Chapter

Dyslipidaemia in African Children and Adolescents

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Abstract

Dyslipidaemia tends to occur in children and adolescents and steadily worsens through to adulthood. The abnormal lipid profile in children with this disease is like what we see in adults with premature cardiovascular disease (CVD). Identifying children with dyslipidaemia and successfully improving their lipid profile may reduce their risk of accelerated atherosclerosis and premature CVD. In those children with severe dyslipidaemia due to a family history, treatment is used to decrease the risk of cardiogenic events. Screening for lipid disorders in children is based on the rationale that early identification and control of paediatric dyslipidaemia will reduce the risk and severity of cardiovascular complications in adulthood. Though lipid disorders and associated diseases are rare in children in Africa, there has been little research in this field. Emerging research indicates that obesity and cholesterol concerns is on the rise within children and adolescents of African descent. The definition of paediatric dyslipidaemia and the approach to screening, and diagnosis of lipid disorders in children are discussed in this chapter.

Keywords: hypercholesterolemia, lipid disorders, cardiovascular risk, dyslipidaemia, lipoprotein cholesterol

1. Introduction

Overweight and obesity are proven cardiovascular risk factors for both adults and children [1]. These conditions are associated with increasing risk of dyslipidaemia [2, 3]. Unfortunately, the world has experienced a huge increase in obesity with a parallel increase in the risk factor for cardiometabolic disease characterised by insulin resistance, dyslipidaemia, and hypertension, known together as metabolic syndrome [4]. These conditions were previously unheard of in children and adolescents but are now documented in the literature [5]. Current evidence has shown that atherosclerosis, predominantly adult diseases marked by the accumulation of fatty material on the inner wall of the arteries, starts in childhood as an alteration of lipid concentration and can be related through puberty to modifications that contribute to the development of this disorder. Children and adolescents with elevated cholesterol levels are more likely to experience dyslipidaemia in adults than their counterparts in the same population [6, 7]. Identification of dyslipidaemia is therefore essential for the prevention or cessation of atherosclerotic processes during childhood and ultimately for the prevention of premature cardiovascular disease.

Lipid disorders and related diseases are rare in children and adolescents in Africa and there is a scarcity of literature on this topic. However, emerging data indicates

that the incidence and prevalence of obesity and dyslipidaemia is on the rise in the population of African children and adolescents, partially due to shifts in economic and lifestyle towards the trends in the Western world [8]. Serious comorbidities, complications, and cardiovascular risk factors, including obesity, diabetes mellitus, hypertension, and smoking, are correlated with dyslipidaemia. As a result, more attention tends to be paid to the increasing problems of dyslipidaemia among the African population in recent years. The key objectives of this chapter are to discuss the burden of dyslipidaemia, diagnosis, risk factors and health problems, as well as gaps in awareness of dyslipidaemia in children and adolescents in Africa.

2. What is dyslipidaemia in children?

From a general biology perspective, lipids are organic and water insoluble compounds which include fatty acids, triglycerides, and cholesterol. Lipoproteins are also soluble in watery environments of human body. Chylomicrons are formed in the intestine after fat is digested. They are then moved to the fat tissue, muscle, and liver. Chylomicrons are hydrolysed into free fatty acids and then metabolised to low density lipoprotein cholesterol (LDL-C) (the major carrier of cholesterol to tissues). Cholesterol is a fatty substance that passes through high density lipoprotein cholesterol (HDL-C) to peripheral tissues and then to the liver. Abnormalities in the pathway lead to dyslipidaemia.

Dyslipidaemias are lipoprotein metabolism disorders that result in the abnormalities of high total cholesterol (TC), high LDL-C, high non-HDL-C, high triglycerides, and low HDL-C. The HDL and LDL cholesterol monitor the amount of cholesterol that can occur in the body, and if there is an excess it can increase the risk of cardiovascular events. Other forms of dyslipidaemia also include high phospholipids and combined dyslipidaemia.

