

Metabolic Syndrome in HIV Infected Children Receiving Free HAART at a Centre of Excellence in HIV Care in Northern India

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Received date: February 15, 2020, **Accepted date:** March 11, 2020

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Abstract

Objective: Children and adolescents infected with HIV through mother to child transmission are exposed to HIV related complications and anti-retroviral treatment adverse effects since conception and are more vulnerable to develop the metabolic complications. This study was carried out to assess the prevalence of metabolic syndrome and associated risk factors in HIV infected children aged 6-15 years using International Diabetes Federation (IDF) criteria.

Methods: A total of 45 HIV infected children in the age group of 6-15 years were enrolled from the Anti-Retroviral Treatment Clinic of a tertiary care hospital in North India. Demographic details, clinical profile, immunological data and treatment details were obtained from clinic records. Anthropometric measurements recorded were weight, height, BMI, waist circumference.

Biochemical parameters measured were fasting lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C), blood sugar, serum insulin level and CD4+ cell count.

Results: More than half of the participants were undernourished (57.7% had weight for age <-2z score). Most common metabolic abnormality noted was low HDL cholesterol levels (53.3%). 6.6% patients were noted to have insulin resistance. Significant association of protease inhibitor-based ART regimes with dyslipidemia was observed (p value=0.02). Metabolic syndrome could not be established in any participant as per the International Diabetes Federation (IDF) criteria since all had waist circumference less than the cut off range.

Conclusion: Although full blown metabolic syndrome could not be established in the study population, significant metabolic derangements mainly dyslipidemia were noted in them even with concurrent malnutrition. Close monitoring and follow up for metabolic derangements and subsequent development of metabolic syndrome should be actively looked for in these children. eradication.

Keywords: Anti-retroviral treatment, Dyslipidemia, Insulin resistance, Metabolic syndrome, Waist circumference

Introduction

Implementation of Highly Active Antiretroviral Therapy (HAART) for patients with HIV has led to the dramatic reduction in AIDS related mortality in both children and adults [1]. With their longer life expectancy and improved quality of life, effects of ageing and other environmental factors are predisposing them to non-AIDS related morbidities, with cardiovascular diseases emerging as an

important threat.

Recent studies have shown the occurrence of cardiovascular events at a younger age in HIV infected patients suggesting an accelerated ageing of the cardiovascular system [2]. Per se disease related factors like persistent immune dysregulation, ongoing inflammation due to HIV infection and adverse effects of prolonged anti-retroviral treatment (lipodystrophy,

dyslipidemia, insulin resistance) along with conventional risk factors like diet, inadequate physical activity, put them at higher risk as compared to general population. Pediatric HIV population being special in terms of early acquisition of HIV infection and prolonged exposure to anti-retroviral drugs associated with the highest metabolic toxicity, makes them more vulnerable and different from those infected during adulthood.

Metabolic Syndrome (MetS), an independent risk factor for cardiovascular diseases although is a well recognized complication in HIV infected adults yet does not have a consensus definition for pediatric patients. In 2007, the consensus definition given by International Diabetes Federation (IDF) for pediatric MetS using age specific criteria (Table 1), is currently the reference standard [3]. With very few published literatures on the prevalence of metabolic abnormalities in HIV infected children using recently accepted IDF criteria, this study was done with the objective to assess the prevalence of MetS and associated risk factors in HIV infected children aged 6-15 years using IDF criteria. This may help in early identification and intervention that can halt the progression of these risk factors into serious illnesses in adulthood.

Methods

This cross sectional study was conducted in the Anti-Retroviral Treatment clinic of Department of Pediatrics and Department of Biochemistry, Lok Nayak Hospital, Maulana Azad Medical College, a tertiary care referral centre in New Delhi, over a period of 12 months (February 2017-January 2018), after approval from the Institutional Ethics Committee.

All children in the age group of 6-15 years with established HIV infection attending the ART clinic irrespective of their ART status were enrolled after taking an informed written consent/assent from the patients or their caregivers as appropriate. Children having comorbidities affecting serum lipid levels like nephrotic syndrome, hypothyroidism and children on steroid therapy for any reason were excluded from the study.

