# RISK FACTORS FOR MACRO VASCULAR DISEASES IN RELATION TO GLYCEMIC CONTROL AMONG TYPE 1 DIABETIC CHILDREN AND ADOLESCENTS ATTENDING DIABETIC CLINIC AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM

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**"A Dissertation Submitted in Partial Fulfilment of the Requirements for the Degree of Master of Medicine (Paediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences".**

**Muhimbili University of Health and Allied Sciences**

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## CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation entitled: "***Risk factors for macro – vascular diseases in relation to glycemic control among type 1 diabetic children and adolescents attending diabetic clinic at Muhimbili National Hospital, Dar es Salaam***" in (partial) fulfillment of the requirements for the degree of Master of Medicine, (Pediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences (MUHAS).

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## DECLARATION AND COPYRIGHT

I, Isabella Sylvester, declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature ……. Date.....

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## DEDICATION

This work is dedicated to my father, who is a known type 2 diabetic.

My adorable sons Martin Mazoya and Kamilius Niyilagila

## ABSTRACT

**Background** Type 1 Diabetes Mellitus (T1DM) is the most common endocrine-metabolic disorder of childhood and adolescence. It has important physical and emotional development consequences. Individuals with T1DM confront serious lifestyle alterations. These include an absolute daily requirement for exogenous insulin, the need to monitor glucose level, and pay attention to dietary intake.

Hyperglycemia is the primary mediator of atherosclerosis in T1DM. Serum lipid abnormalities are prevalent in children and adolescents with T1DM. An association between elevated hemoglobin A1C (HbA1c) and serum lipid levels exists. Its association with atherosclerosis requires early intervention, therapeutic and preventive measures.

Children with diabetes are already at an increased risk of early CVD, since diabetes is now recognized as an independent risk factor for future cardiovascular events. Currently available evidence suggests that lipid and lipoprotein abnormalities are more prevalent in children with T1DM compared to their non diabetic counterparts

**Objective** To determine the risk factors for macro vascular disease in relation to glycemic control among type 1 diabetic children and adolescents attending diabetic clinic at Muhimbili National Hospital (MNH).

**Methodology** A hospital based descriptive cross sectional study was done. All children and adolescents aged 2 to 19 years attending diabetic clinic at MNH who met the needed criterion were enrolled in the study. Bio-data such as age, sex, weight, etc was collected using a structured questionnaire designed for the purpose of the study. Venous blood was taken from the anterior cubital fossa of each child for determination of glycosylated hemoglobin (Hba1c) and lipid profile. Abdominal ultrasound was done to 85 study participants for fatty liver assessment. SPSS version 17 was used for data entry and analysis. P - value of less than 0.05 ($p < 0.05$) was considered statistically significant. Ethical clearance to carry out the study was sought from MUHAS higher degree research and publication committee and MNH respectively.

**Results** Ninety eight (98) participants were recruited into the study, 51% were females. Dyslipidemia was found in 73.5%.The main abnormality was high low density lipoprotein cholesterol (LDL – C) found in 29.6% patients. Other abnormalities were high TC in 25/98 (25.5%), low HDL cholesterol in 13/98 (13.3%) and high triglycerides in 5/98 (5.1%) patients. It was found that high LDL and TC increased with age.

Poor and very poor glycemic control, duration of diabetes and overweight was associated with high LDL and total cholesterol. Among the 85 children and adolescents who had liver ultrasound done 15.3% were found to have mild fatty liver. Among those with mild fatty liver 46.2% had high LDL – C, 38.5% had high TC and15.4% had low HDL- C.

**Conclusion and Recommendation** Children and adolescents with T1DM at MNH had high proportions of abnormal lipid profile. The commonest abnormal lipid profile found was high LDL – C followed by high TC. Abnormal lipid profile becomes prevalent as the glycemic control worsens. These results highlight on the importance of glycemic control in children and adolescents with T1DM. There is an intense need of early screening for dyslipidemia and early treatment so as to prevent cardiovascular disease in high risk diabetic patients.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AHA | American Heart Association |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CAD | Coronary Artery Diseases |
| CETP | Cholesteryl Ester Transfer Protein |
| CVD | Cardiovascular Diseases |
| DSM | Dar - es - Salaam |
| DBP | Diastolic Blood Pressure |
| HbA1c | Glycosylated Hemoglobin |
| HDL – C | High Density Lipoprotein Cholesterol |
| NAFLD | Non Alcoholic Fatty Liver Diseases |
| LDL – C | Low Density Lipoprotein Cholesterol |
| LpL | Lipoprotein Lipase |
| MHN | Muhimbili National Hospital |
| MUHAS | Muhimbili University of Health and Allied Sciences |
| SBP | Systolic Blood Pressure |
| SSA | Sub Saharan Africa |
| T1DM | Type 1 Diabetes Mellitus |
| T2DM | Type 2 Diabetes Mellitus |
| TG | Triglycerides |
| TC | Total Cholesterol |
| VLDL | Very Low Density Lipoprotein |

# CHAPTER ONE

## 1.0 INTRODUCTION AND LITERATURE REVIEW

### 1.1 Background

From as early as the turn of the twentieth century and up to the early 1960s, diabetes mellitus was considered to be rare in sub-Saharan Africa (SSA) [1]. However, over the past decades, diabetes has emerged as an important medical problem in developing areas of the world including Africa. Although its prevalence varies and is thought to be lower than in Europe and North America, diabetes is relatively commonly encountered and today, few major African hospitals are without a diabetes clinic [2].

From projected global estimates for the years 2000–2010, Amos et al[3] reported that the incidence of T1DM was projected to increase from 3.5 to 5.5 million by 2010. For Africa, type 1 diabetes is expected to increase from 85,000 to 219,000 between 1995 and 2001. For SSA, there have been only two published reports each on the prevalence of type 1 diabetes in population-based studies [4] and of incidence studies [5, 6]. Studies indicate prevalence rates of 0.95/1000 in Sudan[4] and 0.3/1000 in Nigeria. The reported incidence of type 1diabetes is 10.1/100 000 per year in Sudan [5]and 1.5/ 100 000 per year in Tanzania [7].

In the developed world, enormous efforts are made to reduce the chronic complications of diabetes. In the developing world, the incidence of these complications in children is not known, making their management more difficult. Information on chronic complications of diabetes in SSA is scarce; however, the incidence has gone hand in hand with the growing disease prevalence, demonstrating the importance of assessing complications [7] .

In a previous study done to T1DM children and adolescents by Majaliwa et al found that, all children had poor glycemic control, except one who had good control (A1C $\leq$7.5%). A high percentage of children (24.2%) had very poor glycemic control (A1C $\geq$12.5%). The mean duration of diabetes was similar in all three groups [7].

## 1.2 Introduction

Diabetes mellitus (DM) is a common, chronic, metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature. The major forms of diabetes are classified according to those caused by deficiency of insulin secretion due to pancreatic β-cell damage (type 1 DM, or T1DM) or and those that are a consequence of insulin resistance occurring at the level of skeletal muscle, liver, and adipose tissue, with various degrees of β-cell impairment (type 2 DM, or T2DM [8].

T1DM is the most common endocrine-metabolic disorder of childhood and adolescence, with consequences for physical and emotional development. Individuals with T1DM confront serious lifestyle alterations. This includes an absolute daily requirement for exogenous insulin, the need to monitor their glucose level, and to pay attention to dietary intake [8].

Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient. It is often unclear which abnormality is the primary cause of the hyperglycemia [9].

Morbidity and mortality occurs from acute metabolic derangements and are related to long-term complications (usually in adulthood) which are related to metabolic disturbances [8]. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs. Manifestations occur especially in the eyes, kidneys, nerves, heart, and blood vessels. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes [10, 11].

## 1.3 Pathophysiology

The basis for the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. T1DM, previously termed insulin-dependent diabetes mellitus, provides a much clearer understanding of the relationship between diabetes,

insulin deficiency, and lipid/ lipoprotein metabolism. In poorly controlled T1DM, hypertriglyceridemia and reduced HDL are commonly reported [11].

Replacement of insulin in these patients may correct these abnormalities. Well controlled diabetics may have increased HDL and lower than average triglyceride levels. Several factors are likely to be responsible for diabetic dyslipidemia. These include insulin effects on liver apoprotein production, regulation of lipoprotein lipase (LpL), actions of cholesteryl ester transfer protein (CETP) and peripheral actions of insulin on adipose and muscle [11, 12].

Insulin may modulate the production of a number of other proteins that affect circulating levels of lipoproteins. Hepatic lipase is an enzyme synthesized by hepatocytes that hydrolyzes phospholipids and triglycerides on HDL and remnant lipoproteins. Some' studies suggest that this enzyme is reduced by insulin deficiency. One effect of hepatic lipase deficiency is to decrease the clearance of postprandial remnant lipoproteins [12].

LpL is the major enzyme responsible for conversion of lipoprotein triglyceride into free fatty acids. This protein has an unusual intercellular transport; LpL is synthesized primarily by adipocytes and myocytes, but must be transferred to the luminal side of capillary endothelial cells, where it can interact with circulating triglyceride-rich lipoproteins such as VLDL and chylomicrons [12].

**1.4 Risk factors for macro vascular disease in T1DM include;**

1. Dyslipidemia
2. Overweight / Obesity
3. Hypertension

**1.4.1 Dyslipidemia and T1DM:** Diabetes is well known as a cardiovascular risk factor. Hyperglycemia is the primary mediator of atherosclerosis in T1DM. Serum lipid abnormalities are prevalent in children and adolescents with T1DM. An association between elevated hemoglobin A1C (HbA1c) and serum lipid levels exists. Its association with atherosclerosis

requires early intervention, therapeutic and preventive measures [13]. Ladeia A. M et al reported that, total prevalence of high TC was 54.6%. These high percentages predominated in younger patients, 43.9% ($p$<0.002) for TC, and 51.5% ($p$<0.001) for LDL. A low HDL level was present in 37.2% of the patients studied. Younger patients, under 19 years old, (eight of 66 [12.1%]) presented with high values TGs [13].

In a study done by Shamir R et al [14] showed that, intensive insulin monitoring in adolescents with T1DM results in significant reduction in HbA1c. Reduction in Apoprotein B serum levels and oxidative stress are implicated in the pathogenesis of atherosclerosis. The mortality and morbidity of cardiovascular disease (CVD) is increased 2–4 fold in T1DM [15]. The major cause of morbidity and mortality in people with type 1 diabetes is premature and extensive atherosclerosis and cardiovascular disease (CVD). Several studies have shown that mortality from CVD is increased two- to twenty fold in T1DM patients [15, 16]. The prevalence of CVD in the T1DM population points to the importance of early identification of known CVD risk factors and early intervention. The progression of atherosclerotic disease and the severity of atherosclerosis relate not only to the presence and extent of cardiovascular risk factors, but also to the persistence of risk factors over time [15].

CVD has now overtaken diabetic nephropathy as the leading cause of premature death in young adults with diabetes[14]. Children with diabetes are already at an increased risk of early CVD, since diabetes is now recognized as an independent risk factor for future cardiovascular events [16]. Recent attention has focused on risk factors for CVD in children with T1DM. Currently available evidence suggests that lipid and lipoprotein abnormalities are more prevalent in children with T1DM compared to their non diabetic counterparts [10].

Margeirsdottir H.D. et al found that, there was no difference between boys and girls with regard to the proportion of patients per risk factor, except for LDL-cholesterol and HDL-cholesterol. Higher proportion of the girls had LDL-cholesterol >2.6 mmol/l (p=0.001) and a higher proportion of the boys had HDLcholesterol <1.1 mmol/l (p=0.001)[17]. The most common pattern of dyslipidemia is hypertriglyceridemia and reduced HDL cholesterol levels. Although intervention data are lacking, the AHA categorizes type 1 diabetic children in the

highest risk for cardiovascular diseases and recommends both lifestyle and pharmacologic treatment for those with elevated LDL cholesterol levels [12].

McGill HC, Jr et al [18] in their study found that, atherosclerotic changes in the vessel wall begin long before symptoms appear. The first intimal lesions (fatty streaks) appeared in all the aortas and in 50% of the right coronary arteries in the youngest age group (15–19 years), and increased in both prevalence and extent through to the oldest age group (30–34 years). Similarly it was found that, VLDL and LDL cholesterol were positively associated with both fatty streaks and raised intimal lesions. HDL cholesterol was negatively associated with these changes. Elevated HbA1c values has been associated with an excess of fatty streaks and raised lesions in the right coronary artery and aorta. Atherosclerosis has also been found to be associated with hypertension and BMI [18].

