Original Research Article

THE METABOLIC SYNDROME IN ADOLESCENTS AGE 11-18 YEARS WITH FAMILIAL HISTORY OF EARLY ONSET TYPE 2 DIABETES (T2DM)

ABSTRACT

Background: Some studies have noted an association between family history of diabetes and the Metabolic Syndrome (MS) in childhood

Aim: To determine the prevalence rate of the metabolic syndrome in adolescents with familial history of early onset (T2DM) and BMI < 95th percentile for age.

Study Design: A cross-sectional analysis.

Place and duration of study: Department of Basic Medical Sciences University of the West Indies, Jamaica, 2012.

Methodology**:** Anthropometric and biochemical measurements were evaluated for 25 adolescents 11-18 years of BMI < 95th for age and family history of early onset T2DM. Thirty two (32) adolescents of similar age and BMI without familial history of diabetes served as controls. Measurements included: Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), fasting glucose, glycosylated hemoglobin ($HbA1_c$), insulin, BMI, waist circumference and insulin resistance (HOMA-IR). The prevalence rate of MS was determined in the childhood/adolescence criteria as recommended by the National Cholesterol Education Program Adult Treatment Panel Third (NCEP-ATP III) modified standard.

Results: Sixteen percent (16%), 16% and 20% of adolescents with familial history of early onset T2DM had glucose intolerance, dyslipidemia and abdominal obesity respectively. Twenty percent of these adolescents were insulin resistant and 8% were diagnosed with diabetes mellitus. Approximately 3.1%, 9.4 % and 6.3 % of adolescents without familial history of diabetes had dyslipidemia, abdominal obesity and insulin resistance respectively. No adolescent presented with blood pressure. The prevalence rate of MS in adolescents with familial history of early onset T2DM and BMI < 95th percentile for age was 19.1%. MS was not present in adolescents without familial history of diabetes

Conclusion: Adolescents of BMI < 95th percentile and family history of early onset T2DM are more likely to develop MS than adolescents of similar BMI without family history of diabetes.

Key words: Adolescents, early onset type 2 diabetes mellitus, metabolic syndrome

1. INTRODUCTION

Children are presenting with chronic metabolic conditions such as hypertension, insulin resistance and dyslipidemia that were previously associated with the adult population. MS in adults has been classified as the clustering of some dangerous interrelated risk factors such as hyperglycemia, dyslipidemia and hypertension which pre-disposes the individual to metabolic dysfunction such as diabetes and coronary heart disease [1 -3]. Clustering of features of MS has also been noticed in children and adolescents [3-5].

Studies have shown an association between MS and family history of T2DM in children and adolescents [6,7]. Studies have however reported factors such as insulin resistance and obesity as having more impact on the prevalence rate of MS than familial history of T2DM [8,9]. The prevalence rate of MS in Brazilian children/adolescents between 10-19 years with familial history of T2DM has been reported as 6.0% with approximately 24.0% having ≥ 1 features of MS [10].The prevalence rate of MS for 12-19 years old adolescents in USA from the general population was reported as 4.2%, when only obese adolescents were considered, the prevalence rate jumped to 28.7% [11]. Using two different standards, one standard that incorporated impair fasting glucose ($MetS_{IFG}$) and another which incorporated the Homeostasis Model Assessment for insulin resistance ($MetS_{HOMA}$) to determine MS in adolescents, showed how impactful insulin resistance and obesity are on MS rates. The $MetS_{IFG}$ and $MetS_{HOMA}$ prevalence rates were the same at 0.3% for normal weight adolescents, 2.6% and 5.9% respectively for the overweight and 22.9% and 35.1% respectively for obese adolescents. Approximately 37.8% of these obese adolescents were insulin resistant [12]. Therefore studies that seek to examine the impact of family history of diabetes on MS rates should weigh the effects of these two confounding factors in context with family history of diabetes.

