

Original Paper

Vascular Compliance in Lean, Obese, and Diabetic Children and Adolescents: A Cross-Sectional Study in a Minority Population

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Key Words

Vascular compliance · Type 2 diabetes mellitus · Obesity · Children · Insulin levels · HOMA-IR

Abstract

Background: In adults, both obesity and type 2 diabetes mellitus (T2DM) are positively correlated with cardiovascular disease mortality and arterial stiffness. Several studies of adults have shown that both obesity and T2DM are independently associated with increased arterial stiffness. However, little is known about the relationship between arterial compliance and cardiovascular disease risk in children. We assessed whether large and small arterial compliance is impaired in obese and diabetic pubertal children. **Methods:** One hundred children of African-Caribbean ethnicity, aged 14–16 years, including 21 lean children (between the 25th and 75th percentile), 40 obese children (>95th percentile), and 39 children with T2DM diagnosed by American Diabetes Association criteria were studied. Arterial compliance of the large (C_1) and small (C_2) vessels was measured using radial arterial diastolic pulse wave contour analysis. **Results:** C_1 did not differ significantly between lean, obese, and T2DM subjects. C_2 was significantly greater in obese and T2DM subjects (10.9 ± 1 and 10.4 ± 0.7 ml/mm Hg \times 100 ml, respectively) compared to lean subjects (7.8 ± 0.8 ml/mm Hg \times 100 ml; $p < 0.05$). C_2 was also significantly greater in T2DM subjects receiving antihypertensive drug therapy than in diabetic subjects not on antihypertensive treatment. **Conclusion:** Increased compliance in diabetic and obese children compared to lean subjects could be secondary to premature maturation of the vascular system; whether this early maturation can translate into a subsequent rise in the incidence of cardiovascular events related to diabetes and obesity can only be determined by long-term follow-up of these patients.

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Introduction

Cardiovascular disease (CVD), the major cause of death worldwide, is the end result of vascular aging and atherosclerosis, which has been demonstrated to have its origins in childhood [1]. The severity of atherosclerosis has been correlated with the intensity of exposure to risk factors such as hypertension, dyslipidemia, and diabetes mellitus. The prevalence of obesity has increased in the United States from 5 to 16% between 1963 and 2010, and continues to be in epidemic proportions [2]. The weight gain in this age group has been paralleled by an increased incidence of hypertension and type 2 diabetes mellitus (T2DM), rarely before seen in childhood. Longitudinal observations of children, adolescents, and young adults have shown that central obesity clusters with components of the cardiometabolic syndrome, such as hyperinsulinemia, insulin resistance, dyslipidemia, and hypertension, risk factors that track into adulthood with a high concordance rate [3, 4]. Therefore, early detection and prevention of risk factors for CVD beginning in childhood are important.

Measurement of vascular compliance has assumed increasing importance as a marker of early disease of the vascular wall and as a predictor of future vascular disease. Quantifying the stiffness of the arterial wall has been facilitated by various noninvasive methods for estimating vascular compliance that include diastolic pulse contour analysis, pulse wave velocity, and ultrasonic ECHO tracking. Pulse contour analysis is a validated, reliable indicator of arterial stiffness in adults; however, limited data on arterial compliance in children are available utilizing this technique [5–7]. Although vascular pathology in obese and diabetic children has been described, the time course of development of vascular function abnormalities and anatomic pathology have not been clearly delineated. In contrast, decreased vascular compliance is closely related to obesity and diabetes in adults.

The purpose of our study was to determine whether large (C_1) and small (C_2) vessel compliance is impaired in obese and T2DM children and adolescents compared to lean controls.

Methods

A total of 100 African-Caribbean children, aged 14–16 years, including 21 lean children, 40 obese children, and 39 children with T2DM participated in the study. Written informed consent was obtained in accordance with the guidelines of Kings County Medical Center and State University of New York, Downstate Medical Center Institutional Review Boards for human subjects. The criterion for inclusion in the normal weight group was a body mass index (BMI) between the 25th and 75th percentile based on 2000 Centers for Disease Control (CDC) growth charts. Children in the obese group (Ob) had a BMI >95th percentile based on CDC growth charts. Children in the T2DM group were diagnosed according to American Diabetes Association guidelines. Children in the lean and Ob were free of diabetes, cardiovascular, and other chronic diseases. The T2DM children were receiving no insulin. None of the participants were on lipid-lowering agents. A pediatrician completed a medical history and physical examination on each participant and determined the pubertal status based on Tanner staging. Height and weight were measured and expressed as a percentile using CDC norms for the child's age and sex. All patients were studied after a 10-min rest in the supine position following an overnight fast.

Clinical and Laboratory Measurements

Arterial compliance of the large (C_1) and small (C_2) vessels was measured using the radial arterial diastolic pulse wave contour analysis (Cardiovascular Profiling Instrument; HDI, Eagen, Minn., USA). Radial artery pulse waveforms were recorded noninvasively by applanation tonometry after stabilizing the wrist in a plastic splint. An appropriately sized blood pressure cuff was placed on the left arm. After a stable baseline and optimal waveforms were achieved, they were recorded for 30 s and then digitized at 200 samples per second to determine large artery and small artery elasticity indices. Blood pressure was measured oscillometrically over the contralateral brachial artery with the use of a calibration system internal to the device.