Jarvisalo, M.J. et al [19] in their study showed that, in children with a mean age of 11 years and mean diabetes duration of only 4 years, intima–media thickness of the carotids and aorta was significantly greater than in healthy age-matched controls. The thickening was more prominent in the aorta than in the carotids, and the magnitude of the increase was more observed in children with hypercholesterolemia and T1DM.

In another study done by Maahs DM et al [20], showed that 18.6% of children screened for dyslipidemia were abnormal for TC or HDL, and thus have a second cardiovascular risk factor, supporting the importance of regular screening for dyslipidemia in children with T1DM. In addition, there was a significant relationship between glycemic control and TC and non-HDL levels and a significant relationship between BMI and HDL and non- HDL levels.

In a study done by Azad et al [21] among 51 diabetic subjects examined in the fasted state, 39% had serum total cholesterol above the cutoff point of 5.2 mmol/l (25% had raised cholesterol alone; serum triglyceride concentration exceeding 1.7 mmol/l was found in 14%). Children

with a raised triglyceride concentration also had raised cholesterol. None of the children had hypertriglyceridaemia alone.

Another study done by Qureshi et al [22] showed that, mean total cholesterol, LDL-cholesterol were significantly higher in diabetic children than control group whereas no statistically significant difference was observed in serum TG levels in male diabetic children but its value was higher in female children. Serum LDL-cholesterol levels were also statistically significant. Serum HDL-Cholesterol levels were statistically significant.

Guy, J et al [23] found that, youth with optimal A1C levels compared with control subjects had similar mean levels of total cholesterol, LDL cholesterol, non-HDL cholesterol, and LDL particle size; lower levels of triglyceride higher HDL cholesterol levels; and a lower triglyceride–to–HDL cholesterol ratio. Type 1 diabetic youth with suboptimal levels of A1C had a more atherogenic lipid and lipoprotein pattern, such that mean values were significantly higher than those in control subjects for total cholesterol, LDL cholesterol, non-HDL cholesterol, and apoB and significantly lower for LDL particle size. Nevertheless, even youth with suboptimalA1C had higher HDL cholesterol levels than control subjects Guy, J et al [23] .

In Morocco, a study done by Hicham M et al [24] showed that, increase of TG and LDL-C levels confirmed the dyslipidemia pattern in T1DM patients. T1DM patients including metabolically well controlled diabetic patients form peroxides at a very early stage of diabetes. Increased LDL-C and TG levels provide evidence for an increased lipid peroxidation and possible tissue damage by free radicals. T1DM children are thought to be at high risk of vascular complications of diabetes mellitus and atherosclerosis.

**1.4.2 Overweight/Obesity and T1DM:** Obesity results from an imbalance between energy intake and energy expenditure. Excesses in adipose tissue mass also can be viewed as a pathological derangement in the feedback between energy intake and expenditure. The prevalence and severity of childhood overweight has been increasing dramatically. Childhood

overweight is one of critical public health problems that threaten to ultimately reverse the favorable trends in cardiovascular morbidity and mortality that have occurred during the past half-century [25]

In a study done by Kafyulilo 2006 [26] showed that, the prevalence of overweight and obesity in Tanzania rose steadily as well as progressively from 3.6% in 1995 to 9.1% in 2004 and over 23% in urban areas in Tanzania. It also revealed that physical inactivity (sedentary life), and nutrition have significant effects to overweight and obesity among primary school children. Children and adolescents at risk of developing obesity and its complications must be identified early and interventions begun. Overweight is associated with a number of co morbidities in children. The amount of information available about youth is less than that about adults. It is clear that children experience many detrimental effects of overweight similar to adults [25].

The major concern is focused on long-term consequences. The Harvard Growth Study showed a doubling of the death rate from cardiovascular disease in males who were overweight during adolescence. The Bogalusa Heart Study observed that, children with a BMI above the 85th percentile were more likely to have hypercholesterolemia, hypertriglyceridemia, or hypertension than other children [8]. Higher blood pressure (BP) and a higher prevalence of hypertension occur in overweight children, independent of race, sex, and age. The metabolic syndrome (hypertension, glucose intolerance, hypertriglyceridaemia, decreased HDL – C level, abdominal central obesity) confers an excessively high risk of cardiovascular disease, with an overall prevalence of 4% in adolescents and approximately 30% in overweight adolescents [8].

Obesity is not generally considered a typical feature of type 1 DM (T1DM), but the world wide trend towards increased body weight is apparent in these patients. Although the information about the prevalence of obesity in those with T1DM is limited, the burden of the concurrent problems of obesity and T1DM can have notable medical, psychological, and social implications for both patients and their families. Ladeia et al [13] found that only 3.2% of

94 patients with T1DM were overweight and this did not appear to be an important predisposing risk factor for insulin resistance, high BP, and dyslipidemia.

Another complication of obesity that has not been very well studied in pediatric group is Nonalcoholic fatty liver disease (NAFLD). It is a spectrum of disorders that ranges from simple hepatic steatosis without significant inflammation or fibrosis to nonalcoholic steatohepatitis (NASH) with varying degree of inflammation and fibrosis. NAFLD is an important cause of chronic liver disease (cirrhosis) in children when fat may no longer be present. The primary pathophysiological derangement in most patients with NAFLD is insulin resistance. Insulin resistance leads to increased lipolysis, triglyceride synthesis, increased hepatic uptake of free fatty acids, and accumulation of hepatic triglyceride [27-29] .

NAFLD is characterized by a mild increase in transaminases, a hyper echoic liver on ultrasound. Progression to liver cirrhosis may occur with time [8]. El-karaksy et al,[30] found the prevalence of NAFLD to be 38.5% in obese children and adolescents in Egypt. Also it t showed that, BMI together with ultrasonographic assessment with hepatic ecchogenicity and laboratory variables including (insulin resistant and dyslipidemia) were good predictors of NASH among obese children.

In a study done by Targher, G et al [31], findings suggest that NAFLD is very common in type 1 diabetic subjects and is associated, independently of several confounding factors, with a higher prevalence of CVD. In their study 69.8% participants met the criteria for diagnosing NAFLD. NAFLD was present in 44.4% of the analytic cohort, and it represented the most common cause (69.8%) of hepatic steatosis on ultrasound examination.

**1.4.3 Hypertension and T1DM:** Systemic hypertension is uncommon in infants and younger children with a prevalence of less than 1%. When present it is usually indicative of an underlying disease process (secondary hypertension). In contrast, adolescents may develop

primary or essential hypertension (with no underlying cause). Essential hypertension during childhood may track into adulthood, as demonstrated by several large clinical studies [8].

Children with blood pressure >90th percentile have a 2.4-fold greater risk of having hypertension during adulthood. Nearly half of all hypertensive adults had a blood pressure >90th percentile as children. There is also a correlation between early childhood hypertension and early atherosclerosis [8]. Children with T1DM have an increased incidence of hypertension which increases the risk and progression of nephropathy and atherosclerosis. Adolescent children with diabetes have higher diastolic blood pressure at rest [32].

Diabetic patients with higher HbA1c and higher insulin doses tended to have higher diastolic blood pressure (DBP). Increasing DBP was positively correlated with increasing HbA1c ($P < .025$). The association between higher HbA1c and increased DBP does not necessarily mean there is a causative relationship. There was no association between systolic blood pressure (SBP) and HbA1c [33]. Torchinsky MY et al [33] also reported that, elevation of DBP early in the course of diabetes appears to be clinically relevant. Small elevations of DBP even within the normal range appear to increase the risk for development of diabetic nephropathy.

In a study by Margeirsdottir H.D. et al [17] among 1,658 patients with type 1 diabetes, BP level (systolic and/or diastolic) was above the 90$^{th}$ percentile by age, sex and height in 7% and above the 95$^{th}$ percentile in 4% of their study participants. Of those with elevated BP (above 90$^{th}$ percentile), 72% had elevated systolic BP (SBP), 7% elevated diastolic BP (DBP) and 21% had both SBP and DBP elevated.

Ladeia et al [13] reported that, the mean systolic and diastolic BPs were 102.1±12.3 mm Hg and 67.3±9.2 mm Hg, respectively. A high normal diastolic BP (within the 90th– 95th percentile for age and height) was found in six patients (6.4%): two men and four women. Among these six patients, two of the three had diabetes for 5 years or more. Of the patients in the study, dyslipidemia was found in 42.2% and 23.4%, respectively. U weis et al [34] in their study found

that reversible or modifiable risk factors such as dyslipidemia, renal impairment and systolic hypertension were integrally linked to the risk of cardiovascular mortality and death in those with type 1 diabetes.

## 1.5 STATEMENT OF THE PROBLEM

There are very few studies reporting the burden of chronic complications of diabetes in sub-Saharan Africa [35]. The only study evaluating both adults and children reported a 14% prevalence of retinopathy and a 7.5% prevalence of nephropathy [36]. Another study done at Dar es Salaam, Tanzania reported a high prevalence of dyslipidemia (94.7%) in adults with diabetes. The commonest deranged lipid component was triglyceride levels [37].

T1DM is a common chronic disease in children and adolescents. It is usually not diagnosed early in developing countries due to lack of awareness both by the community and health care providers and or lack of diagnostic facilities. Its burden is also significant in developing countries due late diagnosis and inadequate availability, affordability and accessibility of insulin. Due to these variables, the natural history of type diabetes and its complications is largely unknown.

Overweight and obesity among school-age children is a global problem. The prevalence and severity of overweight is increasing in children and adolescents. The increased prevalence of obesity has also been implicated as a cause for increase in blood pressure among children and adolescents. Thus, the rise in the prevalence and severity of obesity is accompanied by an increase in obesity-related co morbidities, either during childhood or in adulthood because of early-onset, longer-duration obesity.

NAFLD is probably the most common cause of liver disease in the preadolescent and adolescent age groups as in adults. There seems to have been an increase in the prevalence of fatty liver disease along with the dramatic rise in obesity observed in the pediatric population. Other risk factors such as diabetes, insulin resistance and hypertriglyceridemia have been reported to be associated with NAFLD.

Hyperlipidaemia has been incriminated as one of the risk factor for coronary heart disease and atherosclerosis. Diabetes mellitus affects several mechanisms of lipid metabolism. Low insulin levels in T1DM are associated with high levels of chylomicrons and very-low-density lipoprotein (VLDL) and lipoprotein lipase deficiency, resulting in hypertriglyceridemia. No data are currently available on risk factors for macro – vascular diseases in relation to glycemic control among type 1 diabetic children and adolescents attending diabetic clinic at Muhimbili National Hospital, Dar es Salaam.

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## 1.6 STUDY RATIONALE AND JUSTIFICATION

Data on lipid profile in Tanzania children and adolescents with T1DM is scarce. This population is prone to developing chronic complications associated with various risk factors. Patients with diabetes are an increased risk of atherosclerosis and its clinical sequel. Premature atherosclerosis is a risk factor for cardiovascular disease, particularly coronary artery disease and seems to be related to the changes in plasma lipid profile and to poor metabolic control.

Children and adolescents with diabetes have shown to have significant disturbances in lipid metabolism both qualitatively and quantitatively. Level of lipid profile predicts macro vascular complications such as coronary artery disease in patients with T1DM. It contributes substantially to increased morbidity and mortality increasing the cost of health care.

Studies related to lipid profile have been mostly done on adults and not in children with type 1 diabetes. It is important to identify the underlying co-morbidities in this group of patients so as to institute primary prevention and control of complications such as premature atherosclerosis and coronary artery disease. This study aimed to determine the burden of dyslipidaemia and its relation to glycemic control in children and adolescents with T1DM.

### 1.6.1 Study hypothesis

Dyslipidemia is prevalent among children and adolescents with T1DM attending Diabetic clinic at Muhimbili National Hospital, Dar es Salaam.

## 1.7 STUDY OBJECTIVES

### 1.7.1 Broad objective

To determine the risk factors for macro – vascular diseases in relation to glycemic control among type 1 diabetic children and adolescents aged 2 – 19 years with T1DM attending diabetic clinic at Muhimbili National Hospital, Dar es Salaam.

### 1.7.2 Specific objectives

Specific objectives were to determine the

1. Proportion of diabetic children and adolescents with dyslipidaemia by age and sex
2. Proportion of diabetic children and adolescents with dyslipidaemia by levels of glycosylated hemoglobin (HbA1c).
3. Proportion of diabetic children and adolescents with dyslipidaemia by duration of diabetes
4. Proportion of diabetic children and adolescents with dyslipidaemia by Body Mass Index.
5. Proportion of diabetic children and adolescents with dyslipidaemia by Non Alcoholic Fatty Liver Disease (NAFLD).
6. Proportion of diabetic children and adolescents with dyslipidaemia by Blood pressure levels.

