Original Paper

Correlation of Lipid Profile and Risk of Developing Type 2 Diabetes Mellitus in 10-14 Year Old Children

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Key Words

Type 2 diabetes mellitus • Lipid profiles • Obesity • Children

Abstract

Background/Aims: The role of lipid profile in predicting the risk of Type 2 diabetes mellitus (T2DM) in children is not clearly established. Our aim is to screen non-diabetic children aged 10-14 years for risk of developing T2DM and evaluate the association of abnormal lipids and socioeconomic status (SES). **Methods:** Data on race/ethnicity, family history, body mass index percentile, blood pressure and presence of neck pigmentation (acanthosis nigricans) were collected from 149 non-diabetic children. Using these factors, children were classified into low risk (<3 risk factors) and high risk (≥ 3 risk factors) groups. Logistic regression model and chi-square tests were used to evaluate the association of blood lipid profile and demographic variables. Independent *t*-test was used to compare the ratio of Total Cholesterol (TC) and High Density Lipids (HDL) with T2DM risk. **Results:** 60% of children were at high risk for developing T2DM. HDL ($p < 0.001$), triglycerides ($p = 0.02$) and TC/HDL ratio ($p < .001$) were significantly abnormal in high risk group. Low SES showed a marginal association with high risk group. There were no gender or age differences between high and low risk groups. **Conclusions:** The significant determinants associated with high risk group were modifiable factors providing an opportunity for early intervention and prevention.

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Introduction

Obesity is a complex condition and highly associated with dietary and nutritional issues. More than one third of adults and 17% of children are obese in the United States [1, 2]. Obesity leads to multiple health complications including type 2 diabetes mellitus (T2DM), cardiovascular diseases, cancer, musculoskeletal diseases, liver, respiratory, gynecological

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and mental diseases [3-6]. The incidence of T2DM has substantially increased over the past 20 years [7]. Most of the T2DM patients are overweight or obese at the time of diagnosis [8]. T2DM is characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion [9]. Traditionally, T2DM was considered to be an adult onset disease, as it used to be limited to older ages [10]. Recently, there has been an increased prevalence of this disease in children and adolescents [9, 11]. As younger children are becoming obese and remaining obese throughout childhood and adolescent years, diabetes and its complications are occurring earlier in life. According to National Diabetes Statistics, 12.3% (28.9 million) of the United States population under the age of 20 are currently believed to have diabetes [12]. The prevalence of T2DM among children has dramatically increased (>30%) between 2001 and 2009 [13].

Based on current disease progression, the American Diabetes Association (ADA) has developed guidelines for screening T2DM in children which include both invasive and noninvasive markers. It recommends testing children 10 years or older if their body mass index (BMI) is >85 percentile for age and gender and they have two of the following risk factors: 1. Race/ethnicity (American Indian, African American, Hispanic, Asian/Pacific Islander), 2. Positive family history of T2DM in a first or second degree relative and 3. Signs or conditions associated with insulin resistance (e.g., acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome) [8]. Recently, Peterson et al. [14] conducted a study to determine the prevalence of T2DM risk factors in children (4 to 14 years) from rural low-income families using a non-invasive screening method incorporating ADA recommendations. In our study, we have evaluated children aged 10-14 years for the risk of T2DM using a similar method in an urban population.

