Metabolic syndrome (MetS) in children suffered from Otitis media with effusion

Soad Yehia [1], Enas Tawfek[2], Mahasen Ibrahim[a] and Iman Mohamed.

Otorhinolaryngology[1], Pediatric [2], Community Medicine[3] and Clinical Pathology Departments Faculty of Medicine for Girls, Al Azhar University.
soaad201231@gmail.com

Abstract: Objective: To determine the risk of metabolic syndrome(MetS) development in children with recurrent otitis media with effusion as determined by adiponectin, interleukin10(IL10),body mass index(BMI), serum total cholesterol(TC) and triglyceride(TG). Design: A prospective nonrandomized case control study. Setting: Al-Zahraa hospital, Al-Azhar University. Subjects: the study group comprised 30 children aged 4-10 years who received bilateral ventilation tube insertion as surgical operation for the treatment of otitis media with effusion. The control group comprised 20 children with no history of otitis media normal children age and sex matched. Main outcome measures: we determined the difference between the studied and control groups in BMI, serum TC, TG, adeponectin and IL10 concentrations and the difference between both groups. Results: BMI mean values were higher among cases (18.1±2.6 for male &18.1±4.4 for female) than the control subjects (14.8±1.2 for male &15.23±1.3 for females). The mean value of interleukin 10(IL10) was highly significant (P＜0.05) among patients (12.31±2.59 for male&13.78±4.44 for female) than control group (6.43±1.83 in male&6.12±1.8 for female), while the serum level of adiponectin mean value were significantly lower (P＜0.05) among patients (2.63±0.6 in male&2.26±0.49 in female) than control group (12.72±2.82 for male and11.57±3.03 for female). Conclusion: there are a relation between occurrence of obesity and metabolic syndrome in children suffered from recurrent otitis media with effusion.
[Soad Yehia, Enas Tawfek, Mahasen Ibrahim and Iman Mohamed. **Metabolic syndrome (MetS) in children suffered from Otitis media with effusion**. *Nat Sci* 2013;11(1):52-57]. (ISSN: 1545-0740). http://www.sciencepub.net. 8

Keywords: metabolic syndrome in children, otitis media, adiponectin, interleukin10

1. Introduction

The risk of MetS increases with increasing age, affecting less than 10% of people in their 20s and 40% of people in their 60s. However, some research shows that about one in eight school children has three or more components of MetS. Other researchers have also identified an association between childhood MetS and adult cardiovascular disease decades later (**28**).

Metabolic syndrome (MetS) is a complex disorder defined by a cluster of interconnected factors that increase the risk of cardiovascular atherosclerotic diseases and diabetes mellitus type 2. Currently, several different definitions of MetS exist, causing substantial confusion as to whether they identify the same individuals or represent a surrogate of risk factors. Recently, a number of other factors besides those traditionally used to define MetS that are also linked to the syndrome have been identified (**28**).

The term 'metabolic syndrome' (MetS) has been used to describe the clustering of insulin resistance, glucose intolerance, dyslipidemia, hypertension, and obesity which is a common basis for development of cardiovascular disease. Consensus criteria for the metabolic syndrome have yet to be defined in the pediatric age range **(1)**.

Adiponectin an anti-inflammatory protein has been demonstrated to be insulin sensitizing and an anti-atherogenic factor including coronary heart disease, and is considered a key of MetS (**2**).Serum adiponectin level are known to decrease with the increase in number of MetS components (**3**). Interleukin-10 (IL-10) has anti-inflammatory properties and protective effect against atherogenesis (**4**).

After that it was suggested that IL-10 may be involved in the inflammatory network of Mets in relation to adiponectin (**5**). However, the risk of metabolic syndrome was nearly 50% in severely obese young children, and this risk increased with every 0.5-unit increment in BMI, when expressed as z score (**6**). In addition, it has become apparent that elevated fasting insulin levels and increased BMI during childhood are the strongest predictors of metabolic syndrome in adulthood (**7**). Although Eustachian tube dysfunction and bacterial infection have been shown to cause otitis media with effusion (OME), other etiologies are possible. One of the most common medical conditions in children is obesity, which can have effects throughout the body (**8**). Despite the development of antibiotics and surgical techniques the frequency of otitis media with effusion has been increasing. Unresolved acute inflammatory responses or defective immune-regulation of middle ear inflammation can promote chronic inflammatory

processes and stimulate the chronic condition of OME (**9**).

