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Study of oxidative stress and endothelial dysfunction in paediatric obesity

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Abstract

Introduction: Obesity is associated with complications like Diabetes, Asthma, Hypertension and cardiovascular risks which are to be managed of health care worldwide. Increased BMI during childhood and adolescence may lead to premature death from disease and may increase the risk of CVD at adult age.

Methods: 30 obese children with an age group of 8-15 years attending paediatric department and 30 healthy age matched non obese children were taken in the study. BMI was calculated for all and biochemical markers like fasting blood glucose, Insulin resistance (HOMA-IR) were determined using commercial enzymatic kits. MDA, FRAP, and NO was determined by chemical methods.

Results: A significant increased levels of BMI, Insulin and insulin resistance (HOMA-IR), MDA and NO levels ($P<0.05$) was observed in obese children compared to non-obese but, the levels of Fasting blood sugar levels and FRAP were not statistically significant in cases compared to controls.

Conclusions: As childhood obesity can influence many risk factors like diabetes, hypertension, asthma, endothelial dysfunction which may lead to CVD risk and atherosclerosis most of the studies reported that there are possible chances to minimize these risk factors by proper medication and most of the events are even reversible. Therefore the parent should be suggested to have a proper dietary management and medication in order to avoid the progression of these risk factors in adulthood.

Keywords: Paediatric obesity, Endothelial dysfunction, Adipocytokines, Leptin, Vascular smooth muscle cells.

Introduction

Obesity has become a serious public health concern affecting significant portion of the population. It has been estimated that worldwide over 22 million children under the age of 5yrs are obese, and one in 10 children is overweight. Childhood obesity is reaching epidemic proportions and represents the most important chronic disease in this age group[(1)]. Obesity is associated with long lasting physical and mental health consequences resulting in, insulin-resistance, hypertension, and dyslipidaemia. A high BMI during childhood and adolescence has been associated with, increased risk of coronary heart disease at adult age[(2,3)].

Insulin resistance which is most commonly noticed in obesity and an important factor may lead to other metabolic disorders and cardiovascular risk complications. Insulin resistance, decreased biological response to insulin leads to chronic hyperglycaemia[(4)]. In obesity the cause of insulin resistance can be explained that excess adipose tissue metabolites may lead to release of metabolites like adipocytokines and increase release of free fatty acids, which may result in further risks like endothelial dysfunction, metabolic syndrome, dyslipidaemia, PCOS, and Type 2 diabetes[(5)].

Childhood obesity is associated with endothelial dysfunction, which mainly leads to atherosclerosis but a reversible event. Nitric oxide the major vasodilator that causes relaxation of the vascular smooth muscle having atheroprotective activity, preventing aggregation of platelet, proliferation of vascular smooth muscle cells (VSMC) and foam cell formation[(6)]. The endothelial dysfunction will happen when there is an imbalance between the vasodilator and vasoconstrictor compounds and when endothelial vascular wall as gets exposed to elevated lipid levels, insufficient nitric oxide production and increased blood pressure which are mainly observed in obese individuals. This concept needed to be cleared because the endothelial dysfunction mainly leads to atherosclerosis[(7,8)].

Obese individuals are at higher risk of oxidative stress compared to lean individuals[(9)]. There are many factors that lead to increased oxidative stress in obesity that may be due to increased adipose tissue, adipokines, insulin resistance, hyperlipidemia, hypertension which can cause oxidative stress[(10)]. Chronic Oxidative stress leads to damage of cardiovascular system and poor glycemic control indicating that these individuals are more prone to develop atherosclerosis. The oxidative stress in obesity is mainly because of a sedentary life style, decrease intake of antioxidants and vitamins in the diet[(11,12)]. Obesity in childhood is one of the important factors to take into consideration as it may lead to the adulthood early onset of CVD risk. With this background we have taken a case- control study to find out the oxidative stress and endothelial dysfunction in obese children.

Material and Methods

The present case control study was done in MNR Medical College and Hospital, Sangareddy, Telangana

during October 2015 to June 2016. The study includes total 30 obese children with an age group of 8-15 years attending paediatric OP and 30 healthy age matched non obese children were taken as a control group. An informed consent was obtained from all the participants and study protocol was approved by institutional ethical committee.

Sampling and Storage: After overnight fasting venous blood samples were collected in a plain bulb, centrifuged at 2000 rpm for 15 minutes and stored immediately at -80ºC until analysis. 1ml of blood was collected in anticoagulated bulb and plasma collected for analysis of glucose.

Biochemical analysis: Glucose levels were measured by using glucose oxidase-peroxidase technique. Insulin levels were measured by Enzyme linked immunosorbent assay (ELISA) technique and were expressed as µIU/ml. Insulin resistance was determined by the homeostasis model assessment (HOMA- IR). MDA levels were measured by TBARS method. Nitric oxide levels were measured using the cadmium reduction method. All subjects had undergone anthropometric measurements, including Height (m), weight (kg), measurements were used to calculate the body mass index (BMI = Wt / height in m2), evaluation of systolic and diastolic blood pressures.