Dyslipidemia is considered to be a risk factor for the development of T2DM [15, 16]. The experimental studies for developing novel therapeutic strategies for diabetes often targeted on correcting dyslipidemia [17-19]. The expert panel of the National Heart, Lung and Blood Institute (NHLBI) recommended universal lipid screening for children between 9 to 11 years in 2011 and this has been endorsed by the American Academy of Pediatrics (AAP) [20]. This guideline was developed to provide early detection of risks and promote cardiovascular health. Atherosclerotic cardiovascular disease (CVD) is the leading cause of death in adults in North America [12]. Even though CVD is rare in children, the risk factors and the risk behaviors can still be present in children [6]. The routine lipid profile ordered by clinicians includes total cholesterol (TC), high density lipoprotein (HDL) and triglycerides (TG). From these values, low density lipoprotein (LDL), TC/HDL ratio and non-HDL cholesterol are calculated for clinical assessment. Even though the AAP has recommended universal lipid screening in 9 to 11 year old children, there are no established guidelines on how to utilize and interpret these results to predict the risk of T2DM. Numerous studies have suggested the link between dyslipidemia and the risk of getting T2DM; however, none of these studies have performed a detailed analysis to establish an association of abnormal lipids with T2DM risk. Assessing the risk early allows prompt interventions including the adjustments in life style and change in diet to prevent T2DM. It is especially critical and cost effective to determine such risk during childhood.

Materials and Methods

Study Location and Patient enrollment

It is a cross-sectional research study conducted at the University of North Texas Health Science Center (UNTHSC) outpatient clinics in Fort Worth, which is the fifth largest city in Texas. Ninety five percent of the children were recruited from the Pediatric Clinic which is a major outpatient pediatric facility in Fort Worth. It was conducted using a protocol approved by the Institutional Review Board (IRB) of UNTHSC, Fort Worth, Texas. The participants were 10-14 years old, enrolled from representative races and ethnicities attending the clinics. Subjects with chronic diseases (cystic fibrosis, genetic syndromes, hypo or hyper- thyroid conditions, adrenal diseases), already diagnosed with diabetes or who had consumed oral corticosteroids

within the past one year were excluded from the study. Only non-diabetic subjects were enrolled for this study. Typically, blood glucose measuring 100 to 125 mg/dL (fasting) or 140 to 200 mg/dL (random) are considered as elevated levels in children [21]. Blood glucometer (Bayer Breeze 2 Blood glucose monitoring system) was used to determine the blood glucose levels and the children with glucose levels >125 mg/dL (fasting) or >200 mg/dL (random) were excluded from the study [14]. Children with elevated blood glucose (≥ 100 to 125 mg/dL fasting or ≥ 140 to 200 mg/dL random) were included in the study and designated as having elevated glucose levels. During the study period 469 children were screened but due to exclusions, the study was completed with 153 participants.

Data Collection

All participants and their parents or legal guardians had signed IRB approved participant assent form or parent/legal guardian consent form prior to patient enrollment. The parent or legal guardian then completed the study related questionnaire providing the demographic information such as date of birth, gender, race/ethnicity, socioeconomic status (SES) and information about family history (first or second degree relatives) related to T2DM. Low SES was determined using two proxy variables, utilization of free/reduced-cost school lunches and household use of food stamps.

General clinical measurements such as height, weight, and blood pressure (average of two readings) were recorded for all participants. BMI percentile was calculated for age and gender of the subjects and the neck inspection was done by the clinic provider to identify the presence of posterior cervical acanthosis nigricans - dark pigmentation of the skin creases on the back of the neck (AN).

Blood samples were drawn at Quest Diagnostics (located adjacent to the Pediatric Clinic) and tested for lipid profile (TC, HDL, LDL, non-HDL, TG and TC/HDL ratio) in all participants. Abnormal values (TC: ≥ 170 mg/dL; HDL: ≤ 40 mg/dL; LDL: ≥ 110 mg/dL; non-HDL: ≥ 120 mg/dL; TG: ≥ 90 mg/dL) were determined according to established criteria [Cholesterol Levels: Expert Panel, National Cholesterol Education Program (NCEP); non-HDL values: Bogalusa Heart Study].

Identifying 'Low Risk' and 'High Risk' groups

The risk of children developing T2DM was determined using noninvasive measures [14]. The five risk factors used were (1) BMI percentile >85 for age and gender, (2) High blood pressure (history of hypertension or average systolic or diastolic blood pressure reading at or above 95th percentile for height and gender) [22, 23], (3) Presence of AN, (4) High-risk race/ethnicity (American Indian, African American, Hispanic, Asian/pacific islander) and (5) Positive family history of T2DM in a first or second degree relative. Children with less than three risk factors were categorized as 'Low Risk' group, while children with three or more risk factors were categorized as 'High Risk' group.