# CHAPTER TWO

## 2.0 METHODOLOGY

**2.1 Study area:** Study was conducted at the diabetic clinic outpatient department, Muhimbili National Hospital (MNH), Dar es Salaam, Tanzania. Dar es Salaam is the commercial city of Tanzania located along the East Coast of the Indian Ocean. It has three municipalities namely; Ilala, Temeke and Kinondoni. MNH is one of the biggest hospitals in the country and serves both as National referral and teaching hospital for MUHAS.

The diabetic clinic for children and adolescents at MNH in Dar es Salaam runs once every week on Mondays. Patients are managed by a team of 2 nurses, 2 pediatricians trained in endocrinology and 3 other support staff.

At first visit to the clinic, baseline lipid profiles, HbA1c, serum creatinine, thyroid function tests (TSH and fT4) and ophthalmologic examination are done to all patients. Thereafter, HbA1c is determined for all patients every 3 – 6 months and other parameters are repeated yearly. Patients and guardians are also given diabetes education and advice on appropriate nutrition.

**2.2 Study design:** A hospital based Cross sectional study was done.

**2.3 Study duration:** Study was conducted from August 2011 to December 2011

**2.4 Study population:** Children and adolescents aged 2 to 19 years with proved and documented T1DM in their clinical notes.

**2.5 Sample size:** All children attending Diabetes clinic at MNH who met the needed criterion were enrolled in the study. The following formula was used to calculate the sample size;

$$\mathbf{N= Z^2 P (1-P)/E^2}$$

Where;

**Z** is percentage point corresponding to significance level. If significance level is 5%, **Z** is 1.96

**P** is the prevalence of subjects who had either TC or HDL abnormalities which is 18.6% [20].

**E** corresponds to maximum likely error and is 7% this was used in this study because most of the literature reviews used a 7% likely maximum error instead of 5%.

Therefore the minimum sample size **N** was **112**. However 98 children and adolescents met the needed criterion. This is 87.5% of the required sample size which is adequate for the power of the sample size.

**2.6 Sampling technique:** All eligible patients, whose parents/caregivers gave their consent to participate, were recruited consecutively into the study until the sample size of 98 was attained. Recruitment of participants was conducted exclusively on Mondays during clinic hours. Information regarding the study was given to the parents/caregivers. Thereafter, they were requested to sign an informed consent form for participation in the study.

**2.7 Inclusion criteria:** All children and adolescents aged 2 to 19 years with T1DM attending diabetes clinic whose parents/ guardians gave consent to participate in the study.

**2.8 Exclusion criteria:**

- Newly diagnosed type 1 diabetes or those on insulin treatment for less than 3 months.
- No visit made during the whole study period.
- Parents / guardians who did not consent for their children and adolescents to participate in the study.
- Children and adolescents with other chronic complications such as HIV/AIDS, autoimmune diseases like hypothyroidism as documented in their clinical notes.

**2.9 Data collection:** Data was collected using a structured closed ended questionnaire designed for the purpose of the study. Data collected included age, sex, weight, height etc (Annex II).

**2.9.1 Anthropometric measurement:** For each study participant weight and height was taken and recorded. Thereafter Body Mass Index (BMI) was calculated.

**Weight:** Weight was taken using a solar cell SECA weighing scale with a patient putting on light cloths and without shoes. Weight was recorded to the nearest 100g [38].

**Height:** Height was taken using a height board fixed on the wall with a flat stepping floor. Patients were asked to remove their shoes and stood upright on the flat stepping floor of the board facing forward with a chin at 90º. A headpiece was slowly placed on the head at 90º. Height was recorded to the nearest 0.1cm.

**Body Mass Index:** The body mass index (BMI) was calculated according to the Quetelet equation. Patient's body weight in kilograms (Kg) was divided by his/her height in meters squared (m2).

$$BMI = Wt\ (kg) / Ht\ (m^2)$$

Interpretation of BMI was as follows:

- Below 4th percentile: Underweight
- Between 5th to 84th percentile: Normal (healthy) Weight
- Above 85th: Overweight

BMI for age percentiles for boys and girls respectively was used for interpretation [38]. (Annex III)

**2.9.2 Blood Pressure (BP):** BP level was determined for every study participant. Manual mercury sphygmomanometer was used to record BP level. Children below the age of 5 years, BP level were taken while the child sat on her parent/guardian's lap or at any other possible comfortable position.

Children older than 5 years and adolescents sat on a chair quietly for at least 10 minutes in a quiet room at the diabetic clinic close to their parents / guardians before determining the BP level. Appropriate BP cuff sizes for children and adolescents were applied on the right mid

upper arm with his/her forearm relaxed on the examination table. The cuff used covered at least 75% of the upper arm without obscuring the anterior cubital fossa.

BP was measured three times at an interval of five minutes on the same day and at the same sitting. The mean of the three measurements was recorded. The manometer was positioned at the eye level of the person taking the BP to avoid parallax error.

SBP Percentile Interpretation

- Percentile <90: normal systolic blood pressure
- Percentile >90 and <95: pre hypertensive systolic blood pressure
- Percentile >95: hypertensive systolic blood pressure

DBP Percentile Interpretation

- Percentile <90: normal diastolic blood pressure
- Percentile >90 and <95: pre hypertensive diastolic blood pressure
- Percentile >95: hypertensive diastolic blood pressure

BP was interpreted on the basis of sex, age and height [38] (Annex IV).

**2.9.3 Laboratory Investigations:** Blood samples were collected from all eligible study participants. Blood samples were kept at room temperature in the clinic room. At the end of clinic hours blood samples were taken to the laboratory for processing on the same day.

Five milliliters of venous blood was taken from the anterior cubital fossa of each child, using a sterile disposable syringe and needle after a thorough cleaning of the venopuncture site with a swab soaked in 70% alcohol. Study participants were asked not to have their insulin dose in the morning on the day of blood sample collection. They were asked to bring their breakfast with them. They were allowed to have their insulin and breakfast soon after blood sample collection.

Children less than 5 years of age were asked not to take their meals at least 4 hours before taking their blood sample. For older children, they were asked to fast for at least 6 to 8 hours prior to blood collection. Four milliliters of blood were put in an empty sterile bottle for

determination of fasting Lipid profile. The remaining one milliliter of blood was used for HbA1c determination.

**Lipid profile determination:** At the laboratory centrifugation of the blood at 3,500 revolutions per second for 5 minutes was done. The serum obtained was put in an Architect 8000 machine that was ordered according to the identification numbers of the patients.
The serum was incubated into the machine for about 10 minutes and lipid profile results were automatically displayed on the machine screen. Results were printed out and communicated back to the researcher. The lipid profile levels were interpreted on the basis of sex, and age percentiles [10]. (Annex V)

**HbA1c determination:** Blood was put in a capillary tube which was then entered into a reagent cartridge. The cartridge was inserted into the analyzer which is a DCA 2000 + machine. Automated results were read from the machine after a processing time of six minutes.

Glycosylated hemoglobin level:

- Good control ≤7.5%
- Moderate control 7.5–10%
- Poor control 10–12.5%
- Very poor control ≥12.5% [7]**.**

**2.9.4 Imaging:** An abdominal ultrasound was done to all study participants. An ultra sound machine Phillips MD 4,000 and a probe/transducer lurvilinear probes with 3-5 MHZ (frequency) was used. Proper setting of the gain system (TGC/DGC) was done prior to the examination of the study participant. The examination was done while the study participant lied on bed in a supine position. Liver was scanned in longitudinal and transverse views.

The ultrasound was done by an experienced radiologist according to study participants' appointment date. The principal investigator (researcher) was present while the ultrasound was performed. Criterion for the fatty liver was based on the increase ecchogenicity of liver

parenchyma detected as decrease definitions of portal vein walls, gall bladder wall and decrease diaphragm movements when the study participant breathed in and out.

Liver echo pattern was graded as follows:

**Grade 1 (Mild)** Slight diffuse increase in fine echoes in the hepatic parenchyma with normal visualization of the diaphragm and intra hepatic vessel borders.

**Grade 2 (Moderate)** Moderate diffuse increase in fine echoes with slightly impaired visualization ion of the diaphragm and intra hepatic vessel borders.

**Grade 3 (Marked/ Severe)** A marked increase in fine echoes with poor/no visualization of the intra hepatic vessel borders, diaphragm and posterior portion of the right lobe of the liver [39].

**2.10 Data analysis**: All filled questionnaires were coded before entering into the computer data base. Data cleaning was done by consistence checks. Statistical Package for Social Sciences (SPSS) version 17 was used for analysis.

Continuous variables were expressed as means ± SD. Differences in proportions were tested using the chi square ($\chi 2$) test. Fisher's exact test was used where applicable.

P value of less than 0.05 ($p < 0.05$) was considered statistically significant.

**2.11 Ethical Issues/Consideration:** The aims and benefits of the study were explained to the parents/guardians. Children were managed according to the hospital protocol along the routine lines of patient care at the Pediatric Diabetes Clinic.

Children and their parents/ guardians were given health education on the condition and how to manage it on individual basis.

Laboratory results of each child in the study were communicated back to the parents/ guardians / caretaker and physician taking care of the child. Those with complications or any

other medical condition were managed according to the management protocol of each condition.

Parents/ guardians signed a written informed consent prior to participate in the study.

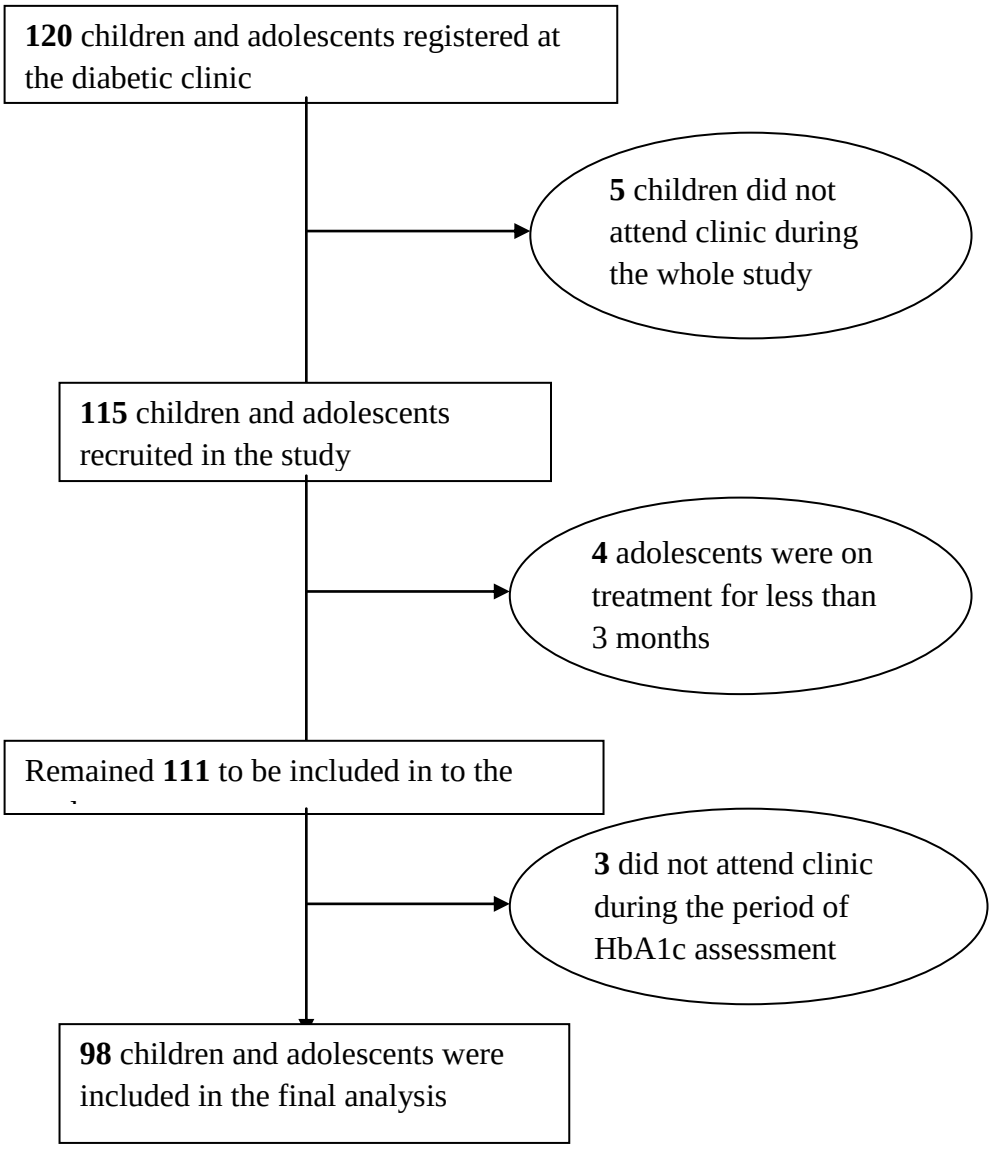
Parents/ guardians who refused to participate in the study were never denied the right to be treated.

