Prediction of Insulin Resistance using Modified Single Point Insulin Sensitivity Estimator and Determination of Atherogenic Index of Plasmain Asthmatic Patients

Rogia Ali Adam[1], Adel Nusr Morsi[2*]

[1, 2]Department of Chemical Pathology, Faculty of Medical Laboratory Sciences, University of Khartoum-Sudan

University of Khartoum, Faculty of Medical Laboratory Sciences, Chemical Pathology Department
Master Degree by Courses Program, Scientific Research Paper

Abstract: _Background: Chronic obstructive pulmonary disease including asthma is the fourth leading cause of death world over. About 235 million people currently suffering from asthma, which is abnormal inflammatory response of the lungs characterized by airflow limitation, airflow obstruction and bronchospasm. Metabolic syndrome is asyndrome that involves at least one of the three disorders of dyslipidemia, insulin résistance, obesity and/or hypertension. There are close links between asthma and metabolic syndrome. Asthma and dyslipidemia are epidemiological linked, similar relationships are also observed with other marker of the metabolic syndrome such as increase prevalence of coronary heart disease, stroke and diabetes. The purpose of this study is to describe the link between metabolic syndrome and asthma using easy and affordable tools for the prediction of disease complication._ _Methodology: A total of 95 individuals, 50 (53%) were asthmatic patients and 45 (47%) were healthy controls were enrolled in this prospective case control study during the period from January to April, 2017.Blood specimens were collected from each individual in heparin anticoagulated container after fasting period of 12 hours, separated within 2 hours stored at 4^oC and analyzed within 2 days. Estimation of total cholesterol, TG, LDL-C, and HDL-C were performedusing (Cobas c311 chemistry analyzer). Calculation of atherogenic index and calculation for insulin resistance was done using SPISE equation._ _Results: The mean of atherogenic index of plasma (AIP) for subjects and control groups were 0.45 ±0.18 and.0.17 ±0.11 respectively(P value 0.000[**]) The mean of insulin resistance (IR) for the patients and controls groups were 6.3 ±0.5 and 7.2 ±0.4 respectively (P value0.000[**])._ _Conclusion: Our study showed that Asthmatic patients have a higher rate of developing cardiovascular disease and insulin resistance than normal subjects._

Keywords: Asthma; Insulin resistance; Atherogenic index of plasma; Lipid profile

1. Introduction

Asthma is a chronic inflammatory airway disorder; it is marked by airway hyper responsiveness with recurrent episodes of wheezing, coughing, tightness of the chest, and shortness of breath.

Typically, these episodes are associated with airflow obstruction that may be reversed.[1]spontaneously or with treatment. Asthma affects approximately 300 million people around the world. [1]Experts believe asthma results from various host factors, environmental factors, or a combination. Host factors include gender, obesity, and genetics.[1]

A strong link between asthma and metabolic syndrome has been found. This relationship has been shown by various researchers.[2]Metabolic syndrome is made up of various components such as elevated triglycerides, reduced glucose tolerance or diabetes mellitus. Markers of metabolic syndrome such as insulin resistance have been associated with reduced lung function and asthma. Resistance on lung function and inflammation is not fully understood.[3]

The metabolic syndrome with insulin resistance may characterize subsets of asthmatics more than is recognized, the relationship between obesity, insulin resistance, and asthma has been clearly established; however, the mechanisms by which they influence the pathogenesis of asthma is unclear.[4]Hyperglycemia could represent a physiological response to stress associated with asthma attacks.

Excess stress hormone could ultimately induce insulin resistance. It has been hypothesized that insulin resistance may play a role in the development of asthma and allergy.[2]

There is evidence that insulin modulates the inflammatory component of asthmatic responses.[5]

The relationship between asthma and type 2 diabetes is complex and requires further investigation, small study which investigated insensitivity to insulin in asthmatic patients.