Statistical Analysis

Data were collected from 153 children over 18 months. After careful review of the data, four of them were excluded from the analysis because of missing values in one or more variables. The remaining 149 subjects were included in the analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 21. The cross tabulations between T2DM risk (low and high) and lipid data, elevated blood glucose (≥ 100 to 125 mg/dL fasting or ≥ 140 to 200 mg/dL random), and demographic variables were performed by chi-square tests to determine the variables significantly associated with T2DM risk. An independent-*t* test was used to compare the TC/HDL ratio between low risk and high risk groups. Finally, a logistic regression model was conducted with all lipid indices, elevated blood glucose and demographic variables to predict the risk of T2DM. A forward-stepwise model selection method was applied to keep only the significant variables in the final model. Odds ratio and their 95% confidence interval (CI) for each significant predictor were also obtained.

Results

Demographic Analysis

Race/ethnic background, gender and age group of the participants were analyzed. The majority of participants were Hispanics (58.4%), followed by African Americans (26.2%), Caucasians (10.1%) and others (5.4%). The female subjects were slightly more numerous

(52.3%) than the male subjects (47.7%). The details of the demographics are given in Table 1.

Evaluation of low risk and high risk groups

The total number of children under 'high risk' or 'low risk' categories, frequency and percentage of each risk factor in the study group are given in Table 2. Overall, the data show an increasing number of children with one to four risk factors (1: 13.4%; 2: 24.2%; 3: 24.8%; 4: 32.2%), while the children with none or all five risk factors were minimal in number (2.7%). In total, 89 subjects were identified as 'high risk' and 60 subjects as low risk.

Prevalence of various risk factors in low risk and high risk groups

The prevalence of each risk factor in relation to risk group was evaluated and the results are shown in Table 3. The high blood pressure, BMI percentile (>85th percentile for age and gender), and AN were highly correlated with the high risk group when compared to race/ethnicity and positive family history. One hundred percent of the children with high blood pressure, 94% with BMI >85th percentile, 88.5% with AN, 66% with high risk race/ethnicity, and 71% with positive family history were in the high risk category.

Lipid profile and blood glucose levels

The results of lipid profile including TC, HDL, LDL, non-HDL and TG were analyzed in all participants. Abnormal levels of (low) HDL ($p<0.001$) and (elevated) TG ($p=0.02$) were significantly greater in the high risk group showing a strong correlation with T2DM risk. Abnormality of other lipid markers such as TC, LDL, non-HDL and elevated blood glucose levels were not significantly different among high risk and low risk groups (Table 4).

The box-plot showing the distribution of the TC/HDL ratio among low risk and high risk groups is presented in Figure 1. Using independent *t*-test, statistical analysis revealed the average TC/HDL ratio was significantly higher in the high risk group than low risk group (0.87 vs 0.70, $t=3.93$, $p<0.001$).

Demographics and T2DM risk analysis

Only the low SES was marginally ($p=0.07$) correlated with high risk group. Other variables, gender and age were not different ($p=0.64$ and 0.46 respectively for gender and age) among low risk and high risk groups (Table 5).