Early onset T2DM is defined as having a family history of diabetes mellitus (DM) in multi-generations with at least 2 first degree relatives diagnosed with T2DM before age 35 years and DM only on the maternal or paternal side of the family [13]. It was hypothesized for this study that because of the strong multi-generational history of T2DM in the cohort, the prevalence rate would be above rates reported for other

studies of MS in adolescents who are non-obese based on BMI percentiles [10,11]. While other studies have looked at MS in children/adolescents with familial history of T2DM [10,14] there is a paucity of information on MS in adolescents with familial history of the atypical diabetes which spans many generations-early onset T2DM. Data on the prevalence of MS in adolescents in developed countries are readily available [11,15]. There is however a dearth of data on MS rates in adolescents in developing countries in the Americas. The study was thus designed to evaluate for features of and determine the prevalence rate of MS in adolescents of BMI <95th percentile and family history of early onset T2DM in Jamaica. Insulin resistance and abdominal obesity in context with family history of early onset T2DM were evaluated in this study because studies have reported the confounding effects of these two variables on MS rates.

2. METHODS

An earlier genomic study between 1993 and 2006 at the University Hospital of the West Indies, Jamaica of families with early onset T2DM were carried out [16]. A secondary analysis of the prevalence rate and features of MS was carried in 2012 on 25 adolescent offspring age 11-18 years and BMI < 95 percentile for age of the women with familial history of early onset T2DM . Thirty two (32) adolescents of similar age with no familial history of diabetes served as controls. The protocol was approved by the Institutional Review Board (IRB) at the University Hospital of the West Indies (UHWI), Jamaica. The procedures were in agreement with Helsinki Declaration of 1975 [17] and the ethical standards of the IRB. Written informed consents were obtained from mothers and assents were obtained from recruited adolescents. Participating adolescents and mothers were interviewed by a research student.

Exclusion criteria for adolescents included: Adolescents with BMI ≥ 95% percentile for age [18], of multi-fetal gestations and or congenital anomalies and siblings.

Inclusion criteria: The adolescent offspring of women who were registered for ante-natal care at the University Hospital of the West Indies from 1993 through 2006.

Consent was given by mothers to have obstetric records and dockets examined for data retrieval. The follow-up studies were performed by contacting the adolescent offspring in 2012 after a review of dockets of the women. Participating adolescents were weighed and had height taken on a calibrated

weight/height scale (Detecto, USA). Body Mass Index (BMI) is defined as weight in kilograms divided by the square of height in meters (kg/m^2). Appropriate percentiles for weight and height were assigned by using the Centers for Disease Control and Prevention (CDC) criteria [18]. Waist circumference was measured at the uppermost lateral border of the ilium and appropriate percentile was assigned [18]. Blood pressure using a standard clinical sphygmomanometer with a calibrated childhood/adolescence cuff was determined in three sequential measurements and the average recorded [19]. Venuous blood was taken for fasting glucose, HbA1c, insulin, TC, HDL, LDL-C and TG. Insulin resistance was also calculated [10,20]. A child/adolescent specific definition was used to determine MS. That is: ≥ 3 of the following factors: Waist circumference >90^{th} for age/sex, high blood pressure and hypertriglyceridemia (≥130 mg/dl)), low HDL cholesterol (≤35 mg/dl)) and impaired fasting glucose (>110mg/dl)[11].

2.1. LABORATORY ANALYSIS

Plasma glucose was measured by using the glucose oxidase method (Sigma Diagnostics, MI, US). TC and TG were measured with the RA-1000 autoanalyser (Technicon Instruments Corporation, NY, US). HDL-C was measured with the RA-1000 autoanalyser (Technicon Instruments Corporation, NY, US) after precipitating out the apo-B-containing lipoproteins. LDL-C was calculated according to Freidwald equation (TC–[VLDL-C ± HDL-C], VLDL-C: TG/5). HbA1c was measured using high performance liquid chromatography (TOSOH Lipoprotein Analytical System,Tokyo, Japan). Serum insulin (fasting) was measured by the sandwich immunoassay method (Roche Diagnostics, IN, USA). Insulin resistance was calculated by the homeostasis model assessment as $insulin_0$ (µIU/mL) x fasting $glucose_0$ (mmol/L) /22.5[19]. Insulin resistance = HOMA–IR ≥2.5 [10].

