International Journal of Research in Medical Sciences
Dhaidan FA. Int J Res Med Sci. 2018 Jun;6(6):1862-1866
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20181963

Original Research Article

Influence of metabolic syndrome on left atrial size among sample of patients attending Al Karama teaching hospital in Iraq

Fuad Abdullah Dhaidan*

Department of Internal Medicine, Al Karama Teaching Hospital, Baghdad, Iraq

Received: 11 April 2018
Accepted: 26 April 2018

***Correspondence:**
Dr. Fuad Abdullah Dhaidan,
E-mail: fharthy16@yahoo.com

ABSTRACT

Background: Left atrial (LA) enlargement has been linked to obesity and insulin-resistance in adults. The aim of this study was to determine the association between LA area and: a) different components of the metabolic syndrome including obesity (OB) measures of body mass index (BMI) and waist circumference (WC)), insulin resistance (IR, proinsulin), and blood pressure (BP) b) left ventricular mass and diastolic function measured by echo doppler.
Methods: 90 subjects, (42 OB (BMI >30, 30, overweight (BMI >25)), 18 non-OB (BMI <25. BMI, WC, BP, tanner stage, and mode M, 2-dimensional and doppler transmitral echocardiography were assessed. A standard oral glucose tolerance test (OGTT) was done, measuring glucose, insulin, and proinsulin concentrations.
Results: Hypertension was only present in OB (30%). LA enlargement (>2 SD) adjusted for height was more frequent in OB and overweight. Significant univariate association (P<0.001) was found between LA area and height (r = 0.52), age (r = 0.45), tanner stage(r = 0.45), BMI (r = 0.66), WC (r = 0.70), systolic BP (r = 0.52), diastolic BP (r =0.53), proinsulin (r = 0.36) and HOMA-IR (r = 0.36). In the multivariate regression analysis, independent variables were entered in a stepwise fashion: initially, gender (P = 0.006), and tanner stage (P = 0.011) were still significant independent correlates of LA area after adjusting for age, gender, and Tanner stage. Subsequently incorporation of WC showed that WC (P = 0.018) was a significant independent correlate of LA area. A regression model constructed to test the significance of adjustment factors, including WC, BP, left ventricular mass, and HOMA-IR showed that WC (P<0.001) was the only significant independent variable.
Conclusions: Waist circumference is the main factor affecting left atrial size among patient with metabolic syndrome.

Keywords: Association, Left atrial size, Metabolic syndrome

INTRODUCTION

The insulin resistance syndrome, a cluster of traits including hyperinsulinemia, dyslipidemia, hypertension, and obesity (OB) is associated with an increased risk of cardiovascular disease (CVD)and all-cause mortality.[1] The prevalence of childhood OB, a multisystem disease with potentially devastating consequences, has risen several-fold in the past two decades.[2] Left atrial (LA) enlargement has been linked to hypertension, OB, insulin-resistance, and early CVD in adults.[3] In the Framingham study it was found that LA enlargement was associated with an increased risk of stroke and death in adults.[4] LA enlargement has been associated with hypertension and OB in adolescents.[5,6] Left ventricular hypertrophy has also been found in children and adolescents with essential hypertension syndrome and OB in children is still debated. To our knowledge, there have been no comprehensive studies during childhood relating metabolic syndrome to LA size. The purpose of this study was to determine the association between LA area and: a) the components of the metabolic syndrome:

OB, defined by body mass index (BMI) and waist circumference (WC), insulin resistance (HOMA-IR, proinsulin), and blood pressure (BP), and b) left ventricular mass, and diastolic function, measured by echo doppler.

METHODS

Ninety subjects, (42 OB (BMI >30),30 overweight (BMI >25)], 18 non-OB (BMI <25) were matched for sex and age. Age, sex, weight, height, WC, and Tanner stage were recorded.[7-9] Weight was measured to the nearest 0.1kg on a medical balance. Height was measured to the nearest 0.1cm. BMI was calculated as weight in kilograms divided by height in meters squared. Overweight (OW) and OB were defined as a BMI >25>30 respectively, according to the centers for disease control growth charts BMI z-score (BMI-z) was also determined. OB children were further classified as severely OB with a BMI-z >4.[10,11]

All subjects had physical examination by the same physician. The physical examinations and hepatic, renal, and thyroid function confirmed by measurement of aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and thyroid stimulating hormone (TSH), respectively, were all normal. No subjects had congenital heart disease, or valvular or primary myocardial disease.