**2.12 Ethical clearance:** Ethical clearance to carry out this study was sought from Muhimbili University of Health and Allied Sciences (MUHAS) higher degree research and publication committee. Permission to conduct the study at Muhimbili National Hospital (MNH) was sought from the Director of Clinical Services.

# CHAPTER THREE

## 3.0 RESULTS

FIGURE 1: Flow chart of study participants.



Baseline characteristics studied are shown in table 1. The mean age was 14.26 ± 3.9 years with a range from 3 to 19 years. Fifty two percent of the study participants were ≥14 years of age. Most of the children and adolescents (35.7%) had HbA1c between 10 – 12.5% and 36.7% had HbA1c more than 12.5%. Mean HbA1c was 11.40±2.24. Mean duration of diabetes 4.44±3.15 years. Most of the patients (57%) had less than 5 year's duration of diabetes.

Majority of the children and adolescents (74.5%) had a normal BMI ($4^{th}$ – $84^{th}$ percentile) with a mean BMI of 19.35 ±4.37. nine children and adolescents (9.2%) had diastolic hypertension (DBP level > 95th percentile) and 14 (14.3%) had pre diastolic hypertension (90 - 95th percentile).

**Table 1: Baseline characteristics of the study participants (n = 98)**

| Characteristics | Mean ± SD | Frequency | |
|---|---|---|---|
| | | N | % |
| Age | 14.26 ± 3.90 | | |
| < 10 years | | 12 | 12.2 |
| 10 - 14 years | | 35 | 35.7 |
| > 14 years | | 51 | 52.0 |
| Sex | | | |
| Males | | 48 | 49.0 |
| Females | | 50 | 51.0 |
| HbA1C (%) | 11.40 ± 2.24 | | |
| < 7.5 | | 3 | 3.1 |
| 7.5 - 10.0 | | 24 | 24.5 |
| 10.0 - 12.5 | | 35 | 35.7 |
| ≥12.5 | | 36 | 36.7 |
| Diabetes Duration | 4.44 ± 3.15 | | |
| < 5 years | | 57 | 58.2 |
| ≥ 5 years | | 41 | 41.8 |
| BMI (Kg/m²) | 19.35 ± 4.37 | | |
| ≤ 4th percentile | | 12 | 12.2 |
| 4th - 84th percentile | | 73 | 74.5 |
| ≥85th percentile | | 13 | 13.3 |
| SBP (mmHg) | 100.71 ± 14.01 | | |
| <90th percentile | | 88 | 89.8 |
| 90 - 95th percentile | | 5 | 5.1 |
| > 95th percentile | | 5 | 5.1 |
| DBP (mmHg) | 72.40 ± 11.29 | | |
| <90th percentile | | 75 | 76.5 |
| 90 - 95th percentile | | 14 | 14.3 |
| > 95th percentile | | 9 | 9.2 |

In table 2, dyslipidemia was found in 72 (73.5%) of the 98 study participants. The main abnormality was high LDL cholesterol found in 29/98 (29.6%) patients. Other abnormalities were high TC in 25/98 (25.5%), low HDL cholesterol in 13/98 (13.3%) and high triglycerides in 5/98 (5.1%) patients.

**Table 2: Frequency distribution of abnormal lipid profile among children and adolescents with T1DM (n = 98)**

| Lipid Subclass | Mean ± SD | No of patients | % |
|---|---|---|---|
| High LDL cholesterol | 4.65 ± 1.39 | 29 | 29.6 |
| High Total cholesterol | 3.05 ± 1.23 | 25 | 25.5 |
| Low HDL cholesterol | 1.35 ± 0.37 | 13 | 13.3 |
| High Triglycerides | 1.18 ± 0.80 | 5 | 5.1 |
| Total | | 72 | 73.5 |

In table 3 below, high LDL - C and TC increased with age. LDL was high (28.6%) in10 -14 age group compared to >14 years (33.3%) age group. The findings were not statistically significant. Females had high proportion of the four dyslipidemia [high LDL – C (36.0%), high TC (34.0%), high TG (8.0%), and low HDL – C (14.0%)]

**Table 3: Abnormal lipid profile by age and sex (n = 98).**

| Variable | Lipid profile | | | |
|---|---|---|---|---|
| | High LDL - C | High TC | Low HDL - C | High TG |
| Age of the patient | | | | |
| < 10 years | 2/12 (16.7%) | 2/12 (16.7%) | 0 (0.0%) | 1/12 (8.3%) |
| 10 - 14 years | 10/35 (28.6%) | 9/35 (25.7%) | 6/35 (17.1%) | 2/35 (5.7%) |
| > 14 years | 17/51 (33.3%) | 14/51 (27.5%) | 7/51 (13.7%) | 2/51 (3.9%) |
| P - value | 0.516 | 0.742 | 0.375 | 0.818 |
| Sex of the patient | | | | |
| Males | 11/48 (22.9%) | 8/48 (16.7% | 6 /48 (12.5%) | 1/48 (2.1%) |
| Females | 18/50 (36.0%) | 17/50 (34.0%) | 7/50 (14.0%) | 4/50 (8.0%) |
| P - value | 0.156 | 0.049* | 0.827 | 0.183 |

Fischer's exact test (age) and Chi square test (sex)

*P – value statistically significant

Children and adolescents with very poor (HbA1c ≥12.5%) and poor (HbA1c 10.0 – 12.5%) glycemic control had high proportion of all the four dyslipidemia. However, this was not statistically significant (Table 4).

**Table 4: Glycemic control in relation to abnormal lipid profile (n = 98).**

| HbA1C (%) | Lipid profile | | | |
|---|---|---|---|---|
| | High LDL - C | High TC | Low HDL - C | High TG |
| <7.5 | 1/3 (33.3%) | 1/3 (33.3%) | 0 (0.0%) | 0 (0.0%) |
| 7.5 - 10.0 | 4/24 (16.7%) | 3/24 (12.5%) | 3/24 (12.5%) | 1/24 (4.2%) |
| 10.0 - 12.5 | 10/35 (28.6%) | 10/35 (28.6%) | 4/35 (11.4%) | 1/35 (2.9%) |
| ≥ 12.5 | 14 /36 (38.9%) | 11 /36 (30.6%) | 6/36 (16.7%) | 3/36 (8.3%) |
| P - value | 0.277 | 0.335 | 0.778 | 0.915 |

Fischer's exact test used

Table 5 below shows that, children and adolescents with long duration of diabetes (≥ 5 years) had high LDL – C (43.9%) and TC (34.1%) compared to those who had duration of diabetes (< 5 years).This was statistically significant for high TC (P – value 0.008).

**Table 5: Diabetes duration and abnormal lipid profile (n = 98).**

| Duration of | Lipid profile | | | |
|---|---|---|---|---|
| Diabetes | High LDL - C | High TC | Low HDL - C | High TG |
| < 5 years | 11/57 (29.3%) | 11/57 (19.3%) | 8 /57(14.0%) | 3 /57 (5.3%) |
| ≥ 5 years | 18/41 (43.9%) | 14/41 (34.1%) | 5/41 (12.2%) | 2 /41(4.9%) |
| P - value | 0.008* | 0.096 | 0.791 | 1.000 |

Chi square test used,*P – Value statistically significant

Majority of the patients had a healthy weight (73/98). All patients who are overweight have high LDL, TC, and TG and normal HDL – C (Table 6).

**Table 6: BMI of the patient and abnormal lipid profile (n = 98).**

| BMI of the patient | Lipid profile | | | |
|---|---|---|---|---|
| | High LDL - C | High TC | Low HDL - C | High TG |
| < 4th percentile | 3 /12 (25.0%) | 2 /12 (16.7%) | 2/12 (16.7%) | 2 /12 (16.7%) |
| 4th - 84th percentile | 20/73 (27.4%) | 18 /73 (24.7%) | 11/73 (15.1%) | 2/73 (2.7%) |
| ≥ 85th percentile | 6/13 (46.2%) | 5/13 (38.5%) | 0 (0.0%) | 1 /13 (7.7%) |
| P - value | 0.404 | 0.467 | 0.339 | 0.067 |

Fischer's exact test used

In table 7 below, patients with SBP < 90$^{th}$ percentile had abnormal lipid profile compared to patients who had a SBP between 90$^{th}$ – 95$^{th}$ percentile and those above 95$^{th}$ percentile. Increasing DBP between 90$^{th}$ – 95$^{th}$ percentile and above 95$^{th}$ percentile was both associated with high LDL – C and TC.

**Table 7: SBP and DBP levels in relation to abnormal lipid profile (n = 98).**

| Variable | Lipid profile | | | |
|---|---|---|---|---|
| | High LDL - C | High TC | Low HDL - C | High TG |
| SBP level (mmHg) | | | | |
| <90th percentile | 29/92 (31.5%) | 24/92 (26.1%) | 12/92 (13.6%) | 5/92 (5.4%) |
| 90 - 95th percentile | 0 (0.0%) | 0 (0.0%) | 1/3 (33.3%) | 0 (0.0%) |
| > 95th percentile | 0 (0.0%) | 1 (33.3%) | 0 (0.0%) | 0 (0.0%) |
| P - value | 1.000 | 0.84 | 0.777 | 0.08 |
| DBP level (mmHg) | | | | |
| <90th percentile | 19/75 (25.3%) | 15/75 (20.0%) | 12/75 (16.0%) | 3/75 (4.0%) |
| 90 - 95th percentile | 6/14 (42.9%) | 6/14 (42.9%) | 1/14 (7.1%) | 0 (0.0%) |
| > 95th percentile | 4/9 (44.4%) | 4/9 (44.4%) | 0 (0.0%) | 2/9 (22.0%) |
| P - value | 0.247 | 0.06 | 0.445 | 0.118 |

Fischer's exact test used

Majority of the patients had normal liver 72/85 (84.7%). All children and adolescents (13) with mild fatty liver had high LDL – C (46.2%), high TC (38.5%) and low HDL – C (15.4%) none had high TG. This was statistically significant for high LDL – C and high TC (Table 8).

**Table 8: Association between fatty liver and abnormal lipid profile (n = 85).**

| Fatty Liver | Lipid profile | | | |
|---|---|---|---|---|
| | High LDL - C | High TC | Low HDL - C | High TG |
| Normal liver | 12/72 (16.7%) | 9/72 (12.5%) | 8/72 (11.1%) | 1/72 (1.4%) |
| Mild fatty liver | 6/13 (46.2%) | 5/13 (38.5%) | 2/13 (15.4%) | 0 (0.0%) |
| P - value | 0.027* | 0.035* | 0.646 | 1.000 |

Fischer's exact test used*P – value statistically significant

# CHAPTER FOUR

## 4.0 DISCUSSION

### 4.1 Age, Sex and Dyslipidemia,

The high prevalence of abnormal lipid profile found in this study was 73.5%. Of these, 29.6% had high LDL – C and 25.5% had high TC. This was comparable to the findings reported by Ladeia et al,(13) in which a high level of LDL was found to be 31.8% and TC was 24.2%. Similarly Maahs et al [20] also showed that 15.4% had abnormal TC values, and 18.6% had abnormal HDL. The findings observed could be due to the fact that children and adolescents with T1DM are predisposed to chronic hyperglycemia. The combination of insulin deficiency and elevated plasma values of the counter-regulatory hormones (epinephrine, cortisol, growth hormone and glucagon), is also responsible for accelerated lipolysis and impaired lipid synthesis. This results in increased plasma concentrations of total lipids, cholesterol, triglycerides, and free fatty acids.

Ladeia et al,[13] reported that the younger patients (19 years and below), eight out of 66 (12.1%) presented with high TG level. This pattern was similar to results of the current study in which 5 out of 98 (5.1%) study participants had high TG. However, low HDL – C (5.1%) was reported in this study. Similar findings were reported by Maahs et al(20) 3.4% of the subjects had abnormal HDL values, different from Ladeia et al [13] in which they reported a high prevalence of low HDL (37.2%).

