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Research Article

Comparative Analysis of Plasma Lipids and Apolipoproteins in Children with Down Syndrome and Implications for Cardiovascular Risk

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Abstract
Children with Down syndrome (DS) often exhibit dyslipidaemia, contributing to increased cardiovascular disease (CVD) risk. This study aimed to compare plasma lipid profiles and apolipoprotein levels between children with DS and non-DS controls to understand their cardiovascular implications. A case-control study was conducted with 69 children (31 with DS, 38 without DS), aged 1-15 years, at the Paediatric Endocrinology Unit of University College Hospital, Ibadan. We used enzymatic spectrophotometry to measure lipid parameters such as total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), and ELISA to measure apolipoproteins (ApoA1 and ApoB). Data analysis was performed using SPSS version 20, with significance set at $p < 0.05$. Children with DS exhibited significantly higher triglyceride levels (183 mg/dL vs. 171 mg/dL, $p = 0.028$) and HDL-C levels (42.3 mg/dL vs. 31 mg/dL, $p < 0.001$) compared to controls. LDL-C levels were significantly lower in DS children (76.6 mg/dL vs. 93.7 mg/dL, $p = 0.036$). No significant differences were found in total cholesterol, ApoA1, ApoB, or the ApoB/ApoA1 ratio between the groups. Children with Down syndrome (DS) have unique lipid profiles, with elevated triglycerides and HDL-C but lower LDL-C, potentially impacting long-term cardiovascular risk. Regular monitoring of lipid profiles, particularly triglycerides, in children with DS should be part of standard clinical care.

Key Words: *Cardiovascular risk, Apolipoproteins, Lipid metabolism, Dyslipidaemia, Metabolic disorders*.

INTRODUCTION

Lipid metabolism emerges as a critical factor, with altered levels of cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides contributing significantly to cardiovascular risk. Down syndrome (DS), resulting from trisomy 21, is a prevalent genetic condition associated with various physical and developmental challenges. Recently, there has been a surge in interest regarding the metabolic and cardiovascular implications of DS, particularly in relation to lipid metabolism. Individuals with DS frequently exhibit lipid profile alterations, leading to a heightened risk of cardiovascular diseases (CVD).

The genetic basis of lipid metabolism and its impact on DS has gained increased attention. Lipidomics studies suggest that specific lipids, including sphingolipids and ceramides, may play a role in the metabolic disruptions observed in DS, thereby emphasising the importance of early detection and management of lipid disorders to lower cardiovascular risks in this population (Després & Lemieux, 2006). Children with DS are particularly susceptible to metabolic issues such as obesity, insulin resistance, and dyslipidaemia, which increase their likelihood of early-onset CVD (Krzesińska *et al*., 2022).

Comparative studies indicate that individuals with DS generally have less favourable lipid profiles than those without DS. These individuals often display lower levels of HDL and elevated triglycerides, both of which are correlated with higher atherosclerotic risk. Additionally, the high levels of LDL observed in DS individuals further exacerbate cardiovascular risk (Flore *et al*., 2008). These lipid abnormalities often begin to appear during childhood or adolescence, highlighting the importance of early screening and timely interventions to mitigate the risk of future CVD (Krzesińska *et al*., 2022). Investigating lipid metabolism and its broader implications for cardiovascular health in DS offers potential insights for developing preventative strategies for CVD in this population (Yin *et al*., 2019).

Apolipoproteins are also significant in assessing cardiovascular risk, particularly apolipoprotein A-I (ApoA-I) and apolipoprotein B (ApoB), which are components of HDL and LDL, respectively. The ApoB/ApoA-I ratio is increasingly recognised as a predictor of atherogenic risk, with a higher ratio suggesting an increased likelihood of developing atherosclerosis. While research on apolipoproteins in DS children is ongoing, early evidence indicates that these individuals may exhibit altered levels of apolipoproteins, which could amplify their susceptibility to cardiovascular events (Després & Lemieux, 2006).