Since cholesterol is an essential component of human cells, cholesterol may also be generated by individual cells or introduced to the body via our diets. However, when cholesterol levels are increased for whatever reason, they may be bad for the human body. Lipid levels in children younger than 19 years of age are different from lipid levels in adults and vary for the same age in different patients. As an infant, the levels of cholesterol and triglycerides are lower than when a person is an adult. Levels grow steadily during the first year of adolescence, then increase more slowly until they reach the age of 9 to 11 years, but then increase slightly faster until they reach adulthood. At puberty, low-density lipoprotein cholesterol (LDL-C) blood levels decrease by about 10% to 20% or more, whereas high-density lipoprotein (HDL-C) levels increase by 50% or more.

The plasma levels of serum lipids and lipoproteins as recommended are in **Table 1**. Normative data are used to establish cut-off points and identify ranges of acceptable, borderline, and abnormal levels as shown. In **Table 1**, the values for plasma lipid and lipoprotein levels are taken from the National Cholesterol Education Program's (NCEP) Expert Panel on Cholesterol Levels in Children as they were observed. Non-HDL-C values from the Bogalusa Heart Study are equivalent to the NCEP Paediatric Panel cut-off points for LDL-C. Values for plasma Apo B and Apo A-1 come from the National Health and Nutrition Examination Survey III (NHANES III). As a usually occurring wide range, the threshold points for high and borderline-high values reflect roughly the 95th and 75th percentiles, respectively. These values fall into the range of the 10th percentile of the standard range for HDL-C and ApoA-1. It should be noted that the ranges for plasma lipoprotein cholesterol in **Table 1** are consistent with the guidelines of the National Heart, Lung and Blood Institute, the American Academy of Paediatrics and the American

Category	Acceptable mg/dL (mmol/L)	Borderline mg/dL (mmol/L)	High mg/dL (mmol/L)
TC	<170 (4.4)	170 to 199 (4.4 to 5.2)	≥200 (5.2)
LDL-C	<110 (2.8)	110 to 129 (2.8 to 3.3)	≥130 (3.4)
Non-HDL-C	<120 (3.1)	120 to 144 (3.1 to 3.7)	≥145 (3.8)
ApoB	<90 (2.3)	90 to 109 (2.3 to 2.8)	≥110 (2.8)
TG			
0 to 9 years	<75 (0.8)	75 to 99 (0.8 to 1.1)	≥100 (1.1)
10 to 19 years	<90 (1 mmol/L)	90 to 129 (1 to 1.5)	≥130 (1.5)
HDL-C	>45 (1.2)	40 to 45 (1 to 1.2)	<40 (1)
ApoA-1	>120 (3.1)	115 to 120 (3 to 3.1)	<115 (3)

Adapted from expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents, national heart, lung, and blood institute [3].

Table 1.
Acceptable, borderline-high, and high plasma lipid and lipoprotein ranges for children and adolescents.

College of Cardiology. However, these cut-off points have not been validated as accurate benchmarks for accelerated atherosclerosis and CVD events in the African children's population.

3. Problem of dyslipidaemia in children

Atherosclerosis and cardiovascular disease (CVD) are the major health problems associated with dyslipidaemia. These disorders are vascular problems associated with more than 17 million deaths worldwide in 2015, a rise of 12.5 per cent from 2005 onwards [9]. While it is acknowledged that a diet low in saturated fat and regulated cholesterol levels are essential for heart health, it is also determined that certain foods can increase the risk of coronary artery disease (CAD) and other cardiovascular problems [10–12]. Although the prevalence of dyslipidaemia has gradually decreased in several high-income and developing countries over the last 20 years, it is currently predicted that the incidence of dyslipidaemia will increase in African countries due to the rapid change in lifestyles to high-income and developed countries [13].

As far back as 1981, evidence from different studies among Caucasians showed that in childhood, serum levels of cholesterol and triglycerides could rise to levels similar to those seen in young adults at around 2 years of age [14]. Concentrations and turnover of such important molecules in blood lipid concentrations do occur in children. Over the years, researchers have found that if there is a family history of CVD, there is greater concern that a CVD will be developed.