Table 1. Demographics of the children participated in the study. The demographic information representing the race/ethnicity of participants. The majority of participants were Hispanics (58.4%), followed by African Americans (26.2%), Caucasians (10.1%) and others (5.4%)

Demographic Variables	Frequency N=149	Percentage
<i>Race/ethnicity</i>		
White/Caucasian	15	10.1
Black/African-American	39	26.2
Hispanic	87	58.4
Multiracial	7	4.7
Other	1	0.7
<i>Gender</i>		
Male	71	47.7
Female	78	52.3
<i>Age</i>		
10	36	24.2
11	29	19.5
12	34	22.8
13	30	20.1
14	20	13.4

Table 2. Frequency of risk factors and classification of risk groups

Number of Risk Factors	n (%)	Risk Category
0	4 (2.7)	Low Risk
1	20 (13.4)	Low Risk
2	36 (24.2)	Low Risk
3	37 (24.8)	High Risk
4	48 (32.2)	High Risk
5	4 (2.7)	High Risk
<3	60 (40)	Low Risk
≥3	89 (60)	High Risk

Table 3. Status of risk factors among 'Low Risk' and 'High Risk' groups. ¹ Body Mass Index above 85th percentile for age and gender. ² History of hypertension or average systolic or diastolic blood pressure reading at or above 95th percentile for height and gender. ³ Posterior cervical Acanthosis nigricans. ⁴ High risk race/ethnicity includes American Indian, African American, Hispanic, Asian/Pacific islander (American Diabetes Association, 2000). ⁵ Positive family history of T2DM in first or second degree relatives. ^aInformation for one subject is missing. As this subject has only one other risk factor, it will not affect the high risk and low risk status. Hence, it was included in the analysis

Risk Factors	Total Subjects (n=149)	Low Risk n (%)	High Risk n (%)
<i>BMI percentile >85¹</i>			
No	66	55 (83.3)	11 (16.7)
Yes	83	5 (6)	78 (94)
<i>High blood pressure²</i>			
No	141	60 (42.5)	81 (57.5)
Yes	8	0 (0)	8 (100)
<i>Acanthosis nigricans³</i>			
No	71	51 (71.8)	20 (28.2)
Yes	78	9 (11.5)	69 (88.5)
<i>High risk race/ethnicity⁴</i>			
No	15	14 (93.3)	1 (6.7)
Yes	134	46 (34.3)	88 (65.7)
<i>^aPositive family history of T2DM⁵</i>			
No	36	27 (75)	9 (25)
Yes	112	32 (28.6)	80 (71.4)

Table 4. Status of lipid indices and blood glucose levels among Low Risk and High Risk groups. Abbreviations: TC - Total Cholesterol; LDL - Low density Lipoprotein; HDL - High density Lipoprotein. Abnormal Values: TC (≥ 170 mg/dL), LDL (≥ 110 mg/dL), HDL (≤ 40 mg/dL), non-HDL (≥ 120 mg/dL) and TG (≥ 90 mg/dL) [Source: Cholesterol Levels: Expert Panel, National Cholesterol Education Program (NCEP); non-HDL values: Bogalusa Heart Study]. ¹ glucose levels <100 mg/dL (fasting) or <140 mg/dL (random). ² glucose levels 100 to 125 mg/dL (fasting) or 140 to 200 mg/dL (random). * Significant at .05 level, ** significant at .01 level

	Low Risk (n=60)	High Risk (n=89)	Chi-square	p-value
<i>Lipid Profiles</i>				
TC				
<170 mg/dL	45	68	0.39	.84
≥ 170 mg/dL	15	21		
LDL				
<110 mg/dL	56	78	1.28	.26
≥ 110 mg/dL	4	11		
HDL				
<40 mg/dL	5	31	13.73	<.001**
≥ 40 mg/dL	55	58		
Non HDL				
<120 mg/dL	48	67	.45	.50
≥ 120 mg/dL	12	22		
Triglycerides				
<90 mg/dL	33	31	5.95	.02*
≥ 90 mg/dL	27	58		
<i>Blood Glucose Levels</i>				
Normal ¹	56	77	1.74	.19
Elevated ²	4	12		

Studying the significant predictors

The logistic regression analysis with forward-stepwise model selection algorithm was used to identify predictors for assessing the risk of T2DM (Table 6). This model detected three variables, HDL, TC/HDL ratio, and low SES. TG was no longer significant when modeled together with the other lipid indices. TG levels were highly correlated with HDL and TC/HDL ratio, therefore, the variance in outcome variable (high risk/low risk) explained by TG was overlapping with the variance explained by HDL or/and TC/HDL.