A sample size of 30 was calculated based on the study by Espiau et al. [4], wherein the prevalence of MetS in a cohort of HIV-infected children and adolescents in Spain was found to be 1.97%. Demographic details, clinical profile, immunological data and details of anti-retroviral treatment were obtained from the Clinic records and noted on predesigned proforma. Weight, height and Body Mass Index (BMI) were recorded during the clinic visit and were expressed as age and sex adjusted Z scores, based on IAP standard growth curves [5]. Waist circumference was analysed using standards for Indian Children published by Khadilkar et al. in 2014

[6]. Puberty was assessed using Tanner's scale of sexual maturity rating. Blood pressure was recorded using non mercury analogue sphygmomanometer in sitting position and was compared with standard readings published by Raj et al. in 2010 for Indian children [7].

Presence of lipodystrophy was noted on the basis of physical examination by an expert clinician and was categorized as (i) Lipohypertrophy: presence of an enlarged dorsocervical fat pad, circumferential expansion of the neck, breast enlargement and abdominal visceral fat accumulation; (ii) Lipoatrophy: subcutaneous fat loss in face, limbs or buttocks; and (iii) Mixed: characterized by both of the above [8].

Biochemical parameters measured were fasting lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C), blood sugar, serum insulin level and CD4+ cell count. These samples were taken after minimum 8 hours of fasting. Lipid profile and blood sugar levels were measured on the same day while separated serum was stored at -80° Celsius for measurement of serum insulin levels till analysis. Cut off for these parameters were as per the IDF criteria [3,9]. Insulin resistance was defined as a calculated homeostatic model assessment of insulin resistance (HOMA- IR; fasting insulin [mU/L]×fasting glucose [mg/dL]/405) with cut off of >2.5 in pre pubertal children (Tanner stage 1) or >4.0 in pubertal children (Tanner stage ≥ 2) [10]. Metabolic syndrome was defined using the IDF consensus definition. However, the cut off for waist circumference was taken at 70th percentile according to the waist circumference standards for Indian Children as described by Khadilkar et al in 2014 which were used in the study, in contrast to 90th percentile as per IDF definition.

Statistical analysis was done using SPSS software version 23. Quantitative data were expressed as mean ± SD. The association with metabolic syndrome was analysed using Student t test and Mann Whitney U test for quantitative and Chi square or Fisher exact test for qualitative variables. Frequency and percentages were used wherever applicable.

Results

A total of 45 children in the age group of 6-15 years with established HIV infection were recruited during the study period. Male preponderance was seen with male to female ratio of 1.25:1. Out of 45 participants, 33 (73.3%) were ≥ 10 years of age. Median age of boys was 12 years and that of girls was 11.5 years. Majority of the children i.e. 42.2% belonged to lower middle-class socioeconomic status as per Modified Kuppuswamy Scale. 28.8% belonged to middle class, 22.2% to lower class and 6.6% to upper middle-class SES.

Anthropometric parameters revealed that out of 45 children, 26 (57.7%) had weight for age less than -2z scores, 21 (46.6%) had height for age less than -2z scores and 11 (24.4%) had BMI less than -2z scores for age and sex. Mean BMI observed was 15.60 ± 2.46 kg/m².

Mean CD4 cell count of these 45 children was 700 cells/μL with 77.8% children having CD4 count of >500 cells/μL. 22.2% had CD4 count in the range of 200-500 cells/μL. None had <200 cells/μL counts suggesting that majority had good CD4 count at the time of recruitment in the study. Out of 45 children, 36 were on ART at the time of enrollment with 30 out of them on treatment for >1-year duration. Mean duration for ART was 4.73 ± 3.24 years. It was noted that out of 36 children on ART, 25 (69.4%) children, were > 10 years of age while 11 (31.4%) were <10 years of age. Out of 36 children on ART, 9 were on protease inhibitor-based regimen with mean duration of receiving PIs being 31 months.

Metabolic profile of enrolled 45 children was analyzed in the two age groups of < 10 years and ≥ 10 years in order to correlate with the IDF consensus definition which has

been defined for three age groups i.e. 6 to <10 years, 10 years to <16 years and ≥ 6 years (Table 1). The details of these parameters are shown in table 2. It was observed that only 4 (8.8%) children had lipodystrophy with 2 children each with lipohypertrophy and lipoatrophy. None had mixed variety. All the recruited children had waist circumference less than 70th percentile and normal blood pressure records. 27.2%, 3% and 6% children in the age group of ≥10 years had deranged serum insulin, fasting blood sugar and HOMA-IR respectively whereas 8.3% children <10 years of age had these derangements. However, these results were found to be statistically insignificant.