Triglycerides are the primary fat in our bodies. People who are overweight tend to have much higher levels of these fats. In this study only 13.3% were overweight and most of the study participants had normal BMI ($4^{th}$ – $84^{th}$ percentile). These can explain why small proportion of study participants had high TG. Obesity has a direct causal link with high levels of triglycerides. The low prevalence of obesity may have contributed to the low proportion of

high TG values among the study participant. Due to the unavailability of the dietary questionnaire the component of diet was not assessed in this study.

In another study by Margeirsdottir H.D et al [17] also reported a high proportion of patients with T1DM had dyslipidemia as in this study. The author went further and reported as many as 35% of the patients had LDL-cholesterol >2.6 mmol/l, 10% had LDL-cholesterol >3.4 mmol/l, while 2% had LDL-cholesterol >4.1 mmol/l. The trend of abnormal lipid profile reported was almost the same as in this study. In the current study mean lipid values were within normal limits similar to that reported by Maahs et al [20]. In their study the mean serum TC level was higher in females than in males (P value = .0009). The mean low HDL – C level did not differ significantly by gender. Contrary to the current study were there was no gender difference found with respect to any subclass of abnormal lipid profile. In the current study it was found that the dyslipidemia was more common in females compared to male counterparts.

This is in contrast to the findings by Margeirsdottir et al [17] who reported that there was no difference between boys and girls except for LDL- C and HDL-C, where a higher proportion of the girls had LDL- C >2.6 mmol/l (p=0.001) and a higher proportion of the boys had HDL - C <1.1 mmol/l (p=0.001). In another study, Qereshi et al [22] reported that serum TG was higher in female children. These findings were similar to the results of the current study which reported a high TG level in females.

In adolescence, the transitional period that begins with puberty, is marked by dynamic physiological changes in both boys and girls. Changes that occur in body composition during adolescence have been well characterized. In boys, fat-free mass tends to increase, and body fat as a percentage of body weight decreases. In girls, both fat and fat-free mass increase, and fat-free mass as a percentage of body weight decreases. Noteworthy is that the risk of becoming overweight during adolescence appears to be higher among girls than it is among boys [25].

### 4.2 HbA1c and Dyslipidemia

John Guy et al [23] reported that patients with T1DM and optimal A1C (HbA1c ≤ 7.5%) values were more likely to be male contrary to this study where by both sexes were more or less equally affected. The author went further and found that, patients with T1DM and suboptimal A1C values (HbA1c ≥ 7.5%) were older (≥ 10 years) and tended to have a lower BMI. Similar to this study, also patients with older age 10- 14 and ≥ 14 years had suboptimal HbA1c. Contrary to John Guy study most patients had normal BMI in the current study. The poor glycemic control with increasing age as demonstrated in the current study may be due to the onset of puberty and the contribution of pubertal hormones. In addition, psychological and social stressors in this age group may result in poor compliance to treatment.

In this study children and adolescents with good control no one had low HDL – C. As the glycemic control gets worse study participants tended to have low HDL – C. This was contrary to study by John Guy et al [23] who have reported that youth with suboptimal HbA1c had higher HDL - C levels than control subjects. Ladeia et al [13] in their study reported that, lipid profile correlates with glycemic control in young patients with T1DM. Patients with poor glycemic control group tended to have higher TC. These findings were similar to the current study which showed that patients who had HbA1c ≤ 7.5% (well controlled group) compared to a group of poor control both had abnormal lipid profile. The findings were statistically insignificant.

Similar findings were reported by Maahs et al [20], HbA1c was significantly greater in subjects with TC levels of > 200 mg/dL (P < .0001) than in those with normal TC. They further reported that HbA1c was significantly greater in subjects with non-HDL levels ≥130 mg/dL than in those with non-HDL levels < 130mg/dL (P < .0001). Similarities observed in these studies could be due to direct effect of glycemic control to lipid metabolism. Relative or absolute lack of circulating insulin which is found in T1DM results in unsuppressed lipolysis. This leads to increase in free fatty acids, leading to an increased LDL - C.

Different from their study, in the current study it was found that majority of the study participants had poor and very poor glycemic control but abnormality in lipid profile was found in both groups. In this study, patients with normal TC also had high HbA1c and in both scenarios were not statistically significant. Similar to the current study, Azad K et al (21)reported that, children with diabetes with poor glycemic control had higher fasting TC, TG and LDL – C. John Guy et al [23] also reported that youth with suboptimal levels of A1C had a more atherogenic lipid and lipoprotein pattern. In this study where we have a high proportion of study population with poor and very poor glycemic control, patients are at greater risk of having abnormal lipid profile. Low prevalence of abnormal lipid profile in other studies could due to a better glycemic control in their study populations.

**4.3 Duration of Diabetes and Dyslipidemia**

In this study, it was found that, children and adolescents with a long duration of diabetes had high LDL – C (43.9%) and high TC (34.1%)**.** However it was shown that, study participants with duration of diabetes less than 5 years had higher TG and low HDL – C compared to those with diabetes more than 5 years. This was not statistically significant. In the current study the mean duration of diabetes was 4.44 ± 3.15 years (3months – 19 years). This was similar to the results of other studies (13, 20, 21) with mean duration of diabetes of 5.0±3.6 years, 3.9 ± 3.3 years, and 5.3 (4.5-6.1) years respectively.

Further more in this study; it was found that duration of diabetes of more than five years was associated with elevated levels of LDL-C. Contrary to this study, Maahs et al, [20] found that duration of T1DM was not statistically significant. Children with longer duration of diabetes ≥ 5 years tend to have poor glycemic control. This can be explained partially by the diminished "honeymoon effect" a common finding in newly diagnosed children with T1DM. This is a period of relatively good glycemic control that occurs due to residual beta cell function in the first 2 years following diagnosis. Of those with diabetes of more than 5 years poor glycemic control results in elevated plasma concentration of total lipids especially high – LDL - C.

### 4.4 Body mass Index and Dyslipidemia

Majority of the patients in this study had a healthy weight (74.5%). Underweight and overweight patients were 12.2% and 13.3% respectively. In a study reported by Ladeia et al [13] it was found that only three of 94 (3.2%) were overweight. This is a lower percentage compared to the current study (13.3%). Ladeia et al [13] reported a low percentage (7.4%) of patients with low BMI(underweight) compared to this study were 12.2% had low BMI. There was no statistical difference observed.

Further, Qereshi et al [22]**,** documented the presence of dyslipidemia and hypertension in overweight T1DM patients. They also admitted that such metabolic disturbances may begin to develop even in type 1 diabetic children and adolescents with normal BMI. This was also true in this study which showed that all patients who were overweight had high - LDL, TC, and TG surprisingly with normal HDL – C. Likewise in the current study, patients with healthy weight also had high LDL – C, high TC, high TG and low HDL – C.

In the above findings probably the very low prevalence of obesity may have contributed to keeping the TG values within the normal range. This can also explain the low prevalence of high TG in this study compared to other studies [13]. Also the low prevalence of obesity in this study can be explained by the effect of chronic ill health on growth and development. Most of the study participants had poor and very poor glycemic control. Chronic hyperglycemia results in loss of calories in the urine (glycosuria), triggering a compensatory hyperphagia. If this hyperphagia does not keep pace with the glycosuria, loss of body fat ensues, with clinical weight loss and diminished subcutaneous fat stores [8]. This could be the explanation as to why majority of the patients in the current study had healthy weight.

The differences observed could be due to different modalities used by different centers in the management of children and adolescents with T1DM especially in the availability of drugs (insulin) and overall glycemic control. Moreover, in this study, the most prevalent lipid profile included high TC and LDL, low HDL, and high TG levels. In non diabetic children and

adolescents, hypercholesterolemia is usually associated with excess weight. This was not the case in this study which showed a low prevalence of obesity. In the current study dyslipidemia probably was related to poor glycemic control.

**4.5 NAFLD and Dyslipidemia**

In a study done by El Karasky et al [30] it was shown that the estimated prevalence of NAFLD was 38.5%. The study was done in obese non diabetic Egyptian children and adolescents. The author went further and reported that 53.9% of the patients had increased ecchogenicity of the liver and 22.4% showed mild fatty liver. In the current study the prevalence of fatty liver was found to be 15.3%. This was a lower prevalence expected as patients in this study besides overweight and obesity had another risk factor for fatty liver which is diabetes mellitus.

Moreover the difference observed can be due to the fact that most of our children had a healthy weight (BMI between 4$^{th}$ and 84$^{th}$ percentile). From this study it was found that of the children and adolescents with normal weight 9/64 (14.1%) and those who were overweight 3/11 (27.3%) had mild fatty liver. Only one study participant was underweight and had mild fatty liver. This can be explained by the fact that underweight, a form of malnutrition is also a risk factor for the development of fatty liver.

In another study by Targher, G et al [31] NAFLD was present in 44.4% of the study population, and it represented the most common cause (69.8%) of hepatic steatosis on ultrasound examination. This was a much higher percentage compared to this study which demonstrated that only 15.3% had mild fatty liver by ultrasound examination. This higher difference observed could be explained by the fact that in their study the mean age (43 years) and mean duration of diabetes (18.5 years) was much higher compared to the current our study population.

With respect to study participants in whom their ultrasound findings were available. Males and females were more or less similar in number with ratio of 1.1:1. Females were observed to have mild fatty liver compared to males (30% Vs 2.2%). This finding was statistically significant (P – value 0.000). Among the three study participants who had good glycemic control, two of them had mild fatty liver. This showed that better control of glucose (HbA1c≤ 7.5%) did not appear to offer protection against fatty liver. In this study, it was found that children and adolescents with normal liver also had high levels of HbA1c.This is contrary to a study done by Giovanni which showed that study population with NAFLD also had higher HbA1c.

All children and adolescents with mild fatty liver had high LDL - C, high TC and low HDL – C none had high TG. Among those with mild fatty liver 46.2% had high LDL – C, 38.5% had high TC and 15.4% had low HDL- C. This was statistically significant. (P – Value for high LDL – C and High TC were 0.027 and 0.035 respectively except for low HDL – C which was statistically insignificant P – value 0.646). High HbA1c reflects poor control of glucose thus chronic hyperglycemia. With the insulin deficiency present in children and adolescents with type 1 diabetes there is impaired lipid synthesis. This results in increased plasma concentrations of total lipids and its sub classes.

**4.6 Blood Pressure level and Dyslipidemia**

From this study, 24.5% of children and adolescents with T1DM had isolated high SBP / DBP or both. The BP (systolic or diastolic) was above the $90^{th}$ percentile by age, sex and height in 19.4% and above $95^{th}$ percentile in 14.3% of the participants respectively. Of those with elevated BP (above $95^{th}$ percentile) 5.1% had elevated SBP and 9.2% had elevated DBP.

There were a higher percentage of patients with elevated SBP and DBP though the proportion of those with elevated DBP was higher than in those with elevated SBP. This study has shown a higher proportion of study participants with high BP level contrary to Margeirsdottir et al [17]**.** They reported that BP (systolic and/or diastolic) was above the 90$^{th}$ percentile by age, sex and height in 7% and above the 95$^{th}$ percentile in 4% of participants.

Margeirsdottir et al,[17] further reported that of those with elevated BP (above 90$^{th}$ percentile), 72% had elevated SBP, 7% elevated DBP and 21% had both SBP and DBP elevated. Contrary to this study where among those with elevated BP (above 90$^{th}$ percentile), 14.3% had elevated DBP. Moreover Dahl Jorgensen et al [15] reported that patients with T1D have stiffer arteries than non-diabetic persons. A higher prevalence of isolated systolic hypertension has been reported in type 1 diabetic patients. This was contrary to the results of this study which showed higher proportion of study participants had elevated DBP.

Vascular changes among children and adolescents with type 1 diabetes mellitus are related not only to time since diagnosis (duration of diabetes) but also to glucose control. DBP is more influenced by peripheral vascular resistance than in SBP [32]. Moreover, it has been reported that type 1 diabetic children and adolescents have higher BP values and they have hypertension or prehypertension more often in comparison with their healthy peers. The relation of pathogenesis of diabetes and hypertension is still a subject of many researches [40].

In this study a high proportion of patients with normal SBP (89.8%) and normal DBP (76.5%) were found. These findings are similar to a study by Ladeia et al [13]**;** who reported that most children and adolescents with T1DM had normal BP level. They found that 23.4% of patients who had high BP had abnormal lipid profile. In this study most patients who had high BP also had deranged lipid profile. Surprisingly even those with normal BP level for age, height and sex had abnormal lipid profile. These findings were statistically insignificant.

