ORIGINAL ARTICLE

PREDICTORS FOR INSULIN RESISTANCE IN METABOLIC DYSFUNCTION ASSOCIATED FATTY LIVER DISEASE

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ABSTRACT

Objective: Metabolic dysfunction-associated fatty liver disease is a new concept to replace NAFLD as it truly reflects metabolic dysfunction associated with fatty liver. The aim of the study is to find the predictors of insulin resistance in term of mid upper arm circumference and triceps fold thickness in MAFLD subjects.

Material and methods: This cross sectional study was conducted at King Edward Medical University in collaboration with Mayo hospital radiology out door patient department from 2016 to 2017 after taking Ethical approval from University (134/RC/KEMU). Total of 148 non diabetic subjects of aged 40-60 years with Nonalcoholic fatty liver disease diagnosed on ultrasonography were enrolled from Mayo hospital. Fasting blood glucose was measured to exclude the diabetic subjects. Mid upper arm circumference and triceps folds were measured following protocol. Subjects were divided into two groups i.e. insulin resistant and non-insulin resistant group(NIR) using cutoff values of HOMAIR. HOMA-IR value ≥ 2.29 were taken as IR group while subject with HOMA-IR value < 2.29 were taken as NIR group.

Results: Study comprised of 148 NAFLD subjects of both genders. Out of total 148 subjects, 107 (72.3%) subjects were IR and 41 (27.7%) subjects were NIR. Spearman's Correlation did not show statistically significant association of IR with mid arm circumference. (P-value 0.70) and triceps fold IR (P- value 0.83).

Conclusion: Insulin resistance is not associated with triceps skin fold and mid arm circumference in obese individual. Triceps fold and mid upper arm circumference cannot be used as clinical interpreter of IR in obese individuals.

Key words: Insulin Resistance, Mid Upper Arm Circumference, Metabolic dysfunction-associated fatty liver disease, Triceps Fold.

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INTRODUCTION

Metabolic associated fatty liver disease (MAFLD) which was formerly known as Nonalcoholic fatty liver disease (NAFLD) is associated with diabetes mellitus insulin resistance and obesity. However, NAFLD is a disease which is considered as the accumulation of fat that is termed as steatosis without major injury to hepatic cells. However, this might progress and involve the spectrum of ballooning degeneration of hepatic cell or tissue fibrosis which is termed as NASH ultimately leading to other life threatening complication. However, there is not well defined clear demarcation between NAFLD and NASH[1]. Since, the nomenclature NAFLD does not depict all the features the subject is passing through thereby lacking for any definitive diagnosis and treatment. Hence, nomenclature recently been improved because of the heterogeneous pattern of the disease and its consequent metabolic features

Rate of prevalence of this disease is hiking with every passing day and has no definitive treatment. It is believed that it is associated with other disorders that themselves are considered as major reasons for morbidity and mortality. Obesity is taken as one of the leading reasons for causing this condition, a condition that also significantly increases the risk for insulin resistance, hypertension and metabolic derangement[2]. This heterogeneous pattern of its pathogenesis referred this condition to be associated with metabolic dysfunction is termed as metabolic associated fatty liver disease (MAFLD). MAFLD is a new emerging concept proposed in 2020concept related to these conditions, as NAFLD does not truly reflect the metabolic deregulation related to fatty liver disease. “MAFLD” was proposed as an appropriate terminology reflecting for these conditions. This will open the new horizons for researchers to upgrade the nomenclature of the disease to hike the translational path for advance management and treatments[3].

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Obesity, especially visceral adiposity including fatty liver, is also an important component of the insulin resistance metabolic syndrome, a group of disorders including dyslipidemia, type 2 diabetes, and hypertension that might itself can lead to patient's health deterioration[2].

Insulin being the vital hormone is responsible for maintaining the human blood sugar levels by utilization of glucose through peripheral tissues. When peripheral tissue utilization is affected in the presence of adequate amount of insulin then this condition is known as insulin resistance(IR)[4]. Hence, raised levels of blood glucose are found in subjects with insulin resistance. Certain tools are now been discovered for measuring the insulin resistance but Matthwes et al, was the first researcher being credited for describing the HOMAIR. It is now been widely used especially in epidemiological studies because of its convenience and need of only single plasma sample for insulin and glucose. It is also described as the indicator of angiographic coronary artery disease in diabetic and non-diabetic subjects as well as for cardio metabolic risk factor[4,5].