HOMA-IR: Homeostatic model assessment (HOMA) is a method for assessing the degree of insulin sensitivity (HOMA %S) and level of beta cell function (HOMA %B) from basal (fasting) plasma glucose and insulin or C-peptide concentrations.

Statistical analysis: The statistical Package for the Social Sciences (SPSS version 11.5 for Windows) was used for statistical analysis. Results were expressed as mean ± SD. Unpaired t-test (one tailed) was used to compare the means, and a P value less than0.05 was considered to be statistically significant.

Results

Table 1: Characteristics of markers in the obese children group and control group

Parameter	Control (Mean ± SD)	Cases (Mean ± SD)	P-Value
BMI (kg/m^2)	19.12±2.12	30.15±5.16	0.001*
SBP(mm of Hg)	92.24±15.12	100.1±10.15	0.230
DBP (mm of Hg)	70.2±5.32	73.1±4.24	0.146
FBS (mg/dl)	90.22±15.52	93.15±18.21	0.216
Insulin (µIU/ml)	3.42±2.28	6.12±4.15	0.000*
HOMA-IR	2.24±1.12	5.42±2.25	0.000*
MDA (mmol/L)	2.19±0.18	5.12±1.12	0.000*
FRAP (mmol/L)	1.15±2.25	1.20±0.15	0.018
Nitric oxide (µmol/L)	55.13±4.21	66.15±4.12	0.001*

The above table showing statistically significant Insulin and insulin resistance measured as HOMA-IR, greater BMI, MDA and NO levels were significantly increased in cases compared to controls but, Fasting blood sugar levels and FRAP were not statistically significant in cases (Table 1).

Discussion

Childhood obesity gone into much interest because obesity increases all causes of mortality risks so, predicting the risk of childhood obesity is much beneficial than in adulthood obesity. The prevalence of Childhood obesity is reaching epidemic in many regions of the world and it was reported that this group is at high risk of developing type-2 diabetes[13]. In the present study, we observed that fasting blood glucose levels were not statistically elevated in obese children compared to non-obese but insulin and resistant measured as HOMA-IR was statistically significant indicating that this group is at increased risk of developing type 2 diabetes. Insulin resistance observed in obesity is one of the metabolic complications that may lead to other complications like cardiovascular risks. Excess adipose tissue observed in obesity release metabolites and adipokines, adiponectin produced by adipocytes is mainly responsible for insulin resistance[14,15]. Matsuzawa et al proposed that adipose tissue has a role in production of inflammatory factors like TNF-α, Interleukin-6 which mediates production of C-reactive protein these compounds are responsible for inflammation in obesity and they are partially related to insulin resistance[16]. Insulin resistance observed in obesity may also lead to essential hypertension because insulin has a role in renal sodium retention and insulin resistance leads to increased sympathetic nervous system activity and stimulation of vascular smooth muscle growth[17].

In our study, we observed that oxidative stress markers are significantly increased in obese children compared to non-obese and antioxidant status assessed by FRAP was decreased but no statistically significant were the same result was shown in the studies done by Keaney et al and Vincent et al[18,19]. Oxidative stress observed in obesity may be due to excess adiposity and fat distribution which leads to increased production of metabolites like adiponectin and other inflammatory products like cytokines, including TNF-α, IL-1, and IL-6. Inflammation is also one of the sources to oxidative stress and the increased production of free radicals will further enhance the production of inflammatory response were all these factors together leads to cardiovascular risk in obesity[20]. Obesity, which leads to oxidative stress have been associated with other disorders like insulin resistance, hypertension, peripheral vascular disease and ischemic heart diseases. So, it is needed to correct the OS process in obesity and

further studies are needed to find out whether antioxidant therapy can be useful in these patients to decrease the CVD risk.

Endothelial dysfunction has gained much importance because it is the main component that regulates vascular tone homeostasis, smooth muscle cell proliferation, trans-endothelial leukocyte migration, and thrombosis. In the present study, we observed significantly increased levels of Nitric oxide indicating that these people are near to develop endothelial dysfunction, which is now regarded as an early pivotal event in atherogenesis[21]. CV risk factors tend to cluster in obese children and include hypertension, high cholesterol, triglycerides, insulin resistance, a pro-inflammatory status, and disturbances in adipocytokines[22]. Nitric oxide, which is mainly used to assess the vascular activity as it is produced by endothelial cells and induces vasodilation by cGMP and also reduces cell migration, foam cell formation, platelet aggregation, macrophage adhesion and inflammation[23]. Inflammatory mediators in adipose tissue may release leptin and low concentrations of adiponectin, Leptin which regulates appetite, concentration increases with increase of body fat leads to oxidative stress in endothelial cells promote vascular calcification and smooth muscle cell proliferation which all leads to early onset of CVD.