Despite the metabolic challenges faced by those with DS, some studies report a surprisingly lower incidence of

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atherosclerosis, possibly due to protective factors such as reduced resting blood pressure (Buonuomo *et al*., 2020). However, with life expectancy in DS individuals now significantly extended, they are more likely to encounter chronic conditions, including CVD (Després & Lemieux, 2006). As the lifespan of individuals with DS continues to rise, it becomes increasingly important to understand and address the long-term cardiovascular risks associated with dyslipidaemia in this population.

Research has demonstrated dyslipidaemia patterns in this group, such as increased LDL, low HDL, and elevated triglycerides, all of which enhance the risk of atherosclerosis and other cardiovascular diseases, underscoring the need for a deeper understanding of these alterations on long-term health outcomes in DS (Krzesińska *et al*., 2022; Buonuomo *et al*., 2020). Given the gaps in current knowledge, it is vital to explore lipid profiles and cardiovascular risk factors in children with DS, as most research has focused on adults. Early identification of dyslipidaemia, particularly when combined with obesity and insulin resistance, may facilitate timely interventions that help prevent the onset of CVD in later life. Furthermore, examining correlations between lipid profiles, apolipoproteins, and anthropometric measures, such as body mass index (BMI), in DS populations can enhance understanding of the underlying mechanisms behind their elevated cardiovascular risk (Krzesińska *et al*., 2022).

This study aims to contribute to this growing field of research by comparing the plasma lipid profiles and apolipoprotein levels in children with DS to those without DS. Through this comparative analysis, it is envisaged that the findings of this study may shed light on the risk of metabolic disturbances in DS and provide a foundation for developing effective screening and management strategies in this population.

MATERIALS AND METHODS

Study Design: This study utilized a case-control design. Children diagnosed with Down syndrome represented the cases, while children without Down syndrome served as the control group. This design allows for a comparison of the lipid and apolipoprotein profiles between the two groups to assess the potential metabolic differences that could contribute to cardiovascular risk.

Study Setting and Site: The research was conducted at the Endocrinology Unit of the Children Out-Patient Department in the Paediatrics Division of the University College Hospital, Ibadan, Nigeria. As a tertiary healthcare facility, it provides specialized care for paediatric patients and serves as a referral centre, ensuring access to a broad and diverse patient population. The clinic's role in managing children with DS and its reputation as a centre for paediatric endocrine disorders made it a suitable location for the study.

Study Population: Participants included children aged 1 to 15 years with a confirmed clinical diagnosis of DS, made by a consultant paediatric endocrinologist based on clinical features, and a control group of age- and sex-matched children without DS. Due to resource limitations, karyotyping to confirm trisomy 21 was not performed. Exclusion criteria was limited to children with chronic illnesses unrelated to DS, to minimize confounding factors in the analysis of lipid profiles.

Sample Size Determination: The sample size was calculated using the formula for comparing the means of two independent groups, drawing from a prior study (Adelekan *et al*., 2012) that assessed plasma cholesterol in children with and without DS from a population in the United States. The final calculated sample size was 48 children per group. However, due to time constraints and challenges in obtaining consent, a total of 69 participants were enrolled: 31 children with DS and 38 children without DS. Although the sample size was smaller than initially planned, it remained sufficient to detect differences in lipid parameters with acceptable statistical power.

Sampling Technique: A convenience sampling method was used to recruit participants as they presented at the clinic for routine visits. While convenience sampling is a non-probability technique, it was appropriate given the study's setting, the relatively small population of children with DS attending the clinic, and the limited availability of potential participants.

Instrument and Data Collection: Data was collected using a structured questionnaire, which gathered demographic, medical history, and lifestyle information. Anthropometric measurements, including height, weight, and body mass index (BMI), were taken using standardised techniques. Height was measured using a stadiometer, and weight was measured using a calibrated scale. BMI was calculated using the standard formula: BMI (kg/m^2) = weight (kg) / height^2 (m). These measurements provided key covariates for the analysis of lipid profiles and cardiovascular risk. Blood samples were collected by venipuncture, with 5 mL drawn into EDTA tubes. Plasma was separated via centrifugation and stored at -80°C until analysis.