There is ample evidence which suggests that there are more children and adolescents with the hyperlipidemia disease. From the 1988–1994 National Health and Nutrition Survey, it was shown that 10 percent of teenagers had the total cholesterol greater than 200 mg per dL [15]. Also, the newly generated age- and gender-specific lipoprotein from data of the Child and Adolescent Trial for Cardiovascular Health showed that over one-tenth of children aged 9 to 10 years had TC levels greater than 200 mg per dL [16].

While data on the severity of dyslipidaemia among children and adolescents in Africa are scarce in published literature, a few observational studies have reported hypercholesterolemia prevalence and associated risk factors. In the Ghana School Survey conducted in two cities, Kumasi and Accra, the proportion of children with

hyperlipidemia was 12.1% for TC, 4.5% for TG, 28.4% for HDL-C and 9.2% for LDL-C [17]. Another study conducted among adolescent school children in the Eti-Osa Local Government Area of Lagos State, Nigeria, recorded that only 3.6 per cent of participants had TC greater than 200 mg/dL [18]. The highest prevalence of high TC among Angolan pre-pubertal adolescents, 7 to 11 years of age, was estimated to be 69.2% [19].

4. Causes of dyslipidaemia

Dyslipidaemias in children and adolescents can be inherited and/or acquired. Acquired causes of dyslipidaemia can be nutritional or secondary to other diseases. Excessive dietary intake of saturated and trans fats can be a major cause of dyslipidaemia. Hereditary types are referred to as primary dyslipidaemias which includes monogenetic and polygenic defects.

In the clinical setting, a primary metabolic disorder indicates that there is a deficiency in the lipid metabolism, and this is designated familial hypercholesterolemia (FH). The FH follows an autosomal dominant pattern of inheritance and is characterised by an increase of high TC and LDL-C since birth. Earlier onset of atherosclerotic cardiovascular disease (ASCVD) is also seen [20, 21]. Studies show that FH arises from genetic mutations in the LDL receptor (LDLR) and from the action of proprotein convertase known as proprotein convertase 9 (PCSK9) when it mutates [22, 23]. Also, FH has been associated with mutations in the apolipoprotein B gene which impedes the binding of LDL particles to the LDL receptor gene [22, 23].

Exogenous causes	**Hepatic causes**
• Alcohol • Drug therapy including corticosteroids, isotretinoin, some oral contraceptives, select chemotherapeutic agents, and select antiretroviral agents	• Obstructive liver disease/cholestatic conditions • Biliary cirrhosis • Alagille syndrome
Endocrine/Metabolic causes	**Inflammatory disease**
• Hypothyroidism/hypopituitarism	• Systemic lupus erythematosus
• Diabetes mellitus types 1 and 2	• Juvenile rheumatoid arthritis
• Pregnancy	**Storage disease**
• Polycystic ovary syndrome	Glycogen storage disease
• Lipodystrophy	• Gaucher disease
• Acute intermittent porphyria	• Cystine storage disease
Renal causes	• Juvenile Tay-Sachs disease
• Chronic renal disease	• Niemann-Pick disease
• Haemolytic uremic syndrome	**Other causes**
• Nephrotic syndrome	• Kawasaki disease
Infectious causes	• Anorexia nervosa
• Acute viral/bacterial infection	• Childhood cancer survivor
• HIV infection	• Idiopathic hypercalcemia
• Hepatitis	• Klinefelter syndrome

Adapted from expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents, national heart, lung, and blood institute [3].

Table 2.
Causes of secondary dyslipidaemia in children and adolescents.

To date, reports of FH cases in Africa have been rare. There may be several explanations for this. Perhaps, the gene implicated in the aetiology of FH is rare in African population. Even though cardiovascular diseases affect many Africans, it is still important for more studies to be performed on genetic factors that can cause dyslipidaemia. This would reduce the burden of cardiovascular disease in Africa.