2.2. STATISTICAL ANALYSIS

Statistical analyses were performed by using a Mann-Whitney *U* test to compare means of the 2 groups depending on the normalcy of the distribution. Comparisons of non-continuous data were by a chi-square test. ANOVA for parametric data and a Kruskal-Wallis test for non-parametric data were used to differentiate between percentiles. Logistic and multiple regression analyses were used to predict outcome of interest. Maternal data were included to help best predict the prevalence rate of MS in

adolescent offspring. Data are expressed as mean ± SD, and a *P* value =.05 was set as significant. Statistical analyses were performed using SSPS version 21 (IBM, USA).

2. RESULTS:

Twenty five adolescents had family history of early onset T2DM, 23 had diabetes history from the maternal side and 2 had paternal history of the disease. Of the 25 adolescents with family history of early onset T2DM, 2(8.0%) were small for gestational age (SGA), 20 (80%) were appropriate for gestational age (AGA) and 3 (12.0) were large for gestational age (LGA). Of the 32 adolescents without familial history of diabetes, 6(18.8 %) were SGA, 25 (78.1 %) were AGA and 1 (3.1 %) was LGA. Weight, BMI, waist circumference, TG and LDL-C, HbA1c, fasting glucose, fasting insulin, HOMA-IR were significantly higher (P<0.05) in the adolescents with family history of early onset T2DM compared to adolescents with no familial history of diabetes (See Table 1).

Table 1: Anthropometric and metabolic parameters of adolescents

	A1	A2	Pvalue
Age (yrs)	15.8 ±4.1	16.1 ±3.8	.35
Male/female (n)	15/13	18/14	.50
Weight (kg)	50.9 ±9.8	65.4 ±10.4	.05
Height (cm)	151.2 ±22.2	160.2±20.9	.05
BMI (kg/m^2)	19.7 ±4.9	23.9± 6.1	.001
Waist Circumference (mm)	62.8 ±7.9	85.1±15.2	.01
Systolic BP (mm Hg)	114±11	117±11	.87

Diastolic BP (mm Hg)	72±6	73±8	.90
Fasting glucose (mg/dL)	81±10.2	89±25.2	.01
Fasting Insulin (pmol/L)	11.0± 2.2	12.3 ± 3.7	.04
HOMA-IR	1.8 ±1.1	2.4 ±1.7	.05
TC (mg/dL)	145±45.8	163 ±31.7	.09
Triglyceride (mg/dL)	76±33.8	97±21.7	.02
HDL –C (mg/dL)	48.2±7.3	44 ±8.2	.01
LDL-C	87 ±25.2	100±32.1	.001

P=.05 indicates statistical significant difference between groups

SBP- Systolic blood pressure

DBP- Diastolic blood pressure

A1- Adolescents without familial history of diabetes

A2- Adolescents with familial history of early onset T2DM

Twenty percent of adolescents with familial history of early onset T2DM were obese based on waist circumference with 8% of the 20% been severely obese (waist circumference >97% for age). Five or 20% fitted the definition of been insulin resistant (HOMA-IR>2.5)[10]. Approximately 19.1% of adolescents with familial history of early onset T2DM fitted the criteria for definition of MS (≥ 3 of 4 features). Two or 8% of adolescents with familial history of early onset T2DM were diagnosed with diabetes mellitus during the study. Approximately (9.4%) of adolescents without familial history of diabetes had abdominal obesity and 3.1% had dyslipidemia. Two or 6.3 % of adolescents without familial history of diabetes were insulin resistant (HOMA-IR>2.5) [10].

Fifty seven mothers gave consent for their adolescents to be enrolled in the study and for antenatal/birth records to be examined. Twenty five mothers had adolescents with family history of early onset T2DM,

and 32 mothers had adolescents without familial history of diabetes. Mothers of adolescents with family history of early onset T2DM gained significantly more (P=.01) weight during pregnancy. Fasting glucose, HbA1c, fasting insulin, HOMA-IR and TG levels were significantly higher (P=.05) in mothers of adolescents with family history of early T2DM. HDL-C level was significantly higher (P=.04) in mothers of adolescents without familial history of diabetes in comparison to mothers of adolescents with familial history of early onset T2DM. Five (20.0%) of mothers of adolescents with familial history of early onset T2DM were diagnosed with GDM during pregnancy.