WC measurement was performed with the subject standing, using a non-elastic flexible tape measure at the level of the umbilicus and recorded to 0.1cm. Each subject underwent a 2-dimensional, M-mode and Doppler echocardiogram. The echocardiograms were obtained as previously described with subjects in a supine position. LA diameter indexed for height and LA area measured by 2D echo were both recorded, the first having the advantage of having a cut point for abnormal, the second being somewhat more accurate.

Blood specimens were obtained after a 12-14 hour fast for determination of plasma glucose, insulin, and proinsulin concentrations. A standard oral glucose tolerance test (OGTT) was administered with 1.75g anhydrous glucose per kg body weight or maximum 75g given after the baseline blood specimens for glucose were obtained. Repeat samples for glucose were taken at 120 minutes post carbohydrate load. Impaired glucose tolerance (IGT) and type 2 diabetes mellitus, were defined according to the American Diabetes Association criteria.

Insulin resistance was assessed by two different approaches using the homeostasis model assessment (HOMA-IR) and proinsulin levels. Proinsulin levels were measured as an index of insulin resistance. Studies of non-diabetic subjects suggest proinsulin elevation is more strongly associated with CVD than is hyperinsulinemia. The Study was approved by the ethics committee of Iraqi ministry of health. Each parent gave written informed consent after explanation of the study and before initiation of research studies and subjects provided assent.

Statistical analysis

Data are presented as mean ±SD. The nature of the quantitative variables distribution was assessed through the Shapiro-Wilks test. When comparing more than three groups and when the data were normally distributed, one-way analysis of variance was used (Student-Newman-Keuls post hoc test). When the homogeneity of the variances could not be proved, we used the non-parametric Kruskal Wallis test instead of analysis of variance.

Chi squared test was used to compare proportions in RXC Crosstabs. When more than 20% of the cells had expected frequencies <5, and for 2X2 tables, Fisher's exact test was used. To measure the strength of association between two variables, a Spearman rank correlation coefficient was used. Multiple linear regression analysis was used to determine which variables were associated with LA area. Binarylogistic regression, forward (likelihood ratio) method, was used to predict the belonging to LA area fourth quartile in function of systolic blood pressure and diastolic blood pressure, and to calculate the odds ratio. In all cases, P values<0.05 were deemed statistically significant. Computations were done using the SPSS statistical software package SPSS 18.

RESULTS

Ninety students (46 females), were evaluated, among whom (30) were overweight, (42) OB, and (18) non-OB. Forty six (53.6%), 20 (23.8%), 10 (11.9%), and 10 (23.8%) had Tanner stage I, II, III, and IV maturation, respectively; mean z-BMI was not different among the four tanner stage groups. Subject characteristics are depicted in Table 1. Insulin resistance increased significantly between Tanner stage I and II, and remained stable through Tanner stage II, III, and IV.

Both OW and OB subjects had HOMA-IR, significantly higher than the non-OB group (P<0.0001). The proinsulin levels were approximately 3-foldhigher in the OB group than in the non-OB group and mean levels were also significantly different between groups (P<0.0001). Hypertension was present in 25% of the OB group but was not present in the other 2 groups (P = 0.002). Mean levels of clinical and laboratory findings of the different groups are shown in Table 1.

LA diameter indexed for height was used because it has the advantage of having a cut point for abnormal. Out of the group with LA diameter >2 SD only 20% of the children had hypertension. LA diameter enlargement was present in 37.8%, 41.7%, and 6.3% of the OB, OW, and non-OB group respectively (P<0.05).

Table 1: Clinical, metabolic and echocardiographic patient characteristics in non-obese (non-OB) overweight (OW), and obese (OB) children.