Utilizing the anthropometric tools relies upon its efficacy to determine pertinent health problems[6]. Body mass index is considered as an important sign to evaluate the degree of obesity or adiposity in adolescents as well as in children. Nevertheless, if alternate to BMI more specify to adiposity, could show strong association with health related outcomes and might impart significant contribution to research, provided that assessing obesity and adiposity with BMI is oppressed with conceptual challenges. Widely used anthropometric tools to determine adiposity are the triceps fold thickness and mid upper arm circumference (MUAC). Though its utility for determining the nutritional status is remarkable but is used rarely for assessing obesity and its associated outcomes including IR and deranged lipid profile. According to studies MUAC can be used as surrogate for HOMA-IR and can be the good predictor of mortality than BMI[7]. Hence our study aims to evaluate the association of mid upper arm circumference and triceps skin fold with insulin resistance because of it convenient utility and application in outdoor patient department and this could be used as a clinical predictor of IR and subsequent metabolic derangements in obese NAFLD subjects. Hence by keeping these causative factors under check we can be able to prevent NAFLD subjects progressing towards vicious cycle of the disease that is responsible for deteriorating subject's condition ultimately leading to early mortality.

MATERIAL AND METHODS

This cross sectional study of 148 obese NAFLD subjects was conducted at King Edward Medical University(KEMU) attached with MAYO Hospital from January 2016 to December 2017.Before conducting the study, ethical(134/RC/KEMU) approval was obtained. Subjects were recruited by non-probability convenience sampling technique.

One hundred and forty eight NAFLD subjects were recruited from outpatient sonology department Mayo hospital attached with King Edward Medical University. History was taken on predesigned proforma. Age, weight, triceps fold thickness and midarm circumference was measured following the protocol. Mid-arm circumference was taken by asking the subject to bend the left arm, then olecranon process and acromion process was marked, mid-point between these two marks was identified, while arm hanging straight down and then measuring the midpoint arm circumference. While triceps fold was measured with help of body fat measuring caliper.

Subject with BMI> 25kg/m2 with normal fasting sugar less than 126mg/dl from age 40-60 were enrolled in the study. However subject with raised fasting blood sugar and known diabetics, subjects with any type of hepatitis, taking steroids and alcohol and on hikmat and homeopathic medicine were excluded. To exclude the diabetic subjects from the study, fasting blood sugar levels were checked using glucometer (model U-RIGHTTD -4251) subject with fasting blood sugar greater then 126g/dl were excluded from the study. Then under aseptic conditions 5ml of blood was drawn for measuring the levels of insulin. Afterwards, it was shifted in serum separator tubes to centrifuge the blood at 3000 rev/min for 15-20 minutes. Insulin levels were checked by ELISA technique. Then NAFLD subject were divided into insulin resistant and non-insulin resistant groups on the basis of values of having HOMA-IR(glucose (nmol/L) * insulin (μU/mL)/22.5]. Subjects with HOMA-IR value ≥2.29 were taken as IR group while subject with HOMA-IR value <2.29 were taken as NIR group.

STATISTICAL ANALYSIS

SPSS version 21.0 was used for analyzing the data. Continuous variables were expressed as mean ± SD. Shapiro's wilk test was used to check the Normality of data, as p value ≤ 0.05, indicating that it was not normally distributed. Manwhitnys U test was performed to compare the median of triceps fold and MUAC among studied group. Spearman's Correlation was used to analyze association of triceps and MAUC with IR. p-value ≤ 0.05 was considered significant.

RESULTS

Hundred and forty eight NAFLD participants of either gender were included this study. Forty three (29.1%) were males and 105 (70.9 %) were females. Descriptive of the studied population is shown in table1. Mean age of studied group was 44.8±6.2 and its median IQR was 43(8).Mean fasting sugar levels were 114.8± 12.8with median (IQR) 118.0(10.0). Mean of triceps and mid arm

circumference of whole population is 2.6±0.4 and 12.5 ±1.09while median(IQR) 2.5 (0.3) and 12.5(0.8)respectively. Out of total 148 subjects, 107 (72.3%) subjects were IR and 41 (27.7%)subjects were NIR. Spearman's Correlation did not show statistically significant association of IR with mid arm circumference. (p value=0.70) and triceps-fold IR (p value=0.83). table2