Obesity is a widespread and growing problem in the world with significant medical, psychosocial and economic consequences. The prevalence of obesity has increased substantially over the last several decades and indications are such that this trend will continue not only in developed but also in developing countries (**10**). In many studies they found a link between ear infections and childhood obesity. Eardrum abnormalities increased the more the child weighted, which might explain the association. The researchers also suggested that parents may be confusing their children's fussiness due to the ear infection with hunger and, therefore, over feeding them (**11**).The incidence of childhood overweight and obesity has also been increasing but the association between childhood MetS and OME has not yet been determined (**9**).

2. Subject and Methods

Objective of this study to determine the risk prevalence of development of MetS in children with OME undergoing to ventilation tube insertion surgery, we correlate the BMI, TG and TC with adiponectin and IL-10 in children with OME and compare the result with age and sex-matched control normal children.

So we studied 30 children (13 females and 17 males) of primary school age attending Pediatric and Otorhinolaryngolgy departments, Alzahraa hospital between June and November-2011 with manifestations of otitis media effusion (OME) diagnosis based on otoscopic findings and tympanometry showing a flat curve and patients underwent surgical myringotomy and insertion of Grommet's tube for middle ear aeration. The control group consisted of 30 pediatric (15 F and 15 M) non obese siblings or patients with no history of otitis media with effusion during the same period.

Children in the control group underwent otoscopic examinations, impedance audiometry to confirm the absence of pathologic conditions in the middle ear and Eustachian tube.

Exclusion criteria: Any secondary obesity syndromes, any medical therapy and any chronic or acute illness, children with head or neck deformities or systemic diseases or those suspected of having congenital or acquired immune deficiencies were excluded.

All patients underwent preoperative physical examination include an evaluation of age, gender, blood pressure measurement, weight(kg), height(cm) and body mass index(BMI) which calculated as the body weight in kilograms divided by the square of the height in meters. Obesity was defined according to the percentile of BMI adjusted for age and sex as follows: $<85^{th}$ percentile= average healthy weight, $>85^{th}$-90^{th} = at risk of being over-weight, $>90^{th}$ -95^{th} percentile = over weight and $>95^{th}$ percentile = obese (**12**).

Laboratory investigations:

Sample collection: 3 ml of venous blood were collected under complete aseptic precautions, the collected blood was put in a plan test tube allowed to clot and centrifuged for serum separation. The separated sera are used for estimation of: serum cholesterol and triglycerides which were done on Cobas C311 auto analyzer. The rest of the samples were collected in epindorph after careful labeling and stored at – 20^{o}C till the time of assay of adiponectin and IL-10.Adeponectin and IL-10 were assayed using ELISA technique by AviBion-AniBiotech Oy-Orgenium laboratories Business Unit. Total cholesterol, serum triglycerides, adiponectin and IL-10 mere measured in all patients and controls.

A triglyceride value exceeding the 95^{th} percentile and a HDL cholesterol value below the 5^{th} percentile for age and sex were considered abnormalities in the fasting levels of lipids (**13**). Systolic and diastolic blood pressures were taken twice with the patient in a sitting position. Elevated systolic or diastolic blood pressure was defined as a value exceeding the 95^{th} percentile for age and sex (**14**).

3. Results:

Our study including 30 patients suffering from OME underwent ventilation tube insertion operation with the mean age and standard deviation (6.44±1.52years) and 20 control non obese subjects not suffering from OME with mean age (6.94±1.48years) with no significant difference between both groups. We divided the study group according to BMI into obese (10 children [33.3%]) and overweight (2 children 6.7%) at risk of being overweight (15 children (50%), normal weight (2 children 6.7%) and (1children underweight 3%) and compared to control group where there are significant difference according to BMI. As regards the blood pressure there is no significant difference between cases with OME and control group (Table 1).