	Non obese	Overweight	Obese	P
	N= 18	N=30	N=42	
BMI (kg/m^2)	15.83 (1.39)	21.04 (2.40)	27.07 (4.19)	<0.0001 *(a)
z-score BMI	-0.52 (0.93)	1.43 (0.22)	2.17 (0.27)	<0.0001 *(a)
WC (cm)	52.72 (3.67)	70.59(10.30)	83.63(13.09)	<0.0001(a)
HOMA-IR	1.20 (0.65)	1.81 (0.78)	2.76 (1.89)	<0.0001 *(c)
Proinsulin (pMol/L)	11.68 (13.71)	14.59 (7.87)	29.35 (29.05)	<0.0001 * (a)
Hypertension (>P°95th)	0%	0 %	25%	0.002 **(b)
Systolic BP (mm Hg)	97.50 (5.16)	102.68 (8.87)	109.38 (13.83)	<0.0001*(b)
Diastolic BP (mm Hg)	61.56 (5.69)	64.46 (8.09)	71.63 (10.52)	<0.001 (b)
LA area (cm^2)	7.96 (1.79)	9.29 (2.72)	11.29 (2.89)	<0.001 (b)
Left ventricular mass (g)	60.25 (17.36)	74.70 (25.98)	98.83 (40.45)	<0.001 (b)
Left ventricular mass/Height (g/ m$^{2.7}$)	27.50 (8.11)	31.52 (8.73)	35.72 (8.87)	0.006 *(d)
E/A wave	1.84 (0.31)	1.93 (0.38)	1.77 (0.31)	0.140 (e)

Table 2: Clinical, metabolic, and echo Doppler results.

HOMA-IR Quartiles	I (n = 21) 0.41-1.08	II (n = 22) 1.08-1.67	III (n = 21) 1.67-2.72	IV (n = 20) 2.72-7.07	P
Age (years)	8.14 (1.53)	8.77 (2.11)	9.19 (2.16)	11.15 (2.08)	<0.001(a)
BMI (kg/ m^2)	19.68 (4.25)	20.98 (4.71)	22.71 (4.12)	28.66 (4.19)	<0.001(a)
z-score BMI	0.91 (1.39)	1.15 (1.25)	1.57 (0.73)	2.06 (0.35)	<0.001(a)
WC (cm)	64.60 (9.57)	69.73 (12.44)	74.07 (10.87)	91.39 (12.12)	<0.001(b)
Proinsulin (pMol/L)	12.13 (12.12)	11.23 (6.08)	20.45 (16.98)	41.90 (33.05)	<0.001(a)
Systolic BP (mmHg)	101.43 (9.89)	101.82 (7.80)	100.95 (6.64)	116.00 (15.27)	<0.001(a)
Diastolic BP (mmHg)	63.57 (8.68)	65.45 (8.58)	64.52 (6.10)	76.25 (10.62)	<0.001(a)
Left ventricular mass (g)	64.07 (19.30)	77.30 (34.11)	80.51 (24.13)	113.60 (43.63)	<0.001(a)
Left ventricular mass/height (g/m$^{2.7}$)	31.42 (7.77)	30.97 (10.29)	33.85 (8.17)	34.98 (10.14)	0.435(c)
LA area (cm^2)	8.64 (2.20)	9.23 (2.61)	10.09 (2.98)	12.12 (2.90)	0.001(a)

Analysis by analysis of variance (mean (SD), (a) quartiles I II III differ from quartile IV, (b) quartile I differs from III and IV; quartile II differs from IV; quartile III differs from IV, (c) No significant differences found between any of the groups

Ninety subjects were divided into four groups by HOMA-IR quartiles for comparison by analysis of variance, with age, BMI-z, and other variables entered as covariates. As insulin resistance increased, BMI, WC, BP, and LA area increased (P<0.001). With increasing insulin resistance, the mean proinsulin also increased, being approximately four times higher in quartile IV than in quartile I. Left ventricular mass did not increase significantly with increasing insulin-resistance (Table 2).

There is significant univariate association between LA area and: height (r=0.52, P <0.001), age (r=0.45, P <0.001). Tanner stage (r=0.45, P <0.001), BMI (r=0.66, P <0.001), WC (r=0.70, P <0.001), systolic BP (r=0.52, P<0.001), diastolic BP (r=0.53, P <0.001), proinsulin (r=0.36, P <0.001), HOMA-IR (r=0.36, P <0.001) and left ventricular mass (r=0.42, P <0.001).

In the binary logistic regression, belonging or not to LA area fourth quartile as the dependent variable and systolic and diastolic blood pressure as covariates, when we introduced variables in a forward method, diastolic blood pressure was the unique significant variable, odds ratio =1.080 (P=0.008), 95% CI: (1.020-1.144), constant-6.417, without including systolic blood pressure. When we introduced only systolic blood pressure as a covariate, there was a significant association between systolic blood pressure and LA area IV quatile, odds ratio 1.056 (P=0.013) 95% CI: (1.011-1.102) constant -6.864.