Conclusion

Obesity is the major risk factors which lead to other complications like insulin resistance, hypertension, oxidative stress, endothelial dysfunction which ultimately may lead to early onset of CVD risk. So, obesity which was observed in children was taken into consideration because identifying these risk factors in childhood itself will help us to correct the events like oxidative stress and endothelial dysfunction that leads to atherosclerosis process in adulthood.

References

1. Kosti RI, panagiotatos DB. The epidemic of obesity in children and adolescents in the world. Cent eur J public health 2006;14(4):151-9.
2. Tirosh, I. Shai, A. Afek et al., "Adolescent BMI trajectory and risk of diabetes versus coronary disease," The New England Journal of Medicine, vol. 364, no. 14, pp. 1315–1325, 2011.
3. P. W. Franks, R. L. Hanson, W. C. Knowler, M. L. Sievers, P. H. Bennett, and H. C. Looker, "Childhood obesity, other cardiovascular risk factors, and premature death," The New England Journal of Medicine, vol. 362, no. 6, pp. 485–493, 2010.
4. Weiss R & Kaufman FR. Metabolic complications of childhood obesity: identifying and mitigating the risk. Diabetes Care 2008 31 (Supplement 2) S310–S316.
5. Matsuzawa Y. White adipose tissue and cardiovascular disease. Best Practice and Research. Clinical Endocrinology and Metabolism 2005:19:637–647.
6. G. K. Hansson, "Inflammation, atherosclerosis, and coronary artery disease," The New England Journal of Medicine, vol. 352, no. 16, pp. 1685–1626, 2005.
7. P. M. Vanhoutte, "Endothelial dysfunction—the first step toward coronary arteriosclerosis," Circulation Journal, vol. 73(4):595–601, 2009.
8. Luc Bruyndonckx, Vicky Y. Hoymans, Amaryllis H. Van Craenenbroeck, Dirk K. Vissers, Christiaan J. Vrints, José Ramet, and Viviane M. Conraads. Assessment of Endothelial Dysfunction in Childhood Obesity and Clinical Use. Journal of Oxidative Medicine and Cellular Longevity, 2013.
9. Keaney JF Jr, Larson MG, Vasan RS, Wilson PW, Lipinska I, Corey D, Massaro JM, Sutherland P, Vita JA, Benjamin EJ. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. Arterioscler Thromb Vasc Biol 23:434–439,2003.
10. Wu B, Fukuo K, Suzuki K, Yoshino G, Kazumi T. Relationships of systemic oxidative stress to body fat distribution, adipokines and inflammatory markers in healthy middle-aged women. Endocr J 56: 773–782, 2009.
11. Vincent HK, Innes KE, Vincent KR. Oxidative stress and potential interventions to reduce oxidative stress in overweight and obesity. Diabetes Obes Metab 9:813–839,2007.
12. Fernando Holguin1 and Anne Fitzpatrick. Obesity, asthma, and oxidative stress. J ApplPhysiol 108:754 – 759,2010.
13. Dietz WH. Overweight in childhood and adolescence. New England Journal of Medicine 2004:350:855–857.
14. Despres JP. Is visceral obesity the cause of the metabolic syndrome? Annals of Medicine 2006:38:52–63.
15. Gil-Campos M, Canete RR & Gil A. Adiponectin, the missing link in insulin resistance and obesity. Clinical Nutrition 2004:23:963–974.
16. Matsuzawa Y. White adipose tissue and cardiovascular disease. Best Practice and Research. Clinical Endocrinology and Metabolism. 2005 19 637–647.
17. Julia Steinberger and Stephen R. Daniels. Obesity, Insulin Resistance, Diabetes and Cardiovascular Risk in Children. Circulation. 2003;107:1448-1453.
18. Keaney JF Jr, Larson MG, Vasan RS, Wilson PW, Lipinska I, Corey D, Massaro JM, Sutherland P, Vita JA, Benjamin EJ. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. Arterioscler Thromb Vasc Biol 23: 434–439, 2003.
19. Vincent HK, Bourguignon CM, Taylor AG. Relationship of the dietary phytochemical index to weight gain, oxidative stress and inflammation in overweight young adults. J Hum Nutr Diet. In press.
20. Jane V. Higdon, Balz Frei. Obesity and Oxidative Stress A Direct Link to CVD? Arterioscler Thromb Vasc Biol. 365-367, 2003.
21. E. Falaschetti, A. D. Hingorani, A. Jones et al., "Adiposity and cardiovascular risk factors in a large contemporary population of pre-pubertal children," European Heart Journal, vol. 31, no. 24, pp. 3063–3072, 2010.
22. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med. 1999;340:115–26,
23. A. Enrique Caballero. Endothelial Dysfunction in Obesity and Insulin Resistance: A Road to Diabetes and Heart Disease. Obesity research vol. 11:2003.