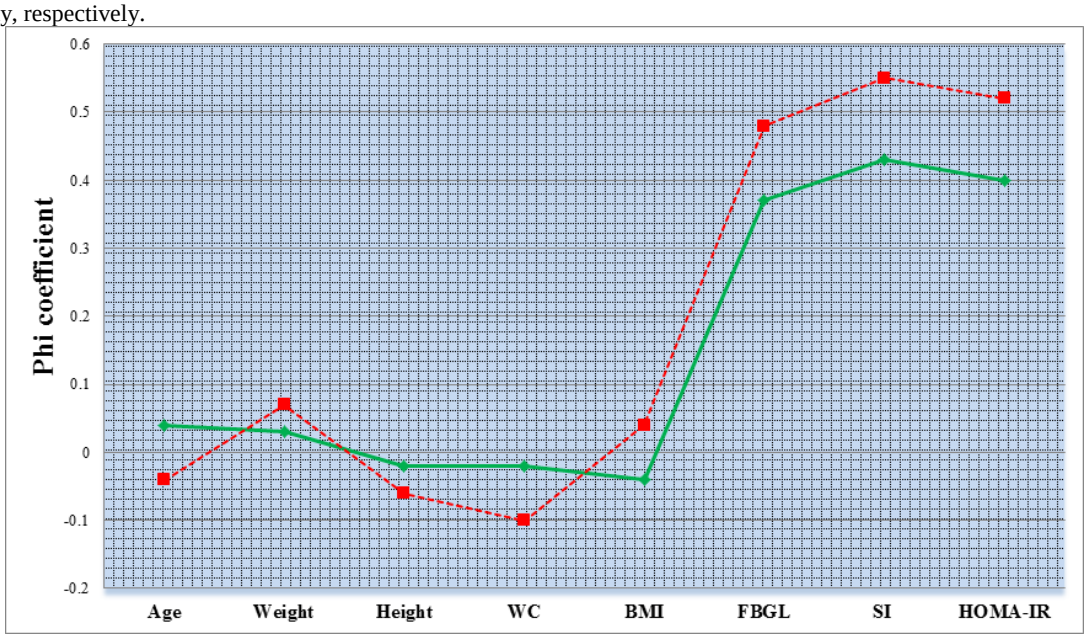

Fig. 1: Assessment of risk and gender based association through comparative phi coefficient analysis. Dotted line with red color (- - - -) indicates female phi coefficient value and green line (——) indicates male values of phi coefficient.

control healthy subjects. After preliminary exclusion (33 subjects) of N^DH^F patients the entire response rate was 71% for this study. Thereafter, the same rate was matched for healthy controls.

Comparison of healthy controls with cases (N^DH^F patients) was done on the basis of gender for both anthropometric markers as well as biochemical analyses of blood serum markers and IR indices. No major

significant differences in the mean values of anthropometric markers were observed when comparison was done statistically with male as well as female case-control subjects (table 1).

Gender based comparative analyses of biochemical marker i.e., FBGL, SI and HOMA-IR showed significantly ($p \leq 0.001$) higher mean values in both male and female N^DH^F patients compared with those of healthy matched controls (table 1).

Strong (positive) association was observed in (male and female) FBGL, SI and HOMA-IR status. Risk measurement in N^DH^F patients through OR with 95% CI of FBGL and HOMA-IR in female (20.8 and 10.4 times high risk, respectively) subjects indicated significantly ($p<0.001$) double risk as compared to male (9 and 5 times high risk, respectively) subjects. Whereas, in SI, three fold risks was measured in females (18 times high risk) as compared to male (6.8 times high risk) subjects (table 2). This were later verified with significant Pearson and Fisher Exact Probability Test (FEPT) values with two-tailed estimates of probability in χ^2 (Chi –Square) estimation test. Overall OR depicted odds of exposure in cases are significantly greater than in control. Weak risk estimates were computed in anthropometric markers (table 2).

Phi coefficient for measurement of risk associations showed weak-positive correlation in both genders subjects in case of FBGL, SI and HOMA-IR (fig. 1). In both gender very least correlation based risk association in anthropometric measures in N^DH^F patients was found, especially in females' decreased risk in body height and waist circumference was observed. Whereas, clinical markers assessment like FBGL, SI, and HOMA-IR provides better positive correlation estimates, comparatively more high in female patients (fig. 1).

DISCUSSION

Metabolic dysfunction(s) in terms of alterations in biochemical pathways and cardiovascular risk are the two integrated entities that mainly linked with absolute or relative deficiency of insulin (Mosterd & Hoes, 2007; Chia *et al.,* 2018; Iguchi *et al.,* 2013; Rader, 2007). IR as one of the features of metabolic syndrome along with conditions like hypertension, obesity, dyslipidemia and associated ailments were found directly related in previously studies (Azmi *et al.,* 2017; Abou-Seif & Youssef, 2004; Appleton *et al.,* 2013; Iguchi *et al.,* 2013; Rader, 2007). The pre-existed conditions relevant with heart failure were elaborated by the American College of Cardiology and according to them stage A patient that have high risk with no symptoms is exemplified with hypertension and diabetes mellitus (Mosterd & Hoes, 2007). In this regard the objective of the present study clearly relates with the risk assessment of IR with anthropometric measure in non-diabetic heart failure patient in comparison with healthy matched controls.