Mothers of adolescents without familial diabetes had more live births (parity), smoked and drank significantly more alcohol (P=.05) than mothers of adolescents with a family history of early onset T2DM (see table 2)

Table 2: Maternal demographics of mothers of studied adolescents

	A1(n=32)	**A2(n=25)**	**P<value**
Age at delivery (years)	35.2±9.1	33.5±11.2	.10
Height (cm)	166.0 ±14.1	164.2 ±18.1	.09
Pre-gravid weight (cm)	64.5±10.1	67.2 ±16.2	.06
Pre-gravid BMI (kg/m^2)	23.2 ±5.1	23.8 ±5.2	.09
Weight gain (kg)	10.1±3.1	13.4 ±2.9	.04
Parity (n)			
0-1	24	18	.01
>1	10	5	.01
Fasting glucose (mg/d/L)	111.1 ±12.9	127±14.3	.01
Postprandial glucose (mg/dL)	135 ±13.1	183±25.9	.06
Fasting Insulin (pmol/L)	14± 2.8	16±4.9	.04
HOMA-IR	1.9 ±0.7	3.4 ±1.4	.05

TC (mg/dL)	158.6±30.4	169.3 ±40.8	.06
TG (mg/dL)	83.5 ±20.3	91.8 ±19.6	.01
HDL cholesterol (mg/dL)	48.0±7.3	46.0 ±6.2	.04
LDL-C (mg/dL)	90.2±21.2	97.1±22.8	.05
Smoke (yes/no)	7/15	3/16	.05
Drink alcohol (yes/no)	3/19	1/18	.09

P=.05 indicates statistical significant difference between groups

4. DISCUSSION

Adolescents with or without family history of diabetes in this study presented with normal blood pressure. Waist circumference >90th for age/sex, high blood pressure and hypertriglyceridemia (≥130 mg/dl)), low HDL cholesterol (≤35 mg/dl)), impaired fasting glucose (>110mg/dl) confirmed MS [11] in the study. The factors are discussed in ascending order based on the impact on the MS rate in the cohort.

4.1 HYPERTENSION

Conflicting data have been reported on the relationship between family history of diabetes and blood pressure. One study found no significant relationship between family history of diabetes and blood pressure in 17 years old adolescents [20]. Another study found that family history of diabetes was positively associated with blood pressure in in children and adolescents [7]. No relationship has been found in this study between family history of diabetes and blood pressure in adolescents.

4.2. GLUCOSE INTOLERANCE

Glucose intolerance or high fasting glucose (>110mg/dl) was present in 16% of adolescents with family history of early onset T2DM. Glycosylated hemoglobin (HbA1c) ranged from 5.7-5.9 % for the 16% of adolescents with glucose intolerance; HBA1c values ≥5.7% have been associated with MS in

adolescents in another study [22]. Family history of T2DM has shown a significant association with glucose intolerance in adolescent girls in South India [23]. Fasting glucose was significantly higher (P=.01) in mothers with family history of diabetes (table 2) and their adolescent offspring had higher fasting glucose levels (table 1). Libman and Arslanian reiterated that glucose intolerance has a hereditary component and children with family history of T2DM are at risk of developing this condition [24]. High fasting glucose values in the adolescents with familial history of early onset T2DM are consistent with data from other studies that indicate that fasting glucose is one of the common features of MS in adolescents with familial history of T2DM[14,23].