Laboratory Procedures: We determined lipid profiles using enzymatic spectrophotometric methods, except for LDL-C, which was calculated using the Friedewald formula (Tseng *et al*., 2023). We measured ApoA1 and ApoB levels using enzyme-linked immunosorbent assay (ELISA) kits, adhering to the manufacturer's instructions (Eick *et al*., 2017). We immediately processed the samples by centrifuging them at 3000 rpm for 10 minutes to separate the plasma from the cellular components. The plasma was then aliquoted and stored at -80°C until laboratory analysis was performed. Plasma total cholesterol (TC) was measured using an enzymatic spectrophotometric method based on the CHOD-PAP (Cholesterol Oxidase Phenol 4-Aminoantipyrine Peroxidase) technique, as described by Cohn *et al*., (1988). An enzymatic GPO-PAP (Glycerol Phosphate Oxidase-Phenol 4-Aminoantipyrine) method described by Yang *et al*., (2016) was used for determining TG levels. The phosphotungstic acid magnesium precipitation method (Koren *et al*., 1985) was used to determine the high-density lipoprotein cholesterol (HDL-C).

Data Analysis: Statistical analysis was performed using SPSS version 20. Descriptive statistics were used to summarize continuous variables, expressed as means and standard deviations. We summarised categorical variables, such as participant characteristics, as frequencies and percentages. The independent sample t-test was used to compare anthropometrics, and the Mann-Whitney U test was used to compare the mean values of plasma lipids between cases and controls. Chi-square tests were used to compare categorical variables. Pearson correlation was used to assess the associations between the BMI, lipid profile and

apolipoproteins. Statistical significance was set at $p < 0.05$ for all comparisons.

Ethical Considerations: Ethical approval was obtained from the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Committee prior to data collection (Approval number: UI/EC/22/0397). Written informed consent was obtained from the parents or guardians of all participants before enrolment. Informed consent was aligned with the ethical principles outlined in the Declaration of Helsinki and additional safeguards for paediatric research outlined by the U.S. Food and Drug Administration, which emphasize minimizing risk, ensuring voluntary participation, and ensuring that children are not subjected to unnecessary or harmful procedures. Children older than 5 years provided accent before participation. The study ensured that all participants and their caregivers fully understood the study's purpose and procedures.

RESULTS

Table 1:
Comparative Overview of Socio-demographic and Patient Characteristics

Characteristics	Cases (n = 31)	Control (n = 38)	Statistics
Age Group			
1-5 Years	20 (76.9)	6 (23.1)	p < 0.001
6-10 Years	8 (47.1)	9 (52.9)	
>10 Years	3 (11.5)	23 (88.5)	
Gender			
Male	17 (47.2)	19 (52.8)	p = 0.689
Female	14 (42.4)	19 (57.6)	
Religion			
Christianity	21 (38.9)	33 (61.1)	p = 0.056
Islam	10 (66.7)	5 (33.3)	
Educational Status			p < 0.001
Primary	6 (19.4)	14 (36.8)	
Secondary	0 (0.0)	24 (63.2)	
None	25 (80.6)	0 (0.0)	
Family History of Cardiovascular Disease			
Yes	2 (6.5)	0 (0.0)	p = 0.112
No	29 (93.5)	38 (100.0)	

Socio-demographic and Patient Characteristics: The study enrolled a total of 69 participants, with 31 (44.9%) categorised as cases (children with Down syndrome) and 38 (55.1%) as controls (children without Down syndrome). The median age of the participants was 8 years, with an interquartile range (IQR) of 4 to 13 years. Both the case and control groups had equal representation of children aged 1-5 years and those older than 10 years, each constituting 37.7% of the study population, while 24.6% of participants were aged between 6 and 10 years. The comparison of socio-demographic characteristics between children with Down syndrome (cases) and children without Down syndrome (controls) is as shown in Table 1. In terms of age distribution, the study shows that a significantly higher proportion of children with Down syndrome were within the younger age group (1-5 years), with 76.9% of cases falling within this category compared to only 23.1% of controls ($p < 0.001$). In contrast, the proportion of older children (>10 years) was higher in the control group (88.5%) compared to the Down syndrome group (11.5%).