The low prevalence of elevated BP in this study may be a consequence of the mean duration of the disease (4.44 ± 3.15 years). This is a relatively short period for the development of this complication. Hypertension is uncommon in infants and younger children. When present, usually indicates an underlying disease process (secondary hypertension). In children with T1DM it is usually secondary to diabetic nephropathy. In contrast, adolescents may develop primary or essential hypertension [8].

Contrary to this study, Margeirsdottir et al [17], found that the proportion of patients in their study with BP above the 90th and 95th percentiles was within the range expected for the general population. It is, however, important to remember that an elevated BP is a risk factor for CVD both in people with diabetes and in the general population.

### 4.7 Study limitations

1. The small study population size at our clinic may have failed to demonstrate a significant associations
2. The study being a cross sectional study, only association between different variables could be demonstrated. It was not possible to study the causal relationships.
3. Dietary questionnaire could not be evaluated in this study due to the unavailability of methods of estimation of different calories for different groups of food.

# CHAPTER FIVE

## 5.0 CONCLUSIONS

1. The prevalence of abnormal lipid profile among children and adolescents with T1DM attending diabetes clinic at MNH is high (73.5%). The commonest abnormal lipid profile was high LDL – C (29.6%) followed by high TC (25.5%).
2. Abnormal lipid profile becomes more prevalent as the glycemic control worsens. High lipid profile along with poor glycemic control is an important risk factor for chronic complications of diabetes mellitus.
3. This study showed that 74.5% of the study population had normal weight and 15.3% had ultrasound-diagnosed mild fatty liver.

## 5.1 RECOMMENDATIONS

1. These results highlight the importance of glycemic control in children and adolescents with T1DM to prevent occurrence of dyslipidemia.

2. Regular screening for dyslipidemia in children and adolescents with T1DM. Early identification and early treatment are needed so as to prevent cardiovascular disease in high risk children and adolescents with diabetes.

3. Further studies are needed to identify other risk factors and causal relations for the development of fatty liver in children and adolescents with T1DM.

**REFERENCES**

1. McLarty DG, Pollitt C, Swai AB. Diabetes in Africa. Diabet Med. 1990; 7(8):670-84.

2. Motala AA, Omar MA, Pirie FJ. Diabetes in Africa. Epidemiology of type 1 and type 2 diabetes in Africa. J Cardiovasc Risk. 2003; 10(2):77-83.

3. Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabet Med. 1997; 14 Suppl 5:S1-85.

4. Elamin A, Omer MI, Hofvander Y, Tuvemo T. Prevalence of IDDM in schoolchildren in Khartoum, Sudan. Diabetes Care. 1989; 12(6):430-2.

5. Elamin A, Omer MI, Zein K, Tuvemo T. Epidemiology of childhood type I diabetes in Sudan, 1987-1990. Diabetes Care. 1992; 15(11):1556-9.

6. Afoke AO, Ejeh NM, Nwonu EN, Okafor CO, Udeh NJ, Ludvigsson J. Prevalence and clinical picture of IDDM in Nigerian Igbo schoolchildren. Diabetes Care. 1992; 15(10):1310-2.

7. Majaliwa ES, Munubhi E, Ramaiya K, Mpembeni R, Sanyiwa A, Mohn A, et al. Survey on acute and chronic complications in children and adolescents with type 1 diabetes at Muhimbili National Hospital in Dar es Salaam, Tanzania. Diabetes Care. 2007; 30(9):2187-92.

8. Kliegman RM, Richard E. Behrman, Hal B. Jenson, Bonita F. Stanton, Nelson Textbook of Pediatrics, Philadelphia, PA, USA, Elsevier's Health Sciences Rights Department 2008.

9. Report of a WHO Consultation. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. 1999(WHO/NCD/NCS/99.2).

10. Lipman TH, Hayman LL, Fabian CE. Risk factors for cardiovascular disease in children with type I diabetes: Part II. J Pediatr Nurs. 1997; 12(6):318-22.

11. American Diabetic Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care Suppl 1, 2010;33.

12. Goldberg IJ. Diabetic dyslipidemia: Causes and consequences. J Clinical Endocronology Metabolism. 2001; 86(3): 965-971

13. Ladeia AM, Adan L, Couto-Silva AC, Hiltner A, Guimaraes AC. Lipid profile correlates with glycemic control in young patients with type 1 diabetes mellitus. Prev Cardiol. 2006 spring; 9(2):82-8.
14. Shamir R, Kassis H, Kaplan M, Naveh T, Shehadeh N. Glycemic control in adolescents with type 1 diabetes mellitus improves lipid serum levels and oxidative stress. Pediatr Diabetes. 2008; 9(2):104-9.
15 Dahl-Jorgensen K, Larsen JR, Hanssen KF. Atherosclerosis in childhood and adolescent type 1 diabetes: early disease, early treatment? Diabetologia. 2005; 48(8):1445-53.
16. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, et al. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia. 2003; 46(6):760-5.
17. Margeirsdottir HD, Larsen JR, Brunborg C, Overby NC, Dahl-Jorgensen K. High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study. Diabetologia. 2008; 51(4):554-61.
18. McGill HC, Jr., McMahan CA, Malcom GT, Oalmann MC, Strong JP. Relation of glycohemoglobin and adiposity to atherosclerosis in youth. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb Vasc Biol. 1995; 15(4):431-40.
19. Jarvisalo MJ, Jartti L, Nanto-Salonen K, Irjala K, Ronnemaa T, Hartiala JJ, et al. Increased aortic intima-media thickness: a marker of preclinical atherosclerosis in high-risk children. Circulation. 2001 11; 104(24):2943-7.
20. Maahs DM, Maniatis AK, Nadeau K, Wadwa RP, McFann K, Klingensmith GJ. Total cholesterol and high-density lipoprotein levels in pediatric subjects with type 1 diabetes mellitus. J Pediatr. 2005; 147(4):544-6.
21. Azad K, Parkin JM, Court S, Laker MF, Alberti KG. Circulating lipids and glycaemic control in insulin dependent diabetic children. Arch Dis Child. 1994; 71(2):108-13.
22. Qureshi, A.  yslipidemia in recently diagnosed young subjects of Type 1 Diabetes Mellitus with normal/ favourable BMI: A risk factor of macrovascular disease. Biomedica. 2008; 24.

23. Guy J, Ogden L, Wadwa RP, Hamman RF, Mayer-Davis EJ, Liese AD, et al. Lipid and lipoprotein profiles in youth with and without type 1 diabetes: the SEARCH for Diabetes in Youth case-control study. Diabetes Care. 2009; 32(3):416-20.
24. Hicham Mohammadi AEM, Mohamed Hassar, Brahim Bouchrif, Fatima Qarbal, Fatima Dahbi, Latifa Hilal, Noreddine Ghalim. Glycaemic control, HbA1c, and lipid profilein children with type 1 Diabetes Mellitus. European Journal of Scientific Research. 2009; 29:289 - 94.
25. Daniels SR, Arnett DK, Eckel RH, Gidding SS, Hayman LL, Kumanyika S, et al. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. Circulation. 2005; 19; 111(15):1999-2012.
26. Ayoub C. Kafyulilo FMSM. Prevalence of overweight and obesity among primary school children in Tanzania: Experiences from Kinondoni and Njombe Districts. 2006.
27. Nanda K. Non-alcoholic steatohepatitis in children. Pediatr Transplant. 2004; 8(6):613-8.
28. Mathur P, Das MK, Arora NK. Non-alcoholic fatty liver disease and childhood obesity. Indian J Pediatr. 2007; 74(4):401-7.
29. Patton HM, Sirlin C, Behling C, Middleton M, Schwimmer JB, Lavine JE. Pediatric nonalcoholic fatty liver disease: a critical appraisal of current data and implications for future research. J Pediatr Gastroenterol Nutr. 2006; 43(4):413-27.
30. el-Karaksy HM, el-Koofy NM, Anwar GM, el-Mougy FM, el-Hennawy A, Fahmy ME. Predictors of non-alcoholic fatty liver disease in obese and overweight Egyptian children: single center study. Saudi J Gastroenterol.; 17(1):40-6.
31. Targher G, Bertolini L, Padovani R, Rodella S, Zoppini G, Pichiri I, et al. Prevalence of non-alcoholic fatty liver disease and its association with cardiovascular disease in patients with type 1 diabetes. J Hepatol; 53(4):713-8.
32. Newkumet KM, Goble MM, Young RB, Kaplowitz PB, Schieken RM. Altered blood pressure reactivity in adolescent diabetics. PAediatrics. 1994; 93(4):616-21.
33. Torchinsky MY, Gomez R, Rao J, Vargas A, Mercante DE, Chalew SA. Poor glycemic control is associated with increased diastolic blood pressure and heart rate in children with Type 1 diabetes. J Diabetes Complications. 2004; 18(4):220-3.

34.Weis U, Turner B, Gibney J, Watts GF, Burke V, Shaw KM, et al. Long-term predictors of coronary artery disease and mortality in type 1 diabetes. QJM. 2001; 94(11):623-30.
35. Sidibe EH. [Main complications of diabetes mellitus in Africa]. Ann Med Interne (Paris). 2000; 151(8):624-8.
36. Neuhann HF, Warter-Neuhann C, Lyaruu I, Msuya L. Diabetes care in Kilimanjaro region: clinical presentation and problems of patients of the diabetes clinic at the regional referral hospital-an inventory before structured intervention. Diabet Med. 2002; 19(6):509-13.
37. Chattanda SP, Mgonda YM, Diabetic dyslipidemia, prevalence and clinical characteristics among patients with diabetes in Dar es Salaam Tanzania Medical Journal. 2007; 23(1).
38. Clinical Growth Charts NCfCDPaH. CDC. 2000.
39. Mottin CC, Moretto M, Padoin AV, Swarowsky AM, Toneto MG, Glock L, et al. The role of ultrasound in the diagnosis of hepatic steatosis in morbidly obese patients. Obes Surg. 2004; 14(5):635-7.
40. Pietrzak I, Mianowska B, Gadzicka A, Mlynarski W, Szadkowska A. Blood pressure in children and adolescents with type 1 diabetes mellitus--the influence of body mass index and fat mass. Pediatr Endocrinol Diabetes Metab. 2009; 15(4):240-5.

## ANNEXES

### ANNEX I Consent Form (English Version)

**ID no**……..

Consent to participate in the study, to determine the lipid profile and associated factors in relation to glycemic control among children and adolescents aged 2 – 19 years T1DM attending Muhimbili National Hospital.

**Greetings**! My name is Isabella Sylvester .I am a postgraduate student at MUHAS, investigating lipid profile and associated factors among children and adolescents aged 2 – 19 years T1DM attending diabetic clinic at Muhimbili National Hospital.

**The purpose of the study;** To determine the risk factors for macro vascular diseases in relation to glycemic control among children and adolescents aged 2 – 19 years T1DM attending diabetic clinic at Muhimbili National Hospital.

**What participation involves**:

If you agree to participate in the study, you will be interviewed, and a detailed clinical history regarding your child's illness will be requested. Data including age, sex, weight, height etc using a structured questionnaire will be collected. The body mass index (BMI) will be calculated according to the Quetelet equation. Patient's body weight in kilograms (Kg) will be divided by his/her height in meters squared (m2). Blood pressure will be measured and will be interpreted on the basis of sex, age and height. Five milliliters of venous blood will be taken from the anterior cubital fossa of each child for glycosylated hemoglobin level and lipid profile analysis.

**Confidentiality:**

All information collected on questionnaires will be entered into computer with identification number. The questionnaires will be handled with greater secrecy in order to maintain confidentiality.

**Risks:**

There are no risks associated with this study

**Right to withdraw and alternatives:**

Taking part in this study is completely voluntary choice. If you choose not to participate in the study, your child will continue to receive all services that are normally provided in the hospital. **Benefits:**

If you agree to take part in this study, your child will benefit by knowing the glycemic control, and patterns of lipid profile, and whenever there are derangements appropriate medications will be prescribed and you will be advised accordingly.

**In case of any injury:**

Apart from us taking a blood sample from your child we do not expect any harm.

**Who to contact:**

If you have any question about the study, you should contact Isabella Sylvester on 0712 269569. If you have questions about your rights as a participant, you may contact Prof M. Aboud,Chairman of MUHAS Research and Publications Committee. P.O.BOX 65001 Dar es Salaam. Tel 2150302-6

Do you agree?