The Single point insulin sensitivity estimator SPISE was introduced as a promising tool for estimating insulin resistance. [6]The advantage of this ratio is the universal availability of measurement of circulating lipids in preclinical settings, such as in general practices. Thus, it is an affordable tool to estimate insulin resistance and does not include insulin.[6] The novel formula for SPISE was computed as follows: SPISE = 600 × HDL-C0.185/(TG0.2 × BMI1.338), with fasting HDL-C (mg/dL), fasting TG concentrations (mg/dL), and BMI (kg/m2). A cutoff value of 6.61 corresponds to an M-value smaller than 4.7 mg/kg/min (aROC, M: 0.797). SPISE showed a significantly better aROC than the TG/HDL-C ratio[6]

Asthma is also associated with long term disability.[7, 8]

It has been reported that people with asthma have an increased risk of cardiovascular diseases and metabolic disorders due to direct involvement of common inflammatory mediators. Cardiovascular diseases are a serious concern in chronic inflammatory diseases.[9]COPD included asthma is associated with significantly increased cardiovascular morbidity and mortality. [10]

As atherosclerosis starts early in life, progresses slowly and asymptomatically with aging, eventually resulting in atherosclerotic cardiovascular disease, adverse vascular events and death. [11, 12]

Various algorithms for predicting coronary atherosclerosis have been established, most of which are based on large epidemiologic and cohort studies. Atherogenic index in recent years has started to gain importance as an indicator of atherosclerosis.[13, 14]Atherogenic index has been suggested to be less susceptible to disease activity variation during large periods of time. This makes it more attractive to be used in cardiovascular diseases risk prediction in this group of patients as compared with lipids concentrations.[15]

2. Materials and Methods

A prospective case control study was carried out at Khartoum state during the period of January to April 2017, a total of 95 subject were fully informed about the study and their informed consents were taken50 of them were known asthmatics of5 different age, sex and period of disease and 45 of them were health subject selected randomly as control.

Diabetic, hypertensive, obese, chronic heart disease patients and smokers were excluded from this study. Fasting venous blood was collected from each participant, centrifuged and the plasma was separated for analysis, Fasting lipids profile (total cholesterol, LDL-C, HDL-C, and triglycerides) were determined by enzymatic method using full automated instrument (Cobas c311 chemistry analyzer). Insulin resistance was calculated using modified single point insulin sensitivity estimator (SPISE): -

$$SPISE = 600 \times HDL\text{-}C^{0.185}/ (TG^{0.2} \times BMI^{1.338})$$, With fasting HDL-C in (mg/dL), fasting TGconcentrationsin (mg/dL), and BMI (kg/m2). A cutoff value of 6.61 corresponds to an M-value smaller than 4.7 mg $\ast$ kg^{-1} $\ast$cm^{-1}.

atherogenic index of the plasma was calculated as follow:

$$AIP = Log\ TG / HDL\text{-}C$$

TG in mg/dl, HDL-C in mg/dl

Statistical Analysis: Comparison of various parameters were performed by "t" test, correlation between two variables were performed by Pearson's correlation co-efficient "r". Data were analyzed using SPSS(version 22), significance was defined by P value <0.05.

3. Results

A total of 95 individuals were enrolled in this study, 50 (53%) were asthmatic patients and 45 (47%) were healthy controls. The level of cholesterol was significantly higher in subjects than control group with mean 167mg/dl±28 and 152 mg/dl ±12 respectively (P value 0.001**).

The level of LDL was significantly higher in subjects than control group with mean 101 mg/dl ± 30 and 73mg/dl ±10 respectively (P value0.000**).

The level of HDL was significantly lower in subjects than control group with mean 42 mg/dl ± 12 and 70mg/dl ± 5 respectively (P value 0.000**).

The level of triglyceride was significantly higher in subject than control group with mean 121 mg/dl ± 43 and 104 mg/dl ±22 respectively (P value0.020*).

The mean of insulin resistance (IR) for the subjects and control group were 6.3 ±0.5 and 7.2 ±0.4 respectively (P value0.000**).

The mean of atherogenic index of plasma (AIP) for subjects and control groups were 0.45 ±0.18 and.0.17 ±0.11 respectively (P value0.000**).

Difference of insulin resistance and atherogenicindex of plasma between asthmatic patients and control groups (p-value 0.000, 0.000) respectively.