Gender distribution did not show a significant difference between the two groups. Among cases, 47.2% were males, while among controls 52.8% were males ($p = 0.689$), suggesting that gender was not a significant factor between the groups. Educational status, however, demonstrated a striking contrast. A significant proportion of children with Down syndrome (80.6%) had no formal education, compared to none of the controls ($p < 0.001$). Additionally, 63.2% of the children with secondary education were from the control group, with none of the Down syndrome cases having secondary education.

Other characteristics, such as religious affiliation and family history of cardiovascular disease of Down syndrome, did not show statistically significant differences between the groups. A majority of participants in both groups were Christian, and there was no reported family history of Down syndrome in either group. Family history of cardiovascular disease was noted only in 2 cases, with no occurrence in the control group ($p = 0.112$).

Anthropometric Characteristics of Participants: The anthropometric characteristics of the study participants, including height, weight, and body mass index (BMI), are presented in Table 2. There was no statistically significant difference in the heights of children with Down syndrome compared to controls ($p = 0.962$). Both groups showed similar mean height values, indicating that height was not a distinguishing factor between the two groups.

However, a significant difference was observed in the weights of the two groups. Children with Down syndrome had a significantly lower mean weight (17.5 ± 9.3 kg) compared to controls (35.9 ± 14.7 kg), with a p-value of <0.001. This indicates that children with Down syndrome tended to weigh less than their non-Down syndrome counterparts. In terms of BMI, although children with Down syndrome had a slightly lower mean BMI (17 ± 4.7 kg/m²) compared to the controls (18 ± 4.2 kg/m²), this difference was not statistically significant ($p = 0.457$). This suggests that despite the significant difference in weight, the BMI values between the two groups were relatively comparable.

Table 2:
Anthropometric Characteristics of Study Participants

Anthropometric Measure	Cases (n = 31)	Control (n = 38)	p-value
Height (m)	1.3 ± 1.1	1.4 ± 0.2	0.962
Weight (kg)	17.5 ± 9.3	35.9 ± 14.7	<0.001*
BMI (kg/m²)	17 ± 4.7	18 ± 4.2	0.457

*Statistically significant at $p < 0.05$

Plasma Lipid Levels in Study Participants: The plasma lipid levels of the study participants, including total cholesterol, triglycerides, HDL-C, LDL-C, and apolipoproteins (ApoA1 and ApoB), are summarized in Table 4. There was no statistically significant difference in the levels of total cholesterol between the two groups ($p = 0.530$). The mean total cholesterol concentration in children with Down syndrome was 156.5 mg/dL compared to 161.4 mg/dL in the control group.

However, significant differences were observed in other lipid parameters. Children with Down syndrome had significantly higher triglyceride levels (183 mg/dL) compared to controls (171 mg/dL), with a p-value of 0.028. HDL-C levels were also significantly higher in children with Down syndrome (42.3 mg/dL) than in controls (31 mg/dL), with a p-value of <0.001, suggesting that children with Down syndrome may have altered lipid metabolism leading to higher protective HDL levels. LDL-C levels, on the other hand, were significantly lower in children with Down syndrome (76.6 mg/dL) compared to controls (93.7 mg/dL), with a p-value of 0.036.

Regarding apolipoproteins, there were no significant differences between the two groups in terms of ApoA1 (p = 0.192) and ApoB (p = 0.128). The ApoB/ApoA1 ratio also did not differ significantly between cases and controls (p = 0.117).