Table (1) description of the studied groups (no=60)

Studied variables	Cases (OME) n=30		Controls (non-OME) n=30		Total	Chi- square test		
	No (%)	Mean±SD	No (%)	Mean± SD	(N=60)	value	df	Sig(2-ided)
1. Gender								
• Males	17 (56.7%)		15 (50%)		32 (53.3%)	2.05	2	0.357
• females	13 (43.3%)		15 (50%)		28 (46.7%)			(non-sing)
2. BMI		18.18±3.57		15.04±1.26		21.351	3	0.000 (sig)
*Underweight	1(3 %)		28(93.3%)		29 (49.5%)			
*average weight	2 (6.7%)		2 (6.7%)		4 (6.6%)			
*at risk of being over-weight	15 (50 %)		0		15 (25%)			
*overweight	2(6.7 %)		0		2 (3.3%)			
*obese	10 (33.3%)		0		10(16.6 %)			
3. Age group		6.44±1.52		6.94±1.48		1.317	2	0.518
• 4-<6 yrs	11(36.7%)		7 (23.3%)		18 (30%)			(non-sing)
• 6-<8 yrs	13(43.3%)		15 (50%)		28 (46.7%)			
• 8-≥10 yrs	6 (20%)		8 (26.7%)		14 (23.3%)			
4.**blood.pressure group**						2.05	2	0.357 (non-sing)
*diastolic <85	20 (66.7%)		**24 (80%)**		44 (73.3%)			
*diast.85 -<90	8 (26.7%)		**5 (16.7%)**		13 (21.7%)			
*diast. ≥90	2 (6.7%)		**1 (3.3%)**		3 (5.0%)			

The mean values of studied variables among cases, control and total sample, were the BMI mean values were higher among male and female cases (18.1± 2.6 for males &18.1± 4.4 for females) than controls (14.89± 1.20 for males &15.2± 1.26 for females), without significant difference between males and females of same sample regarding all studied variables. The study group had normal value of triglycerides in comparison to control group and significant increase in cholesterol concentrations but serum adiponectin levels were significantly lower and level of IL-10 were significantly higher in cases with OME than normal subjects (Table 2).

Table (2): Mean values of studied metabolic variables among cases and controls according to gender:

Metabolic variables	**Cases (n=30)** mean± SD		**Controls (n=30)** mean± SD		**f-test**	**Sig *P* value**
	Male	Female	Male	Female		
BODY MASS INDEX	18.10±2.6	18.18±4.46	14.89±1.20	15.23±1.36	19.783	0.000
Cholesterol mg/dl	171.47±16.02	176.40±14.53	152.71±13.55	153.00±17.96	28.585	0.000
Triglycerides mg/dl	83.93±15.67	88.33±15.87	78.94±15.19	81.92±19.12	1.984	0.164
Adiponectin mg/dl	2.63±0 .69	2.26±0.49	12.72±2.82	11.57±3.03	320.619	0.000
Interleukin 10	12.31±2.59	13.78±4.44	6.43±1.83	6.12±1.80	82.223	0.000

Significant Values < 0.05

The mean value of interleukin 10 was significantly increased among cases (12.31±2.59 in male and 13.78±4.44 in female) than control group (6.43±1.83 in male and 6.12±1.80 in female). Table (3) show the correlation of IL10 and adiponectin in studied group with BMI and cholesterol level there are significant increase of IL10 and significant decrease in correlation with Adiponectin, significantly (P <0.05) different between cases. Non-significant difference in TG in correlation with IL10 and Adiponectin.

The mean value of interleukin 10 was significantly increased among cases (12.31±2.59 in male and 13.78±4.44 in female) than control group (6.43±1.83 in male and 6.12±1.80 in female). Table (3) show the correlation of IL10 and adiponectin in studied group with BMI and cholesterol level there are significant increase of IL10 and significant decrease in correlation with Adiponectin, significantly (P <0.05) different between cases. Non-significant difference in TG in correlation with IL10 and Adiponectin.