Table 1: The mean, SD and significance of the difference between means of the patients and control parameters

Variables	Subject means	Control means	P. value
T.C in mg/dl	167 ± 28	152 ± 12	0.001**
LDL in mg/dl	101 ± 30	73 ± 10	0.000**
HDLin mg/dl	42 ± 15	70 ± 5	0.000**
TG in mg/dl	121 ± 43	104 ± 22	0.020*
IR	6.3 ± 0.5	7.2 ± 0.4	0.000**
AIP	0.45 ± 0.18	0.17 ± 0.11	0.000**

**: significant at 0.05 level of probability, ns: no significant difference.

There was insignificant correlation between age and insulin resistance (r= 0.151, P = 0.145), but there was a significant negative correlation between insulin resistance and duration of the disease (r =-0.297, P=0.036).

The correlation of atherogenc index of plasma with age insignificant negative correlation (r =-0.170, P = 0.099), there was insignificant positive correlation between duration of the disease and atherogenic index of plasm (r = 0.248, P = 0.082).

Table 2: Correlation of lipid profile, IR and AIP with age and duration of disease:

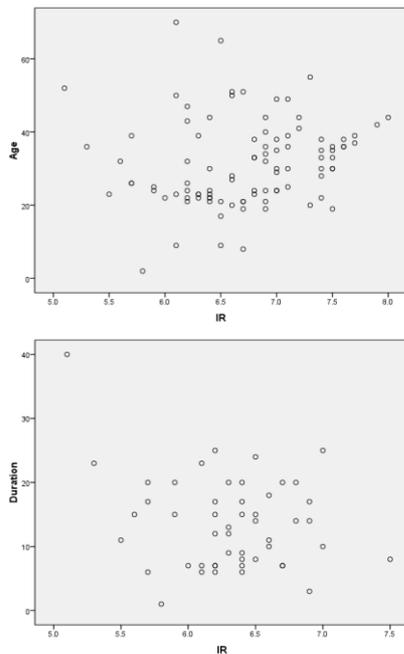| Variables	Coefficient	Age	Duration
T.C in mg/dl	R	0.041	0.178
	P	0.695^{ns}	0.217^{ns}
LDL in mg/dl	R	-0.015	0.411
	P	0.883^{ns}	0.003**
TG in mg/dl	R	-0.138	0.067
	P	0.181^{ns}	0.644^{ns}
HDL in mg/dl	R	0.189	-0.295
	P	0.066^{ns}	0.037*
IR	R	0.151	-0.297
	P	0.145^{ns}	0.036*
AIP	R	-0.170	0.248
	P	0.099^{ns}	0.082^{ns}

Figure 1: Correlation of insulin resistance with age and duration of asthma

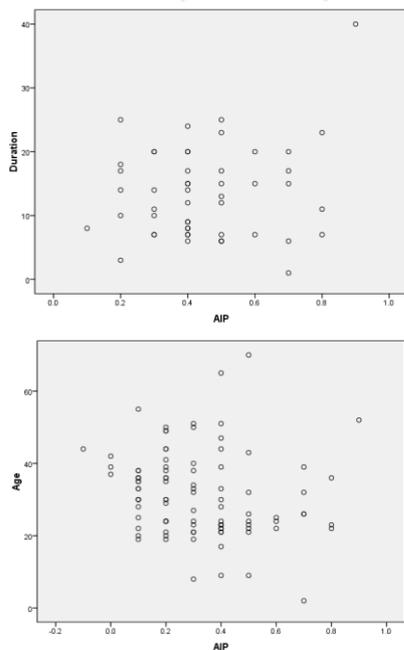(R= -0.297/P.value= 0.036)
(R= 0.151/P.value= 0.145)

Figure 2: Correlation of atherogenic index of plasma with age and duration of the disease
(R= 0.248/P.value= 0.082)
(R= -0.170/P.value= 0.099)

4. Discussion

A bidirectional relationship exists between asthma and metabolic syndrome. a comprehensive literature review was done and founded that any alteration in lipid metabolism increases cardiovascular risk, and insulin resistance among asthmatic patients. This study was primarily designed to estimate insulin sensitivity and atherogenic index in asthmatic Sudanese individuals in an attempt to predict the effects of asthma disease on the carbohydrate and lipid metabolism.