DISCUSSION

Obesity is the growing pandemic worldwide and soaring cause of insulin resistance leading to metabolic disorders[8]. Insulin is the main factor for transporting glucose into skeletal muscles and adipose tissues. 60-70% of glucose uptake in the skeletal muscles and 10% in adipose tissues is via insulin dependent GLUT 4 receptors[9]. Skeletal muscle is a main source of insulin mediated glucose metabolism and can profoundly persuade IR. Obesity results in formation of free fatty acids and ectopic lipids accumulation that triggers the insulin resistance by activating atypical Protein kinase C(PKC). PKC contributes to the reduction of insulin signaling by promoting serine phosphorylation of Insulin receptor substrate 1(IRS 1) that attenuates IRS-1 tyrosine phosphorylation pathway for actual insulin signaling[10]. Moreover, adipose tissue macrophages (ATM) associated with obesity accounts for reduced insulin signaling by releasing inflammatory cytokines that expedites hepatic gluconeogenesis and decline in glycogen synthesis leading to hyperglycemia and oxidative stress[9]. Activation of Toll- like receptors by free fatty acids are additional factor for insulin resistance due to obesity. In turn insulin resistance causes protein catabolism in skeletal muscles and further increase in free fatty acid concentration by decreasing lipoprotein lipase activity in adipocytes and release of adipocytokines like TNFα, IL6and leptin, hence further aggravation of IR[11]. Evidences are available showing the relationship of adiposity with IR and all these factors accounts for nonalcoholic fatty liver diseases (NAFLD).Triceps fold thickness and mid upper arm circumference (MUAC) are important emerging predictors of adiposity and now been focused by the researchers of modern world. It is evident that as greater MUAC was positively associated with higher risks of several cardio-metabolic disorders[12]. It has been suggested by various researchers to use these parameters as a surrogate of HOMAIR[4]. MUAC and triceps skin fold are used to assess nutritional status and lean body mass. Skin fold thickness measurement methods are inexpensive, non-invasive and easy measurable tool, hence providing a direct measurement of subcutaneous layer of fat, can provide direct effect of insulin on lipid metabolism[13,14]. ADDO O also documented the significant utility of skin fold thickness for estimating insulin resistance and serum triglycerides in adolecents[15].

It is salient to highlight the association of indices of skin fold thickness with IR. This study was designed to elucidate the relation between triceps skinfold thicknesses and mid arm circumference with insulin resistance in obese subjects.

Present study did not find any significant correlation of MAUC with IR in obese studied subjects. Current

Table 1: Descriptives of the studied population

	Group	N	Mean (SD)	Median (IQR)
Age	IR	107	44.6(6.1)	43(8)
	NIR	41	45.1(6.6)	45(7)
Fasting blood sugar	IR	107	115.2(10.3)	118(9)
	NIR	41	113.6(17.8)	119(11.5)
Weight	IR	107	80.9(10.0)	82(10)
	NIR	41	75.9(9.4)	76(11.5)
Height	IR	107	1.5(0.1)	1.6(0.8)
	NIR	41	1.5(0.1)	1.6(0.9)
Insulin	IR	107	27.6(27.4)	19.6(33.20)
	NIR	41	24.9(22.2)	16.6(32.35)

Table 2: Comparison of skin fold thickness among the studied group by Mann Whitney U test

	Triceps fold n=148		MUAC n=148	
	Mean±SD	Median(inter-Quartile range)	Mean±SD	Median (inter-Quartile range)
IR	2.65±0.44	2.5(2.8-2.5)	12.67±0.89	12.5(13.0-12.5)
NIR	2.64±0.56	2.5(2.7-2.5)	12.38±1.48	12.5(13.0-12.0)
P value	0.837		0.705	

*P value ≤0.05 is taken as significant.

results are justified by Chao et al study, which reported the interesting finding that they found significant positive association on MAUC with IR only in non-obese subjects, however they did not find similar association among the obese subjects[4].

Our results are not in agreement with previous Pakistani study conducted at Lahore by Zafar U et al, which reported significant correlation of IR with MAUC[16]. These local results were in accordance with other studies also showing significant positive correlation between the AC and HOMA-IR[17].

Our study did not find any significant association of triceps fold with IR and this was in line with very old study by Freedman et al, which also did not find any association between triceps fold thickness and IR and concluded that the Triceps skin fold thickness did not provide independent information on any outcome[18]. However current study is not in agreement with another Pakistani investigation who documented the strong association of triceps fold with IR , hence suggesting it as one of best predictor of IR and stated that it might be helpful in identifying the population at risk for IR and subsequent metabolic syndrome.16Findings of the aforementioned previous study had emphasized on the reduction in Central and upper body fat that might cause in improving insulin sensitivity and delay metabolic disorders due to insulin resistance.

More adiposity in the skeletal muscle of obese subjects limits the estimation of muscle mass by MUAC. Accumulation of fat in skeletal muscle results in transition of type I more oxidative fibers into type II muscle less oxidative fibers that already lack insulin sensitivity. Finding of the current study suggested that the triceps skin folds and MUAC cannot be used as a surrogate of HOMA IR to predict IR in obese subject, most probably because of inability to assess the excessive amount of fat accumulated outside and inside the muscle. Further researches on broader scales are required concerning use of other anthropometric measurements like waist circumference (WC) and calf circumference (CC) as surrogate for HOMA IR to establish easily accessible methods for predicting IR frail obese individuals.

CONCLUSION

Insulin resistance is not associated with triceps skin fold and mid arm circumference in obese individual and they are not use as clinical predictor of IR.

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LIMITATION:

Causal inferences are not established due to cross-sectional nature of the study.

It is a single center study, so results may not be generalized to whole population.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Altaf B:	Conception, data collection, writing up
Jawed S:	Data collection, statistical analysis
Salam RMT:	Literature research bibliography
Jawed S:	supervision

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.