Table (3) partial correlation coefficients of Interleukin 10 and adiponectin with studied metabolic variables

Studied variables	Interleukin 10 Spearman correlation		Adiponectin Spearman correlation	
	Value	Significance	Value	Significance
BMI percentiles	0.349	0.006	0.694	0.000
CHOLESTEROL LEVEL	0.410	0.001	-0.496	0.000
TRIGLYCERIDS	0.206	0.07 (non-sig)	-0.235	0.07 (non-sig)

Figure (1) comparison of Adiponectin and Interleukin10 mean values between cases and controls

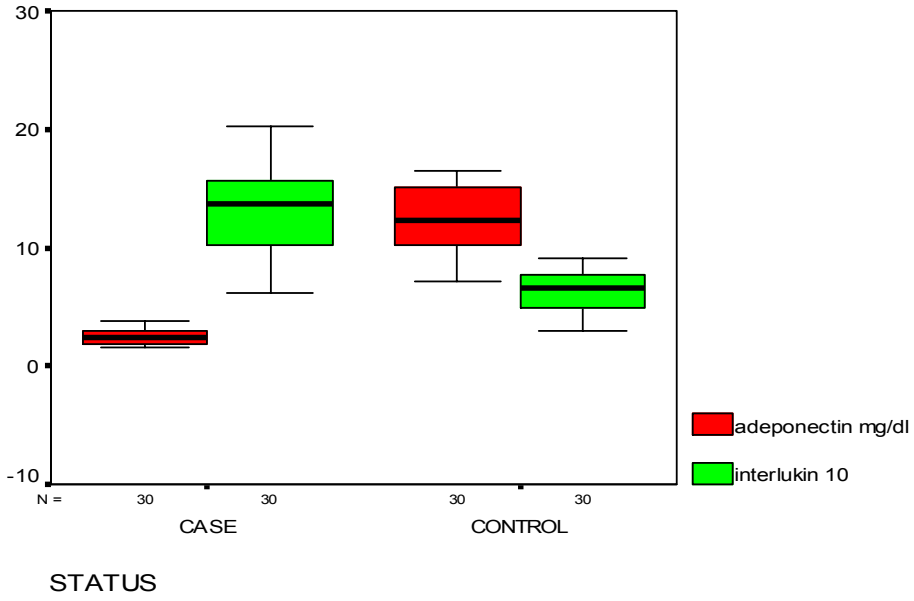

Figure (1) demonstrates that there are significant decrease in adiponectin in cases with OME than control group and significant increase of IL10 in cases than control group.

Discussion:

Otitis media with effusion is a condition in which fluid is retained in the middle ear cavity, but without otalgia, fever, and other symptoms. This condition has been shown to be caused by complex reactions involving the dysfunction of the Eustachian tubes (**9**). Among the factors shown to predispose to OME include upper respiratory tract infection, age, race, season of the year, hereditary factors and attendance in day care centre nurseries, whereas factors that do not significantly influence OME include bronchitis, cystic fibrosis, socioeconomic status, smoking by parents, and antibiotic abuse (**15**). A recent research has demonstrated that adipose tissue produces and secretes various bioactive substances , conceptualized as adipocytokines, and their dysregulation in abdominal or visceral obesity may participate in the development of obesity and Mets syndrome (**16**).The need to precisely define MetS stems from the need to detect accurately individuals at high risk for CVD and DM type2. All the components of the various MetS definitions are involved in conferring risk for CVD and DM type 2. In particular, the three components of atherogenic dyslipidemia (increased low-density lipoprotein (LDL), decreased HDL and high blood triglyceride concentrations) are individually associated with a cardiovascular risk (**27**).

The risk of adult obesity is associated with obesity during childhood and adolescence, with 50% to 75% of adult obesity shown to originate from juvenile obesity (**13**).Whether or not obesity persists into adulthood, preventing excess weight gain and obesity among children is important in obesity control and will lead to a decreased risk of chronic diseases among adults (**17**).

Using serum TC,IL10 and Adiponectin concentration as the standard, we study 30 children's who underwent ventilating tube insertion as a surgical treatment for recurrent otitis media with effusion and 30 control non obese subjects with age and sex matched.

Our study reported that BMI, serum cholesterol concentrations were significantly higher in children undergoing tympanic ventilation tube surgery for OME than in control children and that childhood obesity may be associated with the development of OME.

Serum TG and TC concentrations have been used to predict the risk of development of cardiovascular disease and MetS. Although serum TG and TC concentrations were found to be significantly higher in obese than in non-obese individuals (**18**) this is agree with our result were the Mean value of total cholesterol level and triglycerides were higher range in recurrent otitis media with effusion cases (173.93±15.24) than among controls (152.83±15.32).