In the multivariate regression analysis independent variables were entered in a stepwise fashion: initially, gender (P = 0.006), and tanner stage (P=0.011) were significant independent correlates of LA area after adjusting for age, gender, and Tanner stage. Subsequently, incorporation of WC showed that WC was an independent correlate of LA area (P<0.001), applying a larger model that tests the adjustment factors, including the significant factor WC from the prior model, BP, left ventricular mass, and one measure of insulin resistance

(HOMA-IR) showed that WC was the only significant independent variable (P<0.001) with an R^2=0.532; that it means 53.2% of the total variance is explained by the model. This suggests that LA size is closely associated with abdominal obesity (Table 3).

Table 3: Linear regression analysis (stepwise method) for explanation of LA area (n=84).

Variable	Regression coefficient (95% confidence interval)	P value	R^2
Sex	1.693 (0.632-2.755)	0.002	0.348
Tanner stage	1.494 (0.992-1.996)	<0.001	
WC	0.148 (0.117-0.179)	<0.001	0.532

DISCUSSION

Cardiovascular risk factors are seen in children and adolescents with the highest degree of insulin-resistance, suggesting that adult CVD might develop in these young people. LA enlargement may be important because it is related to adverse CVD in adults, including atrial fibrillation, stroke, and congestive heart failure. LA enlargement has been noted in adolescents with essential hypertension.[12] There are no large studies that have linked LA enlargement to OB and OW in children with and without hypertension, and it is, therefore, unknown if the association with hypertension is due to the blood pressure elevation itself or to the association of hypertension with obesity and the metabolic syndrome. Furthermore most studies have focused on adolescents whereas in our study more than 50% of the subjects were pre-pubertal (Tanner stage 1, mean age 9.29±2.25). We found abdominal obesity and insulin-resistance to be strong and independent predictors of LA enlargement in children. The prevalence of LA diameter indexed for height >2 SD was higher in the group of OB and OW children than in the non-OB group. In the non-OB group 1 of the 16 subjects had LA enlargement, which is not significantly different than the expected rate of 2.3% if the non-OB group were a true sample of the population. Among the clinical factors analyzed, WC was most strongly associated with LA area. WC has proved to be a useful tool for measuring abdominal obesity related to CVD. A more central deposition of fat (android pattern) has been shown to be associated with elevation of triglycerides, decreased HDL cholesterol, increased systolic BP, and increased left ventricular mass in adolescents.[13] These relationships persisted after controlling for other variables such as age, race, gender, and height. The Bogalusa Heart Study also showed that abdominal fat distribution in children aged 5-17 years was associated with an adverse concentration of triglycerides, LDL and HDL cholesterol, and insulin (27, 28, 29). Our study showed that LA area was significantly associated with WC after adjusting variables. Thus, an accumulation of evidence suggests that abdominal obesity may be the greatest risk factor for LA area changes.

It has been noted that LA enlargement is associated with hypertension and obesity in adolescents. In our study, however, we found that 80% of the students with LA enlargement had normal BP. Although systolic and diastolic BPs were significantly associated in the univariate analysis, neither remained significant when controlling for the overall higher age, gender, Tanner stage, and other variables. This interpretation is limited by the dichotomous classification of BP status into "hypertensive" or "normotensive". BP is a continuous variable that is positively correlated with cardiovascular risk across the entire BP range. Unlike in adults, in whom the definition and severity of hypertension are defined by straightforward threshold values based on the risk of outcomes, children require a separate threshold of BP normality at each stage of physical maturity (Tanner stages) because of the normal age and height-related rise in BP throughout childhood.[14] Nonetheless, LA measures were similar in hypertensive and non-hypertensive participants. Therefore, abnormal LA dimensions are related to insulin-resistance and central OB even in the absence of traditionally defined hypertension.

Left ventricular mass was significantly associated with LA area and this association disappeared after accounting for the confounding effects of other variables. LA area was only related with central OB. Longitudinal studies will be needed to validate our cross-sectional observations.