Secondary causes of dyslipidaemia are due to "non-lipid" underlying conditions rather than an inborn lipid metabolism disorder, some of which are shown in **Table 2** [24].

5. Screening for dyslipidaemia in children

Usually, screening tests are performed on people who do not show any symptoms of disease to detect health problems or illnesses. The key goal of screening is early detection, to reduce the risk of illness, or to identify it early enough to treat it more effectively. Childhood lipid disorder screening is focused on the rationale for reducing the risk and severity of cardiovascular disease (CVD) in adulthood by early detection and management of paediatric dyslipidaemia. Universal screening for dyslipidaemia became the recommended practice in 2011 [25]. Currently, in most parts of Africa, screening for hyperlipidemia in children and adolescents is not routinely performed in clinical settings. However, it is appropriate to become aware of the latest guidelines for the diagnosis and treatment of dyslipidaemia by child health practitioners. The National Cholesterol Education Program Expert Panel on Blood Cholesterol in Children and Adolescents issued the first guidelines for paediatric lipid screening in 1992 [26]. By 2011, when the American Heart Association [27] and the American Academy of Paediatrics included parameters to identify high and moderate risk individuals as seen in **Table 3**, thereafter, the guideline developed over several years with modifications [29].

The findings of National Heart Lung and Blood Institute (NHLBI) panel which performed a systematic review and grading of evidence related to the screening and treatment of CVD risk factors, including dyslipidaemia, were released in 2011 in a combined effort to improve the assessment and management of cardiovascular disease risk factors [30, 31]. The universal screening for lipid disorders as recommended in the guidelines means that all children between the ages of 9–11 should

Risk factors	**Risk conditions**
High-level risk factors	*High-risk conditions*
1. Hypertension requiring drug therapy (i.e., BP ≥99th percentile +5 mmHg)	1. Type 1 and 2 diabetes mellitus
2. Current cigarette smoker	2. Chronic kidney disease/end-stage renal disease/ postrenal transplant
3. BMI ≥97th percentile	3. Post-orthotopic heart transplant
4. Presence of high-risk conditions	4. Kawasaki disease with current aneurysms
5. Family history of premature CVD	*Moderate-risk conditions*
Moderate-level risk factors	1. Kawasaki disease with regressed coronary aneurysms
1. Hypertension not requiring drug therapy	2. Chronic inflammatory diseases, such as:
2. BMI ≥95th percentile, but <97th percentile	• Systemic lupus erythematosus
3. HDL-C < 40 mg/dl	• Juvenile rheumatoid arthritis
4. Presence of moderate-risk conditions	3. HIV
	4. Nephrotic syndrome

Adapted from Kwiterovich, P. O., Jr. (2008). Recognition and management of dyslipidaemia in children and adolescents. J Clin Endocrinol Metab, 93(11), 4200–4209 [28].

Table 3.
Risk factors and conditions for dyslipidaemia screening.

get their lipids checked one time. This can be done by determining the plasma level of non-HDL-C with either a fasting lipid profile or a non-fasting test. This universal screening for dyslipidaemia was suggested because studies showed that 30–60 percent of children and adolescents with extreme cholesterol elevations could be missed by using only a selective screening approach based on family history [31].

The universal screening technique is specifically intended to identify children with inherited dyslipidaemia as hypercholesterolemia runs in families. However, due to lifestyle and obesity factors, children with dyslipidaemia, high triglyceride levels and low HDL-C levels may also be identified. In most cases, dyslipidaemias are clinically silent and selective screening for children with family history does not identify a significant number of children with lipid disorders [31, 32].

6. Approach to diagnosis of dyslipidaemia in children

The risk factors for dyslipidaemia are basically those that have been established to increase the likelihood of adults to develop ASCVD as listed in **Table 3**, while risk conditions are specific to paediatric guidelines and involve diseases that increase the risk of developing premature CVD [3]. There will be no noticeable clinical signs and symptoms for most children and adolescents with dyslipidaemia. The lack of clinical features is because, apart from individuals with Homozygous Familial Hypercholesterolemia (HoFH) that may have the first clinical clues in the first 10 years of life, most symptoms and signs only grow after decades [21]. Patients with HoFH are born with elevated LDL-C levels in their blood, and this is one of the reasons behind the early development of serious disease complications [21].