Participant agrees…….. Participant does NOT agree……

I ……have read the content of this form. My questions have been answered and I agree to participate in this study**. Signature of participant…….**

**Signature of witness…… Date of signed consent…….**

**Fomu ya Ridhaa kujiunga katika utafiti (Swahili Version)**

**Matatizo ya aina za mafuta na usahihi wa sukari mwilini kwa watoto na vijana wenye umri kati ya miaka 2 na 19 wenye kisukari wanaohudhuria klinik ya kisukari katika hospitali ya Taifa Muhimbili..**

**Nambari ya usaili** …….

Salaaam! Mimi naitwa Isabella Sylvester ni mwanafunzi wa udhamili Chuo Kikuu cha Sayansi za Afya . Nafanya utafiti wa kuchunguza Matatizo ya aina za mafuta na usahihi wa sukari mwilini kwa watoto na vijana wenye umri kati ya miaka 2 na 19 wenye kisukari wanaohudhuria klinik ya kisukari katika hospitali ya Taifa Muhimbili.

**Madhumuni ya utafiti**

Kujua matatizo ya aina za mafuta na usahihi wa sukari mwilini kwa watoto na vijana wenye umri kati ya miaka 2 na 19 wenye kisukari wapatao 123 wanaohudhuria klinik ya kisukari katika hospitali ya Taifa Muhimbili..

**Jinsi ya kushiriki**

Kama utakubali kushiriki ,nita kuhoji maswali machache kuhusu ugonjwa wa mtoto/ kijana wako na nitaomba kutoa sampuli ya damu ya mtoto wako kwa ajili ya uchunguzi zaidi.

**Utunzaji wa siri**

Taarifa za ugonjwa wa mtoto wako zitatunzwa kwa siri kwa kutumia herufi au nambari badala ya jina la mgonjwa.

**Madhara /Athari**

Hakuna athari au madhara yoyote yanayotegemewa kutokana na utafiti huu.

**Uhuru wa kushiriki** ;

Kushiriki kwenye utafiti ni hiari yako.

Unaweza kujitoa wakati wowote. Kama utachagua kutoshiriki, mtoto wako ataendelea kupata huduma kama hospitalini kama kawaida.

**Faida ya utafiti**

Ukishiriki kwenye utafiti huu , motto/ kijana wako atachunguzwa kama ana tatizo la aina za mafuta na usahihi wa sukari mwilini na atapatiwa matibabu stahili, na pia atapatiwa ushauri itakapohitajika kufanya hivyo**.** Kuna kamati ya kusimamia udhibiti wa Utafiti huu.

**Taarifa**

Endapo unahitaji kupata maelezo kuhusu haki zako au taarifa ,wasiliana na Isabella Sylvester kwa namba ya simu 0712269569 au Prof A. Aboud, Mwenyekiti wa Kamati ya Utafiti S.L.P 651001,Dar es salaam., Simu2150302-6 Je unakubali kushiriki kwenye utafiti? (weka alama) vema ndiyo..... hapana.....

Mimi ....., nimeelezwa na nimesoma maelezo haya. Maswali yangu yamejibiwa.

Nimekubali mwanangu ashiriki kwenye utafiti huu

Sahihi ya mzazi/mlezi .....

Sahihi ya ndugu/shahidi .....

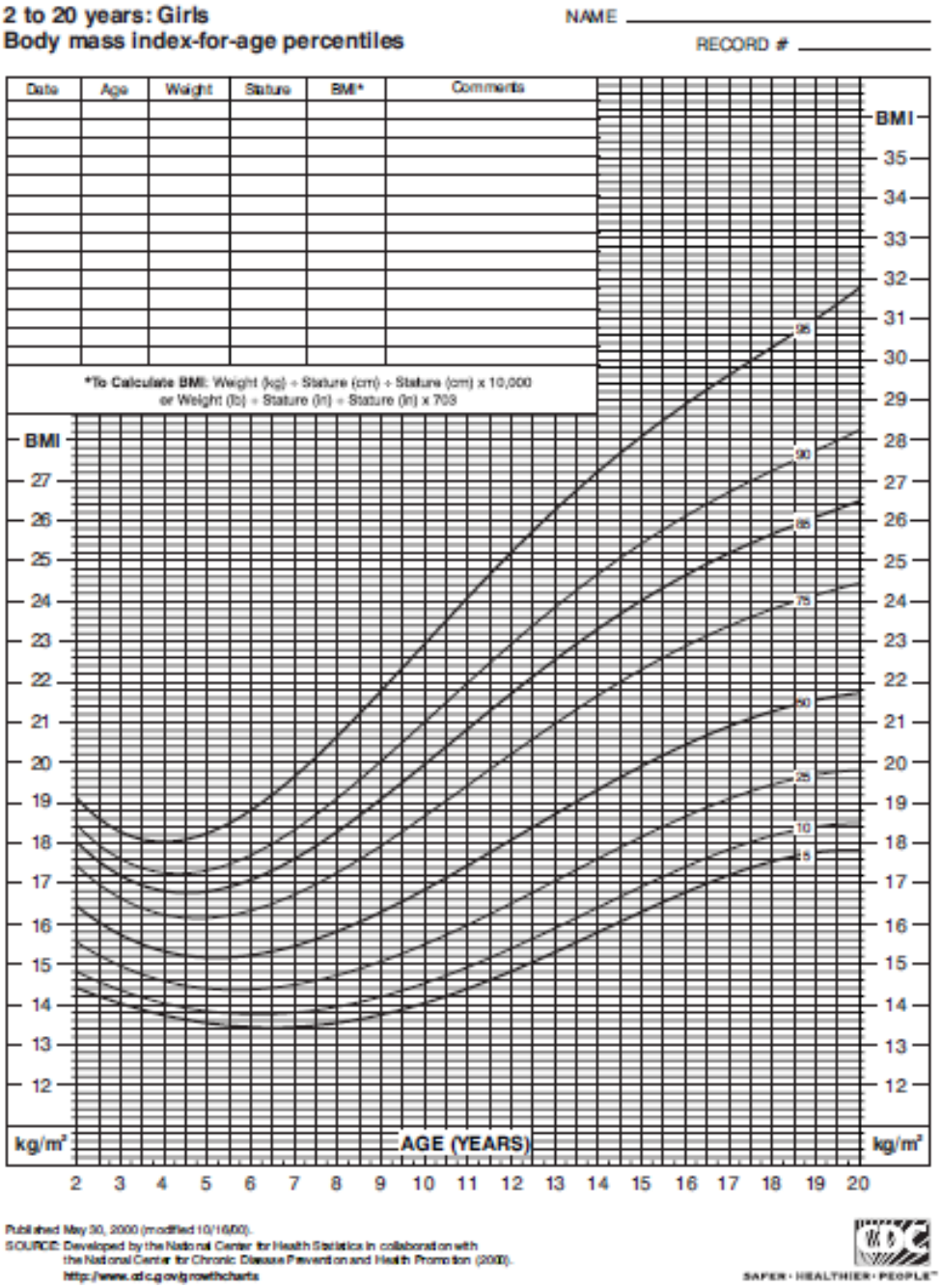
Sahihi ya Mtafiti ..... . Tarehe……

**ANNEX 2 QUESTIONNAIRE**

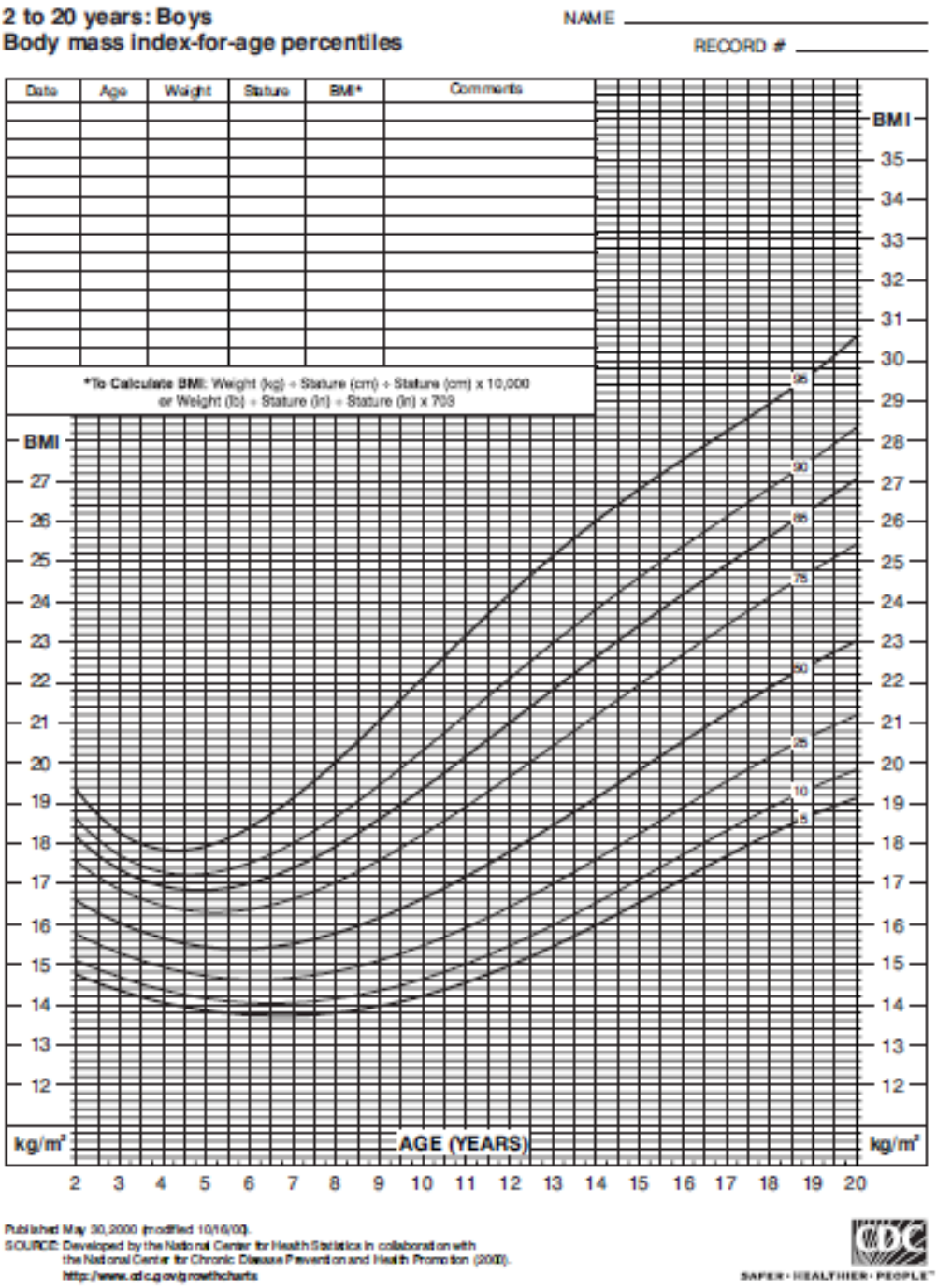
Serial No…….

1. ID No……..
2. Age……..
3. Sex (a) Male (b) Female
4. Weight (Kg)..... Height (cm)…….. BMI……
5. Blood Pressure level
    a. Systolic Blood Pressure level…….
    b. Diastolic Blood Pressure level…….
6. When was you diagnosed type 1 diabetic mellitus.....
7. Duration of diabetes…….
8. Are you on regular use of insulin……..
9. Triglyceride level……..
10. High density lipoprotein (HDL) level……..
11. Low density lipoprotein (LDL) level……
12. Very low density lipoproteins level…….
13. Total cholesterol level……..
14. Glycosylated hemoglobin (HbA1c)…….
15. Liver ultra sound results……..