Because HOMA-IR might be insufficiently precise for estimating insulin resistance, we also measured proinsulin levels. Elevated fasting concentrations of intact proinsulin have been reported to be markers of insulin resistance.[15] Consistent with the present study, increased proinsulin concentration with increasing insulin resistance in girls with OB suggested that such elevations reflect increased ß-cell output proportional to the elevated insulin concentrations in this group, rather than a defect in proinsulin processing or secretion. Proinsulin concentration was approximately 3 times higher in OB children compared to the non-OB group. With increasing insulin-resistance the mean proinsulin level increased, being approximately 4 times higher in quartile IV vs. quartile I. The mechanism of how insulin-resistance is associated with CVD is still unclear. It may be related to endothelial dysfunction, which has been associated with insulin-resistance, free fatty acids, nitric oxide, and inflammatory cytokines.[16]

LA enlargement is present in childhood and is related to abdominla OB and insulin-resistance, independently of BP, suggesting that children with central OB are at increased risk for CVD.[17] To detect early CVD and to identify patients who would be appropriate for secondary prevention programs, OB children should be evaluated by an echo Doppler study even if their BP is in the normal range. Future longitudinal research is needed to

determine the long-term consequences of this cardiovascular abnormality.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Trevisan M, Liu J, Bahsas FB, Menotti A. Syndrome X and mortality: a population-based study: Risk Factor and Life Expectancy Research Group. Am J Epidemiol. 1998;148:958-66.
2. Ebbeling C, Dorota B Pawlak D, Ludwig D. Childhood obesity: public-health crisis, common sense cure. Lancet. 2002;360:473-82.
3. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death: the Framingham Heart Study. Circulation. 1995;92:835-41.
4. Benjamin EJ, D Ágostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death: the Framingham Heart Study. Circulation. 1995;92:835-41.
5. Gottdiener JS, Reda DJ, Williams DW, Materson BJ. Left atrial size in hypertensive men: influence of obesity, race and age. Am. Coll. Cardiol. 1997;29:651-8.
6. Daniels SR, Loggie JMH, Khoury P, Kimball TR. Left ventricular geometry and severe left ventricular hypertrophy in children and adolescents with essential hypertension. Circulation. 1998;97:1907-11.
7. Marshall WA Tanner JM: Variations in patterns of pubertal changes in boys. Arch Dis Child. 1979;45:13-23.
8. Must A, Dallal GE, Dietz WH. Reference data for obesity: 85th and 95th percentiles of body mass index (wt/ht2) and triceps skinfold thickness. Clin Nutr. 1991;53:839-46.
9. Falkner B, Daniels SR, Horan MJ, Loggie JMH, Prineas RJ, Rosner B, et al. Update on the Task Force Report (1987) on High Blood Pressure in Children and Adolescents: a Working Group Report from the National High Blood Pressure Education Program. Pediatrics. 1996;98:649-58.
10. Sahn DJ, DeMaria A, Kisslo J, Weyman A, and the Committee on M-Mode Standardization of the American Society of Echocardiography. Recommendations regarding quantitation in M-Mode echocardiography: results of a survey of echocardiographic measurements. Circulation. 1978;58:1072-83.
11. de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH. Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and of their capacity to predict cardiovascular risk. J Am Coll Cardiol. 1995;25:1056-62.
12. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the ADA Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997;20:1183-1197.
13. Young- Hyman D, Schlundt D, Herman L, De Luca F, Counts D. Evaluation of the insulin resistance syndrome in 5 to 10-year-old overweight/obese African American children. Diabetes Care. 2001;24:1359-2364.
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment; insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. Diabetolog. 1985;28:412-9.
15. Lindahl B, Dinesen B, Eliasson M, Roder M, Hallmans G, Stegmayr B. High proinsulin levels precede first-ever stroke in a nondiabetic population. Stroke. 2000;31:2936-41.
16. Lindahl B, Dinesen B, Eliasson M, Roder M, Jansson JH, Huhtasaari F, Hallmans G. High proinsulin concentration precedes myocardial infarction in a nondiabetic population. Metabolism. 1999;48:1197-202.
17. Yudkin JS, Denver AE, Mohamed-Ali V, Ramaiya KL, Nagi DK, Goubet S, et al. The relationship of concentrations of insulin and proinsulin-like molecules with coronary heart disease prevalence and incidence. A study of two ethnic groups. Diabetes Care. 1997;20:1093-1100.

Cite this article as: Deepak S, Dakshayani KR. Morphometric features of asterion in adult human skulls. Int J Res Med Sci 2018;6:1862-6.