4.3. DYSLIPIDEMIA

The adolescents with a family history of early onset T2DM had significantly lower HDL-C and significantly higher LDL-C and TG levels than adolescents without family history of diabetes. Family history of T2DM has been reported to be associated with dyslipidemia (low HDL-C and elevated TG) in another study of non-obese (based on BMI percentiles) children and adolescents [21]. Twenty percent of adolescents with family history of T2DM had mothers with GDM. Diabetes in pregnancy can precipitate fatty streak in fetal aortas and subsequent deposits of LDL-C [25]. The adolescents with familial history of early onset T2DM also had higher fasting glucose values. High glucose value is linked to low HDL-C and higher TG value. Elevated glucose in the blood may have caused increased glycation of HDL-C, this dysfunction in metabolism is often associated with a rise in triglyceride level [26]. Sixteen percent of adolescents with family history of early onset T2DM in this study had dyslipidemia in comparison to 3.1% of adolescents without familial history of diabetes.

4.4.WAIST CIRCUMFERENCE

Based on BMI percentiles only, the adolescents in this study was non-obese (BMI < 95th percentile) [18], yet the data which evolved showed otherwise. Twenty percent of the adolescents with familial history of early onset T2DM showed abdominal obesity (waist circumference >90th percentile) with approximately 8% of the 20% been seriously obese (waist circumference >97% for age). The data agreed with other studies which indicate that waist circumference as a measure of obesity is more correlated with MS than BMI[27-28].The association of abdominal circumference >90th percentile with MS was independent of age and gender and whether the familial diabetes was passed down from the maternal or paternal side

and persisted in both sexes. Obesity in this study showed a strong relationship with familial history of early onset T2DM. The 8% of adolescents with familial history of early onset T2DM who were diagnosed with DM were severely obese (abdominal circumference > 97% for age). One study reported, the prevalence rates of MS as 15.0% and 25.3% in overweight and obese adolescents respectively [29]. Twenty percent of adolescents with family history of early onset T2DM fitted the definition of been insulin resistant (HOMA-IR ≥2.5). This is consistent with data from Brazil which found that 10.9% and 23% of normal and overweight adolescents respectively with family history of T2DM were insulin resistant [10]. Only 6.3% of adolescents without family history were insulin resistant.

There was a positive correlation between LGA at birth and abdominal obesity in adolescents (r=0.04 and p=0.01). Two (2) out of 3 adolescents with familial history of T2DM who were LGA showed abdominal obesity and 1/1 LGA adolescent without familial history of diabetes had abdominal obesity. A retrospective examination of delivery records showed that the 3 LGA babies who were obese in adolescence had waist circumference >95th percentile. There is a consistent association of LGA with abdominal obesity as seen in other studies [30-31]. The association was independent of familial history of diabetes.

4.5. PREVALENCE OF MS

There is a positive association between familial history of early onset T2DM and the prevalence of MS. MS was present in 19.1% of the adolescents with familial history of early onset T2DM and BMI <95 percentile for age. The results are consistent with data showing that family history of T2DM is significantly associated with MS in adolescents [10,23]. MS however was more prevalent in those who exhibited abdominal obesity. Approximately 40% of the obese adolescents with family history of early onset T2DM had MS. Approximately 30% of those with insulin resistant had MS. Abdominal obesity and insulin resistance were confounding factors in those adolescents with familial history of early onset T2DM who developed MS. The MS rate rose to 49.5% in obese adolescents who were insulin resistant and had family history of early onset T2DM. This study and other studies indicate that insulin resistant and abdominal obesity are associated with higher MS rates in context with familial history of diabetes [10,29]. Some of the adolescents without familial history of diabetes (controls) had features of MS but not the syndrome, 9.4% had abdominal obesity (elevated waist circumference) and 3.1% had dyslipidemia. MS in adolescents can translate into atherosclerotic processes in later life [32].

5. CONCLUSION

To our knowledge, this is the first study to evaluate the prevalence and features of the MS in adolescents with BMI < 95th percentile and familial history of early onset T2DM therefore adding valuable data to the literature on MS and early onset type 2 diabetes. Non-obese adolescents with family history of early onset T2DM are more likely to develop MS than non- obese adolescents without family history of diabetes. Early identification of features of MS in adolescents who are at risk for the syndrome is essential to reduce associated mortality and morbidity rates

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