Fig. 1. Cholesterol ratio: Median Total Cholesterol/HDL- Cholesterol Ratio in children with low (N=60) and high risk (N=89) of developing Type 2 Diabetes Mellitus. For the box plot, the box represents the interquartile range (25th-75th percentiles), and the line in the middle of the box represents the median value. The brackets extending from the box represent the lower and upper adjacent values. TC/HDL ratio is significantly higher in high risk group (0.87 VS 0.70, t=3.93, p<0.001).

According to the calculation of odds ratio in Table 6, the subjects with low HDL were 4.14 (95%CI: 1.32-12.98) times more likely to be categorized under high risk than the subjects with high HDL if their SES and TC/HDL were the same. The subjects with high TC/HDL ratio were 1.79 (95% CI: 1.04-3.06) times more likely to have T2DM risk than those with low TC/HDL if their SES and HDL were same. In addition, low SES group was 2.60 (95% CI: 1.03-6.57) times more likely to have T2DM risk than high SES group if their HDL and TC/HDL were the same.

Discussion

The incidence of T2DM and associated complications has been increasing in children, adolescents and adults [24]. Hence, identifying children at risk for T2DM at an early age would allow timely life style modification and disease preventing interventions. It has been estimated

that about 8.1 million people with T2DM are undiagnosed, many of whom are children [8]. In this study, only children with blood glucose in non-diabetic range were recruited to determine the risk status. Since the onset of T2DM for children is usually at or above the age

Table 5. The relationship between each demographic variable in Low Risk and High Risk groups. 1 Low socioeconomic Status was determined using two proxy variables: utilization of Free/reduced-cost school lunches and household use of food stamps * Significant at .05 level

Demographic Variables	Low Risk	High Risk	Chi-square	p-value
<i>Gender</i>				
Male	30	41	.22	.64
Female	30	48		
<i>Socioeconomic Status</i>				
Low ¹	44	76	3.33	.07
Not Low	16	13		
<i>Age</i>				
10	11	25	3.65	.46
11	15	14		
12	12	22		
13	13	17		
14	9	11		

Table 6. Significant predictors identified using forward stepwise Logistic Regression model for risk of developing T2DM in 10-14 year old Children (Odds Ratio and 95% Confidence Interval). β -coefficient, S.E. - standard error, OR indicates likelihood of risk of developing T2DM, CI - Confidence Interval, *significant at .05 level

Predictors	β	S.E.	Wald	p-value	Odds Ratio (95%CI)
Intercept	-2.48	.918	7.28	.007	
HDL	1.42	.58	5.91	.015*	4.14 (1.32-12.98)
SES	.96	.47	4.08	.043*	2.60 (1.03-6.57)
TC/HDL ratio	.58	.28	4.43	.035*	1.79 (1.04-3.06)

of 10 [8], screening children at 10 to 14 years could be beneficial and cost effective for early identification of risk. We have carefully selected the exclusion criteria to ensure the abnormal glucose and lipid values found in our subjects were not due to other disease processes. To keep our study minimally invasive, we used blood glucometer testing instead of fasting plasma glucose to identify non diabetic children.

The ADA recommended screening criteria for children aged 10 years and above have some limitations. The major drawbacks are assessing the risk using the factors which involve invasive methods, for example, looking for signs or conditions associated with insulin resistance[8]. Children belonging to low SES/minorities are at high risk for developing T2DM but often lack access to preventive health checkups and depend on routine screening at schools. In our study, risk factors were identified using a modified ADA protocol using non-invasive criteria [14]. Only the posterior cervical region was inspected for AN. Other intertriginous areas such as the axillae were not examined. We have not included polycystic ovarian syndrome as a risk factor because it involves detailed history, physical examination and invasive lab tests. These strategies make the evaluation easier and will allow larger number of children to be screened in schools and other public places. Due to the strong association of the five risk factors to T2DM, it is reasonable to conclude that screening methods adopted in this study have accurately stratified low risk and high risk groups [22, 25-30].