None of the children fulfilled the criteria of MetS as per IDF criteria as all had waist circumference below the cut off value. However, assessment of risk factors revealed significant association of PI based ART regimes and deranged lipid profile. No significant difference was noted in deranged lipid profile with CD4 cell counts. Table 3 outlines the risk factors associated with metabolic syndrome and their relationship with deranged lipid profile.

Age group (years)	Obesity (WC)	Triglycerides	HDL-C	Blood Pressure	Glucose (mmol/L) or known T2DM
6 to <10 years	90 th percentile	Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity.			
10 to <16 Metabolic Syndrome	≥ 90 th percentile or adult cut off if lower	>1.7 mmol/L (>150 mg/dL)	<1.03 mmol/L (<40 mg/dL)	Systolic >130/ diastolic >85 mmHg	>5.6 mmol/L (100 mg/dL) (if >5.6mmol/L[or known T2DM] recommend an OGTT)
16+ Metabolic Syndrome	Existing IDF criteria for adults, i.e: Central obesity (defined as waist circumference ≥ 94 cm for Euro pid men and ≥ 80 cm for Euro pid women, with ethnicity specific values for other groups) plus any 2 of the following: 1.Raised triglycerides: ≥ 150 mg/dL. 2. Reduced HDL-C: ≤ 40mg/dL in males & ≤ 50mg/dL in females, or specific treatment for lipid abnormalities. 3. Raised BP: systolic=130 or diastolic=85 mmHg, or treatment of previously diagnosed hypertension. 4. Fasting plasma glucose (FPG) ≥ 100 mg/dL or previously. type 2 diabetes.				

Table 1: The IDF consensus definition of metabolic syndrome in children and adolescents.

Parameter	<10 years (n=12)	≥ 10 years (n=33)
Lipodystrophy		
Liphypertrophy	0	2
Lipoatrophy	1	1
Mixed	0	0
Lipid profile: HDL Cholesterol		
< 40 mg/dL	5 (41.6%)	19 (57.5%)
Triglycerides		
≥ 150 mg/dL	2 (16.6%)	6 (18.2%)
Total cholesterol		
≥ 190 mg/dL	3 (25%)	5 (15.1%)
LDL cholesterol		
≥ 130 mg/dL	1 (8.3%)	1 (3.0%)
Waist Circumference more than 70 th percentile	None	None
S. insulin level >10 μIU/ml	1 (8.33%)	9 (27.27%)
Fasting Blood Glucose		
≥ 100 mg/dL	1 (8.33%)	1 (3.03%)
HOMA-IR		
Above cut off	1 (8.33%)	2 (6.06%)
* >2.5 in pre pubertal children (Tanner stage 1) or >4.0 in pubertal children (Tanner stage ≥ 2)		

Table 2: Metabolic parameters of enrolled participants.

Risk factor	Deranged Lipid Profile	Normal Lipid Profile	P value
ART Duration			
<1 year (n=6)	3	3	0.5
≥ 1 year (n =30)	15	15	
Type of ART			
PIs based regimen (n=9)	8 (88.9%)	1 (11.1%)	0.2
Non-PIs based regimen (n=27)	12 (44.4%)	15 (55.6%)	
Lipodystrophy (n=4)	4	0	
CD4 cells count/μL			
<500 (n=10)	7 (70%)	3 (30%)	> 0.5
≥ 500 (n=35)	22 (62.8%)	13 (37.2%)	

Table 3: Risk factor assessment for metabolic syndrome in enrolled population.

Discussion

With wider availability and accessibility to HAART, there is a paradigm shift in approach to HIV infected patients. The focus is being shifted from infectious complications to long term metabolic abnormalities with cardiovascular diseases amongst the leading one. MetS being an independent risk factor for cardiovascular disease is of interest so that early detection can help in prevention of future complications. Children and adolescents infected with HIV by mother-to-child transmission who are exposed to the adverse effects of HIV, related complications, and adverse reactions of treatment since conception are crucial target population. To our knowledge there is no published literature on MetS in Indian children with HIV infection using IDF (International Diabetes Federation) criteria which is currently the most widely accepted. Primary objective of this study was to assess the proportion of HIV infected children aged 6 to 15 years with MetS using IDF criteria and secondary objective was to study the risk factors for MetS seen in HIV infection.

A total of 45 children in the age group of 6 to 15 years were recruited from the ART clinic of Lok Nayak Hospital, New Delhi, which is a Centre of Excellence (COE) for HIV care established by NACO and caters to a large number of HIV infected population of North India. The mean age of enrolled participants was 11.01 ± 2.38 years. Out of these, 36 children were on ART with mean duration of ART being 4.73 ± 3.24 years.