Table 3:
Plasma Lipid Levels in Study Participants

Lipid Parameter	Cases (n = 31) Mean ±SD	Control (n = 38) Mean ±SD	p-value
Total Cholesterol (mg/dL)	156.5 ± 23.6	161.4 ± 37.6	0.530
Triglycerides (mg/dL)	183 (174-194)	171 (163-188)	0.028*
HDL-C (mg/dL)	42.3 ± 5.3	31.0 ± 5.2	<0.001*
LDL-C (mg/dL)	76.6 ± 23.3	93.7 ± 39.1	0.036*
ApoA1 (mg/dL)	31.5 ± 8.9	33.6 ± 4.2	0.192
ApoB (mg/dL)	5.4 ± 1.1	5.1 ± 0.6	0.128
ApoB/ApoA1 ratio	0.2 (0.1-0.2)	0.15 (0.1-0.2)	0.117

*Statistically significant at p < 0.05

Correlation between BMI and Lipid Profile: The correlations between body mass index (BMI) and various lipid profile parameters were assessed for in children with Down syndrome (cases) and controls (Table 4). In the Down syndrome group, there were no significant correlations between BMI and all the lipid profile. However, in the control group, BMI was significantly positively correlated with total cholesterol (r = 0.383, p = 0.018), HDL-C (r = 0.370, p = 0.022), and LDL-C (r = 0.328, p = 0.045).

Table 4:
Correlation between BMI and Lipid Profile in Study Participants

Lipid Profile	Cases (n = 31)	Controls (n = 38)
Total Cholesterol (mg/dL)	r = -0.023, p = 0.900	r = 0.383, p = 0.018*
Triglycerides (mg/dL)	r = 0.237, p = 0.199	r = -0.040, p = 0.812
HDL-C (mg/dL)	r = -0.026, p = 0.890	r = 0.370, p = 0.022*
LDL-C (mg/dL)	r = -0.094, p = 0.615	r = 0.328, p = 0.045*
ApoA1 (mg/dL)	r = -0.003, p = 0.989	r = 0.161, p = 0.335
ApoB (mg/dL)	r = 0.200, p = 0.282	r = -0.091, p = 0.587

***Statistically significant at p < 0.05**

DISCUSSION

The current study provides a comprehensive comparison of plasma lipid profiles and apolipoprotein levels in children with Down Syndrome (DS) compared to non-DS controls, with significant implications for understanding cardiovascular risk in this population. Our results revealed distinct differences in lipid parameters, including elevated triglyceride and HDL-C levels in DS children and reduced LDL-C levels, suggesting a unique lipid metabolism that could influence cardiovascular outcomes. While the apolipoprotein levels and ApoB/ApoA1 ratio did not differ significantly between the two groups, the overall lipid profile alterations observed in children with DS underscore the metabolic disturbances associated with this genetic condition (Adelekan *et al*., 2012; Chu *et al*., 2004).

The finding of elevated triglycerides in children with DS is consistent with previous studies that have documented dyslipidaemia as a common metabolic disturbance in individuals with DS. Elevated triglycerides are a recognised risk factor for cardiovascular disease (CVD), as they contribute to the formation of atherosclerotic plaques and increase the likelihood of cardiovascular events (Martinelli *et al*., 2007). This finding is concerning, as children with DS are already predisposed to other risk factors such as obesity and insulin resistance, both of which can exacerbate the effects of elevated triglycerides. The elevated triglyceride levels observed in our study suggest that this population may require early interventions aimed at managing dyslipidaemia to mitigate long-term cardiovascular risks (Valkenburg *et al*., 2008).

Interestingly, our study also found significantly higher levels of HDL-C in children with DS compared to controls. HDL-C is traditionally viewed as protective against atherosclerosis, as it helps remove cholesterol from arterial walls and transports it to the liver for excretion (Karthikeyan *et al*., 2009). However, the protective role of HDL-C in individuals with DS is not yet fully understood. While higher HDL-C levels could theoretically reduce cardiovascular risk, the presence of other lipid abnormalities, such as elevated triglycerides, may offset this protective effect. Additionally, the functional quality of HDL-C in DS may differ from that in the general population, and further studies are needed to determine whether elevated HDL-C in this population translates into a lower incidence of cardiovascular events (Juonala *et al*., 2008).