As presented in Table 1, this cross sectional study has a reasonable sample size (149) representing a diverse race/ethnicity. The participants are predominantly (~80%) ethnic minorities (Hispanics and African Americans) from urban areas. The demographic information of the subjects recruited to this study is in agreement with the distribution of various race/ethnic populations who typically visit our clinics.

The number of Hispanic children and adolescents diagnosed with T2DM has been substantially increasing in recent years [31]. The fact sheet (AHRQ Pub. No. 02-P007) released by the United States Department of Health and Human Services (HHS) stated that African Americans are 1.4 - 2.2 times more likely to be diagnosed with T2DM. Due to the high percentage (~80%) of Hispanic and African American subjects in this study, it is possible that a significant number of participants (89) are in the high risk category.

T2DM is a multifactorial disease. It is believed that both genetic and environmental factors play a role in developing the disease. The chance of an identical twin to develop T2DM is approximately 80%, if the other twin is a known diabetic [10]. The genetic basis is very complicated and poorly understood. Interestingly, among the five risk factors tested in the current study, the modifiable factors such as high BMI percentile, high blood pressure and AN were highly correlated with the high risk group as compared to the non-modifiable risk factors (race/ethnicity and positive family history) (Table 3). These results clearly indicate that T2DM can be considered as a potentially preventable disease in children and onset can be delayed in adults.

The primary causes for high BMI and abnormal lipids are attributed to poor diet and sedentary life style. Animal and human studies have shown that high fat diet alone leads to hyperinsulinemia, high blood pressure and kidney damage [32]. Molecular mechanisms showing an association of excessive lipid deposition with insulin resistance is well established [33, 34]. A retrospective study in Mexican children demonstrated positive correlation between elevated BMI and abnormal lipid profiles [35]. Studies on adolescents revealed similar results showing a relationship between lipid profile and risk of diabetes [36-38]. TC/HDL ratio is used to predict the risk of heart disease in adults. A ratio below 3.5:1 is considered good and a higher ratio forecasts higher risk for heart disease. Even though an association of high TC/HDL ratio and T2DM risk has been proposed in some research studies in adults [39, 40], such association has not been shown in children. In our study TC/HDL ratio was significantly elevated in high risk group suggesting a strong association of elevated TC/HDL ratio with risk of developing T2DM.

One of the most important findings of this study was the determination of significant predictors for T2DM risk using the logistic regression model. Low HDL is the most powerful

predictor ($p=0.015$; odds ratio=4.14) followed by high TC/HDL ratio ($p=0.035$; odds ratio: 1.79) and low SES ($p=0.043$; odds ratio: 2.6). In the United States, it is noticeable that SES disparity exists among different race/ethnicity groups [41, 42]. Such disparity could potentially explain the correlation between low SES and T2DM risk noticed in this study.

Obesity is a growing health concern world-wide, surpassing other epidemic diseases such as AIDS and malnutrition [43, 44]. Diabetes and cardiovascular disease (CVD) are the top obesity-related health complications that affect both children and adults [44]. There is some overlap of risk factors among these two diseases. Obesity, high TG, low HDL and hypertension are all considered cardiometabolic risk factors. The presence of two or more of these factors increases the risk of pre-diabetes [45]. Our research study is in agreement with this statement. In addition, a high TC/HDL ratio is also one of the predictors for high risk of developing T2DM. This finding emphasizes the importance of universal lipid screening in children for assessing the cardiovascular as well as T2DM risks allowing early interventions. The significant determinants associated with the high risk of T2DM - low HDL, high TG and TC/HDL ratio and low SES, are all modifiable factors. Hence, early interventions could potentially avoid health complications and unfavorable outcomes in later life.

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure Statement

None declared.

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