This study showed that the asthmatic patients had abnormal lipid profiles when compared to the control group, the TC, LDL-C and TGs were all significantly higher in asthmatic patients than control group (p value < 0.05) these results was agreement with Michoel, B(2009), ErimGlucan et al(2009) and Ho Joo Yoon et al (2016)[16, 17, 18]

In our study, HDL-C was significantly lower in the patients (P value < 0.001).similar finding was reported by Banayiotis K (2014)[19]who found that asthma is associated with low serum HDL-C, whereasYavuz has shown that HDL-C level increases in children with asthma who use inhaled teroids(1996).[20]

The results differences might be due to differences in the characteristics of the patient groups In the present study, mean age and treatment. These factors may have affected the results obtained in this study.

Our study was shown increase in atherogenic index of plasma (AIP) as reported by Michael O'Riordan (2014)[21] who conclude that patient current asthma had a significantly increase risk of stroke, and incident cardiovascular disease. Asthma maybe an independent risk factor for incident stroke but not coronary heart disease in middle age adult this study conducted by J G Schanentet al(2005).[22]

Dyslipidemia is a risk factor for cardiovascular disease by affecting immune and inflammatory reactions, which lead to CVD event via pathways unrelated to traditional risk factors, as it concluded by Ho Joo Yoon et al and Sarah L.et al(2016, 2008)[18, 23]

Any alteration in the levels of lipids in body makes the individuals more prone to develop cardiovascular diseases.
In our results we found a significant difference in insulin resistance (IR) between patients and control groups, such result was found by found by Rosinha Morishiteet al.(2016)[24], and Jamal S et al (2004) [25]

Asthma was associated with insulin resistant through a systemic inflammatory response, while the mechanism of the effect was not yet clear.

5. Conclusion

Asthmatic patients showed to have higher rate of developing cardiovascular disease and insulin resistance than normal subjects.

References

[1] Shari J. Lynn, MSN, RN, and Kathryn Kushto-Reese, MS, RN. Understanding asthmapathophysiology, diagnosis, and management.

[2] EkpeEkpe Lawson. Asthma and Metabolic Syndrome–Correlation and Review of Literature.*American Journal of Laboratory Medicine.*Vol. 1, No. 1, 2016, pp. 1-4. doi: 10.11648/j.ajlm.20160101.11.

[3] Suchita S, Sutapa S, Prakash Y S, Kumar M, Ahmad T, Sing VP et al. Asthma and metabolic syndrome I n search of theinterfaces. *International Archives of Medicine* 2012, 5(20).

[4] Angela L. Linderholm, PhDa, Jennifer M. Bratt, PhDa, Gertrud U. Schuster, PhDb, c, Amir A. Zeki, MD, MASa, Nicholas J. Kenyon, MD, MASa, *.Novel TherapeuticStrategies for Adult Obese Asthmatics.

[5] Mohamed F Lutfi, MSc, PhD*, Mohamed Y Sukkar, PhD **. The hyperglycemic effect of bronchial asthma.

[6] Katharina Paulmichl, 1, 13Mensud Hatunic, 2 Kurt Höjlund, 3 Aleksandra Jotic, 4 Michael Krebs, 5*Asimina Mitrakou, 6 Francesca Porcellati, 7 Andrea Tura, 8 Peter Bergsten, 9 Anders Forslund, 10Hannes Manell, 9, 11 Kurt Widhalm, 1 Daniel Weghuber, 1, 13* and Christian-Heinz Anderwald, 1, 5, 8, 12 on behalf of the RISC Investigators† and the Beta-JUDO Investigators†. Modification and Validation of the Triglyceride-to–HDL Cholesterol Ratio as a Surrogate of Insulin sensitivity in White Juveniles and Adultswithout Diabetes Mellitus:The Single Point Insulin Sensitivity Estimator (SPISE).

[7] Global Strategy for Asthma Management and Prevention.Global initiative for Asthma (GINA) 2012. Available from http:// www.ginasthma.org.

[8] Program NAEAP. Expert Panel Report 3 (EPR-3).Guidelinesfor the diagnosis and management of Asthma-summary Report2007.*J Allergy ClinImmunol*.2007, 120: 594-38.