Recently, it was shown that anti-inflammatory effects of adiponectin may be partially mediated by the induction of IL-10, a potent anti-inflammatory cytokine (**5**). *In vivo*, IL-10 most likely exerts its anti-inflammatory effects on the vascular system through

the inhibition of proinflammatory cytokines and chemokine production by macrophages or lymphocytes and increase incidence of OME (**19**). Our study show that interleukin 10 (IL-10) was significantly higher among patients suffered from otitis media with effusion undergoing to ventilation tube insertion (12.31±2.59 in male and 13.78±4.44 in female) than control normal subjects (6.43± 1.83 in male and 6.12±1.80 in female).

Adiponectin is an adipose-derived protein, with multivalent functions including anti-atherogenic, insulin-sensitizing, lipid-oxidation enhancing and vasodilatory activities. The serum adiponectin levels were associated with Mets more clearly and independently than the other inflammatory factors (**20**).

Therefore, it is possible that decreased plasma concentrations of adiponectin play a significant role in the development of the Mets and OME(**21**).Arita *et al.* **(22)** reported that hypoadiponectinemia is observed in adult obese subjects and that serum adiponectin levels were decreased in patients with Mets but this difference disappeared when controlling the effect of BMI.

Adiponectin mean value was much lower among our cases (2.63± 0.69 in male and 2.26±0.49 in female) than control group ((12.72± 2.82 in male and 11.57±3.03 in female). these is agreed with the study done by Esposito et al (24) who reported that circulating levels of IL-10 are elevated in obese women and that low levels of IL-10 are associated with the MetS. In our OME patients was not associated with low IL-10. Recent studies have demonstrated associations between lower serum IL-10 concentration or production and clinical events (**23**). It is possible that, after the compensatory hyper IL-10 already operative in the pediatric population, children with a reduced capacity of producing IL-10 in adult age presented a progressive decrease of IL-10 and an increased risk for developing type- 2 diabetes and cardiovascular disease.

In contrast with the data reported by Esposito et al (**24)**, in our patients with OME no correlation between adiponectin and IL-10 was found**.** Manigrasso *et al.* **(25)** described that only android obesity is associated with a concomitant reduction of IL-10 and adiponectin and concluded that different fat distribution may be responsible for the decrease levels of this cytochine; in pediatric males and females the difference in body proportions related to puberty influence fat distribution and the different fat distribution with respect to adult age may be responsible for different cytochine production and may explain the absence of correlation.

Furthermore, it is known that puberty is associated with decreased insulin sensitively and that pubertal development influences adiponectin levels and adipokines profiles (**26**); in our patient's serum adiponectin and IL-10 levels showed no differences between sexes, but the relation between IL10 and adeponectin are inversely proportion with each other.

Conclusion: In our study we concluded that there is still a need to develop uniform criteria to determine the relation between MetS and OME, so as to enable comparison between different studies and to better identify patients at risk. We suggest that diagnosis, prevention and treatment of children with OME should better focus on established risk factors as MetS.

Corresponding author
Soad Yehia
Otorhinolaryngology Department, Faculty of Medicine, Al-Azhar University
Soaad201231@gmail.com

References:

1. Tresaco B, Bueno G, Pineda I *et al.* (2005): Homeostatic model assessment (HOMA) index cut-off values to identify the metabolic syndrome in children. J Physiol. Biochem.; 61:381–388).
2. Hong SJ, Seo HS, Rha, SW, *et al.* (2006): Decrease in plasma adiponectin concentrations in patients with variant angina pectoris. Circ J.; 70: 414-8.
3. Matsukawa Y (2006): Therapy insight: Adipocytokines in metabolic syndrome related cardiovascular disease. Nat. Clin. Pract. Cardiovascular. Med.; 3: 35-42.
4. Hawrylowicz CM, O'Garra A (2005): Potential role of interleukin-10-secreting regulatory T cells in allergy and asthma. Nat Rev Immunol. 5:272-83.
5. Nishida M, Moriyama T, Sugita Y *et al.* (2007): interleukin-10 associates with adiponectin predominantly in subjects with metabolic syndrome.Circ. J.; 71:1234-8.
6. Weiss R, Dziura J, Burgert TS *et al.* (2004): Obesity and the metabolic syndrome in children and adolescents. N. Engl. J. Med.; 350:2362–2374.
7. Srinivasan SR, Myers L, and Berenson GS (2002): Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood: the Bogalusa Heart Study. Diabetes. 51:204–209.
8. Lee SK and Yeo SG (2009): Relationship between pediatric obesity and otitis media with effusion.Curr Allergy Asthma Rep Curr Allergy Asthma Rep. (9):465-472.