## ANNEX III Reference value for BMI in females



**Reference values for BMI in males**



## Reference values for BP level in females

*Blood Pressure Levels for the 90th and 95th Percentiles for Female Children and Adolescents Ages 1 to 17*

| | | Systolic BP (mm Hg), by Height Percentile from Standard Growth Curves | | | | | | | Diastolic BP (mm Hg), by Height Percentile from Standard Growth Curves | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | BP Percentile | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 1 | 90TH | 97 | 98 | 99 | 100 | 102 | 103 | 104 | 53 | 53 | 53 | 54 | 55 | 56 | 56 |
| | 95TH | 101 | 102 | 103 | 104 | 105 | 107 | 107 | 57 | 57 | 57 | 58 | 59 | 60 | 60 |
| 2 | 90TH | 99 | 99 | 100 | 102 | 103 | 104 | 105 | 57 | 57 | 58 | 58 | 59 | 60 | 61 |
| | 95TH | 102 | 103 | 104 | 105 | 107 | 108 | 109 | 61 | 61 | 62 | 62 | 63 | 64 | 65 |
| 3 | 90TH | 100 | 100 | 102 | 103 | 104 | 105 | 106 | 61 | 61 | 61 | 62 | 63 | 63 | 64 |
| | 95TH | 104 | 104 | 105 | 107 | 108 | 109 | 110 | 65 | 65 | 65 | 66 | 67 | 67 | 68 |
| 4 | 90TH | 101 | 102 | 103 | 104 | 106 | 107 | 108 | 63 | 63 | 64 | 65 | 65 | 66 | 67 |
| | 95TH | 105 | 106 | 107 | 108 | 109 | 111 | 111 | 67 | 67 | 68 | 69 | 69 | 70 | 71 |
| 5 | 90TH | 103 | 103 | 104 | 106 | 107 | 108 | 109 | 65 | 66 | 66 | 67 | 68 | 68 | 69 |
| | 95TH | 107 | 107 | 108 | 110 | 111 | 112 | 113 | 69 | 70 | 70 | 71 | 72 | 72 | 73 |
| 6 | 90TH | 104 | 105 | 106 | 107 | 109 | 110 | 111 | 67 | 67 | 68 | 69 | 69 | 70 | 71 |
| | 95TH | 108 | 109 | 110 | 111 | 112 | 114 | 114 | 71 | 71 | 72 | 73 | 73 | 74 | 75 |
| 7 | 90TH | 106 | 107 | 108 | 109 | 110 | 112 | 112 | 69 | 69 | 69 | 70 | 71 | 72 | 72 |
| | 95TH | 110 | 110 | 112 | 113 | 114 | 115 | 116 | 73 | 73 | 73 | 74 | 75 | 76 | 76 |
| 8 | 90TH | 108 | 109 | 110 | 111 | 112 | 113 | 114 | 70 | 70 | 71 | 71 | 72 | 73 | 74 |
| | 95TH | 112 | 112 | 113 | 115 | 116 | 117 | 118 | 74 | 74 | 75 | 75 | 76 | 77 | 78 |
| 9 | 90TH | 110 | 110 | 112 | 113 | 114 | 115 | 116 | 71 | 72 | 72 | 73 | 74 | 74 | 75 |
| | 95TH | 114 | 114 | 115 | 117 | 118 | 119 | 120 | 15 | 76 | 76 | 77 | 78 | 78 | 79 |
| 10 | 90TH | 112 | 112 | 114 | 115 | 116 | 117 | 118 | 73 | 73 | 73 | 74 | 75 | 76 | 76 |
| | 95TH | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| 11 | 90TH | 114 | 114 | 116 | 117 | 118 | 119 | 120 | 74 | 74 | 75 | 75 | 76 | 77 | 77 |
| | 95TH | 118 | 118 | 119 | 121 | 122 | 123 | 124 | 78 | 78 | 79 | 79 | 80 | 81 | 81 |
| 12 | 90TH | 116 | 116 | 118 | 119 | 120 | 121 | 122 | 75 | 75 | 76 | 76 | 77 | 78 | 78 |
| | 95TH | 120 | 120 | 121 | 123 | 124 | 125 | 126 | 79 | 79 | 80 | 80 | 81 | 82 | 82 |
| 13 | 90TH | 118 | 118 | 119 | 121 | 122 | 123 | 124 | 76 | 76 | 77 | 78 | 78 | 79 | 80 |
| | 95TH | 121 | 122 | 123 | 125 | 126 | 127 | 128 | 80 | 80 | 81 | 82 | 82 | 83 | 84 |
| 14 | 90TH | 119 | 120 | 121 | 122 | 124 | 125 | 126 | 77 | 77 | 78 | 79 | 79 | 80 | 81 |
| | 95TH | 123 | 124 | 125 | 126 | 128 | 129 | 130 | 81 | 81 | 82 | 83 | 83 | 84 | 85 |
| 15 | 90TH | 121 | 121 | 122 | 124 | 125 | 126 | 127 | 78 | 78 | 79 | 79 | 80 | 81 | 82 |
| | 95TH | 124 | 125 | 126 | 128 | 129 | 130 | 131 | 82 | 82 | 83 | 83 | 84 | 85 | 86 |
| 16 | 90TH | 122 | 122 | 123 | 125 | 126 | 127 | 128 | 79 | 79 | 79 | 80 | 81 | 82 | 82 |
| | 95TH | 125 | 126 | 127 | 128 | 130 | 131 | 132 | 83 | 83 | 83 | 84 | 85 | 86 | 86 |
| 17 | 90TH | 122 | 123 | 124 | 125 | 126 | 128 | 128 | 79 | 79 | 79 | 80 | 81 | 82 | 82 |
| | 95TH | 126 | 126 | 127 | 129 | 130 | 131 | 132 | 83 | 83 | 83 | 84 | 85 | 86 | 86 |

Source: Reprinted from National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents.
Blood pressure percentile determined by a single measurement.

## Reference values for BP level in males

*Blood Pressure Levels for the 90th and 95th Percentiles for Male Children and Adolescents Ages 1 to 17*

| | | Systolic BP (mm Hg), by Height Percentile from Standard Growth Curves | | | | | | | Diastolic BP (mm Hg), by Height Percentile from Standard Growth Curves | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | BP Percentile | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 1 | 90TH | 94 | 95 | 97 | 98 | 100 | 102 | 102 | 50 | 51 | 52 | 53 | 54 | 54 | 55 |
| | 95TH | 98 | 99 | 101 | 102 | 104 | 106 | 106 | 55 | 55 | 56 | 57 | 58 | 59 | 59 |
| 2 | 90TH | 98 | 99 | 100 | 102 | 104 | 105 | 106 | 55 | 55 | 56 | 57 | 58 | 59 | 59 |
| | 95TH | 101 | 102 | 104 | 106 | 108 | 109 | 110 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| 3 | 90TH | 100 | 101 | 103 | 105 | 107 | 108 | 109 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 95TH | 104 | 105 | 107 | 109 | 111 | 112 | 113 | 63 | 63 | 64 | 65 | 66 | 67 | 67 |
| 4 | 90TH | 102 | 103 | 105 | 107 | 109 | 110 | 111 | 62 | 62 | 63 | 64 | 65 | 66 | 66 |
| | 95TH | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 66 | 67 | 67 | 68 | 69 | 70 | 71 |
| 5 | 90TH | 104 | 105 | 106 | 108 | 110 | 112 | 112 | 65 | 65 | 66 | 67 | 68 | 69 | 69 |
| | 95TH | 108 | 109 | 110 | 112 | 114 | 115 | 116 | 69 | 70 | 70 | 71 | 72 | 73 | 74 |
| 6 | 90TH | 105 | 106 | 108 | 110 | 111 | 113 | 114 | 67 | 68 | 69 | 70 | 70 | 71 | 72 |
| | 95TH | 109 | 110 | 112 | 114 | 115 | 117 | 117 | 72 | 72 | 73 | 74 | 75 | 76 | 76 |
| 7 | 90TH | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 69 | 70 | 71 | 72 | 72 | 73 | 74 |
| | 95TH | 110 | 111 | 113 | 115 | 116 | 118 | 119 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| 8 | 90TH | 107 | 108 | 110 | 112 | 114 | 115 | 116 | 71 | 71 | 72 | 73 | 74 | 75 | 75 |
| | 95TH | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 75 | 76 | 76 | 77 | 78 | 79 | 80 |
| 9 | 90TH | 109 | 110 | 112 | 113 | 115 | 117 | 117 | 72 | 73 | 73 | 74 | 75 | 76 | 77 |
| | 95TH | 113 | 114 | 116 | 117 | 119 | 121 | 121 | 76 | 77 | 78 | 79 | 80 | 80 | 81 |
| 10 | 90TH | 110 | 112 | 113 | 115 | 117 | 118 | 119 | 73 | 74 | 74 | 75 | 76 | 77 | 78 |
| | 95TH | 114 | 115 | 117 | 119 | 121 | 122 | 123 | 77 | 78 | 79 | 80 | 80 | 81 | 82 |
| 11 | 90TH | 112 | 113 | 115 | 117 | 119 | 120 | 121 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| | 95TH | 116 | 117 | 119 | 121 | 123 | 124 | 125 | 78 | 79 | 79 | 80 | 81 | 82 | 83 |
| 12 | 90TH | 115 | 116 | 117 | 119 | 121 | 123 | 123 | 75 | 75 | 76 | 77 | 78 | 78 | 79 |
| | 95TH | 119 | 120 | 121 | 123 | 125 | 126 | 127 | 79 | 79 | 80 | 81 | 82 | 83 | 83 |
| 13 | 90TH | 117 | 118 | 120 | 122 | 124 | 125 | 126 | 75 | 76 | 76 | 77 | 78 | 79 | 80 |
| | 95TH | 121 | 122 | 124 | 126 | 128 | 129 | 130 | 79 | 80 | 81 | 82 | 83 | 83 | 84 |
| 14 | 90TH | 120 | 121 | 123 | 125 | 126 | 128 | 128 | 76 | 76 | 77 | 78 | 79 | 80 | 80 |
| | 95TH | 124 | 125 | 127 | 128 | 130 | 132 | 132 | 80 | 81 | 81 | 82 | 83 | 84 | 85 |
| 15 | 90TH | 123 | 124 | 125 | 127 | 129 | 131 | 131 | 77 | 77 | 78 | 79 | 80 | 81 | 81 |
| | 95TH | 127 | 128 | 129 | 131 | 133 | 134 | 135 | 81 | 82 | 83 | 83 | 84 | 85 | 86 |
| 16 | 90TH | 125 | 126 | 128 | 130 | 132 | 133 | 134 | 79 | 79 | 80 | 81 | 82 | 82 | 83 |
| | 95TH | 129 | 130 | 132 | 134 | 136 | 137 | 138 | 83 | 83 | 84 | 85 | 86 | 87 | 87 |
| 17 | 90TH | 128 | 129 | 131 | 133 | 134 | 136 | 136 | 81 | 81 | 82 | 83 | 84 | 85 | 85 |
| | 95TH | 132 | 133 | 135 | 136 | 138 | 140 | 140 | 85 | 85 | 86 | 87 | 88 | 89 | 89 |

Source: Reprinted from National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents.
Blood pressure percentile determined by a single measurement.

**ANNEX V Reference values for normal plasma lipid concentrations in the first two decades of life.**

| Age (years) | Sex | Total cholesterol (mg/dl) | | | Triglyceride (mg/dl) | | |
|---|---|---|---|---|---|---|---|
| | | 5th | Mean | 95th | 5th | Mean | 95$^{th}$ |
| 0-4 | Male | 114 | 155 | 203 | 29 | 56 | 99 |
| | Female | 112 | 156 | 200 | 34 | 64 | 112 |
| 5-9 | Male | 121 | 160 | 203 | 30 | 56 | 101 |
| | Female | 126 | 164 | 205 | 32 | 60 | 105 |
| 10-14 | Male | 119 | 158 | 202 | 32 | 66 | 125 |
| | Female | 124 | 160 | 201 | 37 | 75 | 131 |
| 15-19 | Male | 113 | 150 | 197 | 37 | 78 | 148 |
| | Female | 120 | 158 | 203 | 39 | 75 | 132 |

**Reference values for normal plasma lipoprotein concentrations in the first two decades of life.**

| Age (years) | Sex | HDL-C(mg/dl) | | | LDL-C(mg/dl) | | | VLDL-C(mg/dl) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | Mean | 95th | $5^{th}$ | Mean | 95th | 5th | Mean | 95th |
| 5-9 | Male | 38 | 56 | 75 | 63 | 93 | 129 | 0 | 8 | 18 |
| | Female | 36 | 53 | 73 | 68 | 100 | 140 | 1 | 10 | 24 |
| 10-14 | Male | 37 | 55 | 74 | 64 | 97 | 133 | 1 | 10 | 22 |
| | Female | 37 | 52 | 70 | 68 | 97 | 136 | 2 | 11 | 23 |
| 15-19 | Male | 30 | 46 | 63 | 62 | 94 | 130 | 2 | 13 | 26 |
| | Female | 35 | 52 | 74 | 59 | 96 | 137 | 2 | 12 | 24 |

All values have been converted from plasma to serum.

Plasma value × 1.03 = serum value

To convert mg/dl to mmol/L = mg/dl/38.5