Preference for the use of various anthropometric markers due to their cost effective rational with an appealing interpretation for the local and scientific community has been well recommended (Azmi *et al.,* 2017). Beside the use of other clinical investigation(s), use of anthropometric markers for characterizing the risk of metabolic alterations were more preferred for the adaptation of curative as well as preventive strategies (Azmi *et al.,* 2017). In this manner, our study simply relates with the random allotment of healthy control subjects with non-diabetic heart failure patients. Similarly, the observed outcome from anthropometric markers i.e., age, height, weight, waist circumference and BMI of both cases and control were insinuated by the non-significant probability estimates (table 1). The findings of anthropometric markers was another imputation especially in the non-diabetic heart failure cases that has physically and apparently similar to the numeric outcomes observed in well healthy matched control (table 1).

IR has been characterized as one of the foremost cause with preliminary and pre-existed risk factors like unmanaged glucose tolerance, dyslipidemic consequences, and others, which as a whole progress as metabolic syndrome (Azmi *et al.,* 2017; Iguchi *et al.,* 2013; Gayoso-Diz *et al.,* 2013; Rader, 2007). The main biochemical contributor in this regard is the status of fasting blood glucose level which regulates the body's status of serum insulin (Abou-Seif & Youssef, 2004). In present study prominently elevated status of fasting blood glucose level and serum insulin in similar gender based estimation of probability value set a significant picture of non-diabetic heart failure patient as compared to matched healthy control (table 1). Therefore, in heart failure patients, this may confirm the previously published fact that IR has been evinced to propagate the development of cardiovascular pathologies (atherosclerosis etc) with reference to metabolic syndrome (Appleton *et al.,* 2013; Iguchi *et al.,* 2013; Rader, 2007).

IR has been mainly linked with the chronic development of pathophysiology of metabolic syndrome (Yamada *et al.,* 2012; Rader, 2007). This relationship of IR with the metabolic syndrome has been studied with the aid of homeostatic model assessment of IR (HOMA-IR) on large scientific scale as standard method (Gayoso-Diz *et al.,* 2013). This integration has also used to interpret the clinical outcomes with specific relevance of IR and type 2 diabetes (Appleton *et al.,* 2013; Gayoso-Diz *et al.,* 2013; Ahsan *et al.,* 2017; Rader, 2007). Our findings revealed the association of HOMA-IR with different predictors like BMI, FBGL and serum insulin, were computed in both gender patients, which showed positive association among these variables in non-diabetic cases as compared with healthy controls (table 1).

The impact of decreased insulin sensitivity with associated hemodynamic changes as well as the magnitude of cardio-metabolic risk was preliminary established due to the undiagnosed hyperglycemic status which gradually progress into IR (Abou-Seif & Youssef, 2004; Appleton *et al.,* 2013; Iguchi *et al.,* 2013; Gayoso-Diz *et al.,* 2013; Yamada *et al.,* 2012; Rader, 2007). The prolong influence of undiagnosed hyperglycemia along with heritable factors promoting the increase risk of IR (Singh, 2011), by accelerating the synthesis of cholesterol and triglyceride moieties (Azmi & Qureshi, 2016). On target tissues this amplified production of triglyceride not only involved in the masking of insulin receptors but also leads to hyperinsulinemia (Rader, 2007; Azmi & Qureshi, 2016). These metabolites also serve as substitute source of energy for the cells which may augment the synthesis of versatile intermediary metabolite i.e., acetyl Co-A, that cannot be handled easily by TCA (tricarboxylic acid) cycle and induced the biosynthesis of cholesterol (Rader, 2007; Azmi & Qureshi, 2016). Similar set of observation was found in both male and female patients which validate more strongly about the above aforesaid outcomes as the odds of exposure in non-diabetic heart failure cases was greater in term of fasting blood glucose level, serum insulin and HOMA-IR than the odds of exposure in healthy matched control (table 2). Moreover, this above significant ($p<0.001$) association was found stronger in female non-diabetic heart failure patient as compared to male patients (table 2). Comparatively, the two variables i.e., body height and WC has decreased risk association in female as compared to male patient (fig. 1). However, the high risk computation in female patient were also confirm through Phi coefficient analysis specifically in terms of BMI, FBGL, serum insulin and HOMA-IR, as compared to male subjects. Another interesting findings was the indication of weak negative correlation of anthropometric measures like age, weight, height and WC, whereas, positive correlation of risk (high indication of risk) in markers like BMI, FBGL, serum insulin and HOMA-IR were computed. These findings established that clinical diagnosis is strong indicator for the assessment of risk of disease, in comparison with anthropometric measures.

CONCLUSION

There is an increased risk of IR in female $N^{D}H^{F}$ patients as compared to male patients. Increased in FBGL, IR, HOMA-IR and BMI were also serves as distinguishing findings in $N^{D}H^{F}$ cases as compared with other anthropometric measures.

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