9. Kim JB, Park DC, Cha C et al. (2007). Relationship between Pediatric Obesity and Otitis Media with Effusion; Arch Otolaryngol Head Neck Surg. doi: (4):379-382.
10. Rossner S (2002). Obesity: the disease of the twenty-first century. Int J Obes. 26:S2-4).
11. 11-Saland JM (2007): Update on the metabolic syndrome in children. Curr. Opin. Ped.19: 183-91.
12. Cole TJ, Bellizzi M, Flegal KM *et al.* (2000): Establishing a standard definition for child overweight and obesity worldwide: international survey.BMJ. May 6; 320 (7244):1240.
13. Maffeis C, Pietrobelli A, Salvatoni A, *et al.* (2006): Obesita delbambino e dell'adolescente: Consensua su prevenzione, diagnosi e terapia. In Argomenti di Pediatria 1/06 (ed.P. Salari).Milano:Ist.Scotti Bassani; 31[pubMid].
14. National High Blood Pressure (2004): Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the diagnosis, Evaluation, and Adolescents. Pediatrics. 114:555-76.
15. Calcaterra V, De Amici M, C. Klersy, C. Torre, *et al.* (2009): Adiponectin, IL-10 and metabolic syndrome in obese children and adolescents. 80: 2.
16. Matsuzawa Y, Funahashi T, Nakamura T (2002): Molecular mechanism of vascular disease in metabolic syndrome X.J Diabetes Complications; 16:17-8.
17. Thomas R, Gideon de S, André MT, and Werner A (2006): Long-term follow-up of cardiovascular disease risk factors in children after an obesity intervention. Am. J. Clin. Nutr. 84: 490- 496).
18. Calcaterra V, Klersy C, Muratori T, *et al.* (2008): Prevalence of metabolic syndrome (MS) in children and adolescents with varying degrees of obesity.Clin. Endocrinal (Oxf); 68:868-72.
19. Tedgui A, Mallat Z (2001): Anti-inflammatory mechanisms in the vascular wall. Circ Res. 88:877-87.
20. Ajuwan KM and Spurlock ME (2005): Adiponectin inhibits LPS-induced NF-Kappa B activation and IL-6 production and increases PPARgamma2 expression in adipocytes. Am.J. Physiol. regul. Integr. Comp. Physiol. 288:R1220- R1225.
21. Ryo M, Nakamura T, Kihara S *et al.* (2004): Adiponectin as a biomarker of the metabolic syndrome. Circ. J. 68:975-81.
22. Arita Y, Kihara S, Ouchi N, *et al.* (1999): Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem. Biophys.Res.Commun.257:79-83.
23. Smith DA, Irving SD, Sheldon J *et al.* (2001): serum levels of the anti-inflammatory cytokine interleukin-10 are decreased in patients with unstable angina. Circulation. 104:746-9.
24. Esposito K, Ppntillo A, Giugliano F, *et al.* (2003): Association of low interleukin-10 levels with the metabolic syndrome in obese women. J. Clin. Endocrinal metab. 88: 1055-8.
25. Manigrasso MR, Ferroni P, Santilli F, *et al.* (2005): Association between circulating adiponectin and interleukin-10 levels in android obesity: effects of weight loss. J Clin. Endocrinal Metab.90: 5876-8.
26. Bottner A, Kratzch J, Muller G. *et al.* (2004): Gender differences of adiponectin levels develop during the progression of puberty. J. Clin. Endocrinal Metab. 89:4053-61.
27. Kassi E, Pervanidou P, Kaltsas G, *et al.* (2011): Metabolic syndrome: definitions and controversies.BMC Medicine, (9):48 doi: 10.1186/1741-7015-9 - 48.
28. Gupta A and Gupta V, (2010): Metabolic syndrome: What are the risks for humans? Bio Science Trends; 4(5):204-212.

10/13/2012