The prevalence of metabolic syndrome in adults varies from 18.3% to 25.9% depending on the setting and diagnostic criteria used [11,12]. No Indian study on pediatric MetS is available for comparison. Espiau M et al. (2016) have found the prevalence of MetS in a Spanish cohort of HIV infected children to be 1.97% as per IDF criteria which is also low as compared to adult studies [4]. In our study cohort, we could not establish the diagnosis of MetS in any of the participants as all had waist circumference below the cut off range for abdominal obesity which is a sine qua non feature of IDF consensus definition. Failure to establish MetS may be due to small sample size as well as the baseline malnutrition which may be attributed to lower socioeconomic status, social and financial instability and lack of access to nutritious diet in addition to frequent illnesses secondary to immunodeficiency due to HIV infection. Similar findings have been observed in a study by Padmapriyadarsini et al. done in India where almost half of the cohort was malnourished and yet showed metabolic abnormalities [13].

Amongst the metabolic derangements, dyslipidemia was present in significant number of patients (Table 2). The most common abnormality noted in our study was low level of HDL-C which is consistent with various previous studies [4,14]. In our study, all ART naïve children had deranged lipid profile whereas 61.1% on ART had dyslipidemia with low HDL-C being the commonest in both the groups. This implicates the role of HIV infection itself in causation of dyslipidemia via multiple intrinsic mechanisms. Recent study by Mandal et al. had different figures where 25% ART naïve pediatric patients had deranged lipid profile as compared to 38.3% of HIV patients who were on ART with most common derangements being hypercholesterolemia in the former and hypertriglyceridemia in latter [15].

Greater number of patients having deranged lipid profile in the age group of ≥ 10 years in our study emphasizes the impact of longer duration of illness as well as longer exposure to ART rather than obesity and dietary factors as majority of our cases are malnourished. Although our results did not reach the statistical significance possibly due to small sample size, positive correlation of dyslipidemia with increasing duration of ART has been found in various studies [4,16]. Comparison between PI

based regimen (n=9) and non-PI based regimen (n=27) revealed significantly deranged lipid profile in former (88.9% vs 44.4%) with p value of 0.02. This finding reciprocates with earlier studies implicating protease inhibitors as the predominant cause of dyslipidemia [17].

In this study, all children with lipodystrophy (n=4) had deranged lipid profile and 50% had hyperinsulinemia. Although only 8.8% participants had lipodystrophy which could be explained by the use of non-stavudine based regimens as per the NACO national program guidelines, the presence of dyslipidemia in all of them supports the observation from other studies which demonstrates co-existence of dyslipidemia with lipodystrophy [18-20].

We could not find any significant association between low CD4 cell count and metabolic derangements in the participants which is similar to the findings by Papi et al. [21]. In contrast, Arpadi et al. have shown a significant association of lower CD4 cell count with increasing insulin resistance, whereas we could not establish any such association [22]. However, the incidence of abnormal HOMA-IR was found to be double the incidence of impaired fasting glucose levels in children ≥ 10 years of age, which may indicate the early derangement in HOMA IR as compared to the conventional fasting glucose levels. These results are similar as observed by Espiau et al., suggesting the role of including HOMA-IR in routine assessment of these children for early identification of metabolic complications [4].

Few studies from India have identified the metabolic derangements in HIV infected children on stavudine based regimes. However, no study from India has evaluated the waist circumference along with blood lipid parameters. This is the novel study trying to identify full blown MetS HAART other than stavudine. However, main limitation of the study is small sample size and lack of a control group which limited the statistical analysis of various parameters. Considering the diversity of Indian population in terms of culture, income groups and demographic origin, larger sample size with enrolment from multiple centers would be more helpful.

To conclude, although full blown MetS as defined by International Diabetes Federation for children could not be identified in the study population, we did observe significant metabolic derangements in almost half of the participants although none of them were overweight. The plausibility of concurrent malnutrition halting the evolution of full blown MetS may suggest that IDF criteria may not strictly be applicable to Indian children with HIV infection and necessitates the urgent need to identify other parameters which may help us to define a new appropriate diagnostic criteria for this specific population. Further studies with larger sample size are required to determine

the risk factors implicated in pediatric MetS so that early identification can lead to early intervention and better quality of life.

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