One of the more unexpected findings of our study was the significantly lower LDL-C levels in children with DS compared to controls. LDL-C is a well-established marker of cardiovascular risk, with elevated levels associated with an increased likelihood of developing atherosclerosis and other cardiovascular conditions (Kiptim *et al*., 2023). Our results differ from previous studies that reported higher LDL-C levels in individuals with DS. One possible explanation for this discrepancy could be the younger age of our study population, as lipid profiles tend to change with age. Another possibility is that genetic factors specific to DS may influence lipid metabolism in ways that are not fully understood (Lehtimäki *et al*., 1994). Further research is necessary to elucidate the mechanisms underlying this finding and to assess whether the lower LDL-C levels observed in our study provide any protective benefits against CVD in this population (Lehtimäki *et al*., 1990).

The absence of significant differences in apolipoprotein levels between the DS and control groups is an important observation. Apolipoproteins, particularly ApoA1 and ApoB, are key proteins involved in lipid metabolism, with the ApoB/ApoA1 ratio serving as a strong predictor of atherosclerotic risk (Lamarche *et al*., 1996). Although our study did not find significant differences in this ratio between the groups, it remains possible that apolipoprotein levels could

become more relevant as individuals with DS age and their cardiovascular risk increases. It is also worth noting that the relatively small sample size in our study may have limited our ability to detect subtle differences in apolipoprotein levels. Larger studies are needed to confirm these findings and to determine whether apolipoproteins play a more prominent role in cardiovascular risk assessment for individuals with DS (Juonala *et al*., 2008).

Our study also explored the relationship between body mass index (BMI) and lipid profiles in both DS and non-DS children. While we observed significant positive correlations between BMI and lipid parameters, (such as total cholesterol and HDL-C), there was significant correlations in the control group. These correlations were not significant in the DS group. This finding suggests that the typical associations between BMI and lipid metabolism may not apply as strongly to children with DS. Previous research has indicated that individuals with DS may have unique metabolic patterns that dissociate traditional risk factors, such as BMI, from lipid abnormalities (Karthikeyan *et al*., 2009). These differences could be due to a combination of genetic and environmental factors, including differences in physical activity, diet, and hormonal regulation. Further studies are needed to better understand how BMI influences cardiovascular risk in children with DS and whether alternative markers of metabolic health should be used in this population (Juonala *et al*., 2008).

The implications of these findings are significant, particularly as life expectancy in individuals with DS has increased considerably in recent decades (Lehtimäki *et al*., 1990). As individuals with DS live longer, the likelihood of developing chronic conditions such as CVD also increases. Early screening and intervention for dyslipidaemia in childhood could play a crucial role in preventing the onset of CVD in adulthood. Our results suggest that regular monitoring of lipid profiles, particularly triglycerides, in children with DS should be part of standard clinical care. Interventions such as dietary modifications, increased physical activity, and possibly pharmacological treatment may be necessary to manage elevated triglycerides and reduce long-term cardiovascular risk.

Despite the valuable insights provided by this study, there are limitations that should be acknowledged. First, the relatively small sample size, which was influenced by the challenges of recruiting participants with DS, limits the generalisability of our findings. Additionally, the convenience sampling method used may introduce bias, as the study participants may not fully represent the broader DS population. Future research should aim to address these limitations by including larger, more diverse populations and by employing longitudinal designs to track changes in lipid profiles over time. Moreover, further investigation into the genetic and molecular mechanisms underlying the altered lipid metabolism observed in DS is necessary. Such research could lead to the development of targeted therapies that address the unique metabolic challenges faced by individuals with DS. Additionally, exploring the effects of lifestyle interventions, such as diet and exercise, on lipid profiles in this population would provide valuable information for clinicians seeking to manage cardiovascular risk in DS children.

In conclusion, this study highlights important differences in lipid profiles between children with DS and without DS, with elevated triglycerides and HDL-C levels emerging as key features of the DS lipid profile. These findings underscore the need for early cardiovascular risk assessment and intervention in this population, particularly as life expectancy continues to increase. While the protective role of HDL-C in DS remains unclear, the potential for elevated triglycerides to contribute to long-term cardiovascular risk is a significant concern. Continued research into the metabolic pathways that underlie these lipid abnormalities will be essential for developing effective strategies to mitigate cardiovascular risk in individuals with DS.

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