[9] AkifAcay a, *, MemnuneSenaUlu b, Ahmet Ahsen a, GulayOzkececi c, KasimDemir d, UfukOzuguz e, SerefYuksel b, GurselAcarturk d.

[10] K Begum1, MK Begum2, ZH Sarker3 MRK Dewan4, MJH Siddique5. Lipid Profile Status of Chronic Obstructive _Pulmonary Disease in Hospitalized Patients.

[11] Ikeda U. Inflammation and coronary artery disease. CurrVascPharmacol 2003;1:65–70.

[12] Sogut E, Avci E, Ustuner F, Arikan E. The evaluation of (TG/ HDL-C) ratio as a serum atherogenic index. Turk KlinikBiyokimyaDergisi 2006;4(1):1–8.

[13] AkifAcay a, *, MemnuneSenaUlu b, Ahmet Ahsen a, GulayOzkececi c, KasimDemir d, UfukOzuguz e, SerefYuksel b, GurselAcarturkd.Atherogenic index as a predictor of atherosclerosis in subjects with familial Mediterranean fever.

[14] Angela L. Linderholm, PhDa, Jennifer M. Bratt, PhDa, Gertrud U. Schuster, PhDb, c, Amir A. Zeki, MD, MASa, Nicholas J. Kenyon, MD, MASa, *.Novel TherapeuticStrategies for Adult Obese Asthmatics.

[15] Mohamed F Lutfi, MSc, PhD*, Mohamed Y Sukkar, PhD **. The hyperglycemic effect of bronchial asthma.

[16] Fessler, M.B., Massing, M.W., Spruell, B., Jaramillo, R., Draper, D.W., Madenspacher, J.H., Arbes, S.J., Calatroni, A. and Zeldin, D.C., 2009. Novel relationship of serum cholesterol with asthma and wheeze in the United States. *Journal of Allergy and Clinical Immunology*, *124*(5), pp.967-974.

[17] ErimGulcan, IsmetBulut, AysunToker&Gulcan. Evaluation of Glucose Tolerance Status in Patients with Asthma Bronchiale.

[18] Ho Joo Yoon, Gun Woo Koo, Suk-il, Hye-ran Yoon, Dong Won Park, Tai Sun Park, Ji-yong Moon, Sang-heon Kim MEDICINE, Tae Hyung Kim, Jang Won Sohn, Dong Ho Shin.1068 - ASSOCIATION OF SERUM TRIGLYCERIDE AND CHOLESTEROL WITH ASTHMA IN ADULTS.

[19] Panayiotis K. Yiallourosa, dSavva C.Savvac, OuraniaKolokotronia, b.eKleanthiDimafAikateriniZervafPanayiotis Kouisa Jean BousquetgNicosMiddletonb. Asthma : The Role Of Low High – Density – Lipoprotein Cholesterol in Childhood and Adolescence.

[20] Yavuz, Ö., Türktaş, I. and Çevik, C., 1996. The effectMESA Analysis Uncovers Link Between Persistent Asthma and Cardiovascular Disease

[21] Michael O'Riordan.of high-dose inhaled budesonide on lipid profile in asthmatic patients. *General Pharmacology: The Vascular System*, *27*(1), pp.89-90.

[22] Schanen, J.G., Iribarren, C., Shahar, E., Punjabi, N.M., Rich, S.S., Sorlie, P.D. and Folsom, A.R., 2005. Asthma and incident cardiovascular disease: theAtherosclerosis Risk in Communities Study. *Thorax*, *60*(8), pp.633-638.

[23] SarahL.Appleton, Richard E. Ruffin, RobertJ.Adams.Asthma is associated with cardiovascular disease in a representative population sample.

[24] Morishita, R., Franco, M.D.C., Suano-Souza, F.I., Solé, D., Puccini, R.F. and Strufaldi, M.W.L., 2016. Body mass index, adipokines and insulin resistance in asthmatic children and adolescents. *Journal of Asthma*, *53*(5), pp.478-484.

[25] simple methodRana JS [1], Mittleman MA, SheikhJ, HuFB, MansonJE, ColditzGA, SpeizerFE, BarrRG, CamargoCA Jr..Chronic Obstructive pulmonary Disease, Asthma and Risk of type 2Diabetes in women.