Physical signs, such as lipid deposits, bleeding, and atrophy, occur in the eyes, skin, and tendons. These signs may differ for each person and are therefore not necessarily invariable for the same disease. The heterozygous phenotype is generally present with tendon xanthomas, while the homozygous phenotype is present with both tendon and skin xanthomas. The characteristic lesion of familial hypercholesterolemia is the thickening of the tendons of Achilles. Symptoms caused by these deposits in the tendons and joints include chronic inflammation and joint pain, which can make it difficult for a person to live a good life. Cutaneous xanthelasmas of the eyelids can often be seen in patients with FH, but this symptom is not quite common. It should be noted that the diagnosis of xanthomas in the clinical examination is not only of diagnostic importance but may also signify the possibility of a cardiovascular event, as patients whose xanthomas have been observed in the clinical examination have been shown to suffer from more cardiovascular events. If there is a "white crescentic line" on the skin due to cholesterol accumulation, this also supports the diagnosis of hypercholesterolemia.

Of late, there are arguments surrounding universal screening of children and adolescents for dyslipidaemia, some favour universal screening, while others are against universal screening. While current data still classify approximately one third of children as having elevated lipid levels, some authors have documented the diagnosis of elevated lipid levels in many children without a family history of CVD or hypercholesterolemia [33]. Although it is more common in adults and youth with genetic disorders, selective screening may also be missed in many adults, particularly when their parents are young, free of CVD and unaware of their own lipid levels. Universal screening for these carriers can also be conducted to classify those with undiagnosed heterozygotes for familial hypercholesterolemia or those with more pronounced homozygotes who will then undergo more extensive care, including the possibility of drug therapy. In a meta-analysis, 88–96 percent of all

cases with a false-positive rate of less than 1% were detected in screening for family hypercholesterolemia in the primary treatment clinic [34].

Current literature tells us that risk factors for CVD are most observed in adolescence, and these risk factors are still present in adulthood. Dietary and hygienic treatment and medication are effective for those who have this disease. It is therefore necessary for all children and adolescents to perform a separate lipoprotein test for each of them. However, it can be argued that screening for people who have never smoked should be universal, given the prevalence of obesity in young Africans, the epidemic of metabolic syndrome, and the fact that CVD is quickly becoming a cause of death for individuals under 55 years of age, and will likely be the leading cause of death for all adults under 65 [33].

However, as noted in another publication, concerns have been raised that several longitudinal studies [33] find that when the 75th percentile for triglyceride levels in children is used as a screening cut-off point, only half of those in need of adult treatment are identified by universal lipid screening. In one study, the sensitivity was much lower when screening occurred during puberty, which is likely to indicate a transient downward shift in LDL-C during this time of rapid growth and development [35]. Another unresolved question is whether the detection of elevated TC or LDL-C in children and young adults suggests that these adults will develop premature CVD. If systematic screening for lipid and non-lipid risk factors for CVD was a standard of paediatric treatment, there would obviously be a need for national resources to recognise and treat those found to be at high risk of CVD.

7. Conclusion

Children and adolescents who are predisposed to dyslipidaemia are more likely to remain predisposed to dyslipidaemia throughout their lives. Interventions in childhood and adolescence are immensely helpful in helping to prevent the build-up of fatty deposits in the arteries and other cardiovascular problems later in life. Therefore, abnormalities in the lipid profile of children and adolescents, particularly those with other risk factors, must be identified early, followed, monitored, and treated, if possible. Health care providers should strive to examine, diagnose, and treat prevalent genetic conditions such as familial hypercholesterolemia that affect families for several generations. Lipid screening should be one of the routine therapies for children in Africa.

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