Table 1. Baseline characteristics

Parameter	Lean	Obese	Diabetes
Number	21	40	39
Gender(M/F)	9/12	20/20	15/24
Age, years	14.9±0.4	14.6±0.3	15±0.4
Tanner stage	4.3±0.1	4.6±0.1	4.6±0.2
Diabetes duration, months	–	–	23±5
Antihypertensive treatment, n	0	1	17
Height, inches	63±1	65±1	66±1*
Weight, pounds	120±7	243±9**	214±9**
BMI	20.8±0.6	40.3±1**	34.2±1.1**
Hemoglobin A1c, %	5.4±0.2	5.5±0.2	8.8±1**,†

* p < 0.05 vs. lean; ** p < 0.01 vs. lean; † p < 0.01 vs. obese.

Blood for fasting serum glucose, insulin, and lipids was collected. Glucose and insulin values were used to calculate fasting insulin resistance using the Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) formula [fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5]. Based on receiver operating characteristic analysis, a HOMA value >3.16 was considered diagnostic of insulin resistance in children and adolescents [8].

Statistical Analysis

All values were expressed as mean ± standard error of the mean. Differences in group means were determined by repeated measure analysis of covariance (ANCOVA). Statistical operations were performed using JMP software (SAS Institute, Cary, N.C., USA). Statistical significance was set at p < 0.05.

Results

Demographics (table 1)

All participants were of African-Caribbean descent. Mean ages and Tanner stages were similar in each group, ranging from 14.4 to 15.2 years and stages 4.2 to 4.8, respectively.

The T2DM group had more females than males. The mean duration of diabetes in the T2DM group was <2 years (23 ± 5 months). Most of the T2DM subjects were on oral hypoglycemic agents, mainly metformin. Of 39 T2DM subjects, 17 were receiving antihypertensive agents, mostly ACE inhibitors.

As expected, obese and T2DM subjects were significantly heavier than lean subjects and their mean BMI greatly exceeded the 95th percentile for age and gender compared to lean subjects (40.3 ± 1 and 34.2 ± 1 vs. 20.8 ± 1; p < 0.01). Mean glycosylated hemoglobin levels were 8.8 ± 1% in T2DM compared with 5.5 ± 0.1 and 5.4 ± 0.2% (p < 0.01) in obese and lean subjects, respectively.

Insulin Resistance and Glycemic Control

Fasting serum glucose was significantly higher in T2DM subjects (147 ± 22 mg/dl) compared to lean and obese subjects (83 ± 3 and 87 ± 2 mg/dl; p < 0.01). Fasting plasma insulin levels were 32 ± 6 and 31 ± 5 μU/ml in the Ob and T2DM groups (reference range: 0–23 μU/ml). Plasma insulin levels were not obtained in lean subjects, as they were not expected to have insulin resistance. HOMA-IR values in the Ob and T2DM groups were 5.9 ± 1.5 and 11.6 ± 7.6, respectively (table 2).

Table 2. Serum biochemical measures

Parameter	Lean	Obese	Diabetes
Cholesterol, mg/dl	158±9	168±5	175±8
Triglycerides, mg/dl	109±19	104±7	118±9
HDL, mg/dl	52±6	44±2	44±1
LDL, mg/dl	89±8	107±5**	105±7**
Glucose, mg/dl	83±3	87±2	147±22** [†]
Insulin levels, µU/ml	–	32±6	31±5
HOMA-IR	–	5.9±1.5	11.6±7.6

** p < 0.01 vs. lean; [†] p < 0.01 vs. obese.

Table 3. Vascular compliance data

Parameter	Lean	Obese	Diabetes
Number	20	36	34
C ₁ elasticity (ml/mm Hg ×10)	16.6±1.5	16.2±1	15.5±1.1
C ₂ elasticity (ml/mm Hg ×10)	7.8±0.8	10.9±1*	10.4±0.7*
Systolic BP, mm Hg	111±2	121±2**	119±1*
Diastolic BP, mm Hg	63±1	60±1	61±1
Heart rate, beats/min	78±2	75±2	75±2

BP = Blood pressure. * p < 0.05 vs. lean; ** p < 0.01 vs. lean.

Serum Lipids

Total cholesterol, triglyceride, and HDL cholesterol levels did not differ between groups. LDL cholesterol was significantly higher in obese and T2DM subjects (table 2).

Vascular Compliance (table 3)

C₁ (large vessel elasticity) did not differ significantly between lean, obese, and T2DM subjects. C₂ (small vessel compliance) was significantly greater in obese and T2DM subjects than in lean subjects (10.9 ± 1 and 10.4 ± 0.7 vs. 7.8 ± 0.8 ml/mm Hg × 100 ml; p < 0.05). C₂ was significantly greater in T2DM subjects receiving antihypertensive drug therapy, compared to T2DM subjects not on antihypertensive treatment. Systolic blood pressure was significantly elevated in the Ob and T2DM groups compared to the lean group (121 ± 2 and 119 ± 1 vs. 111 ± 2 mm Hg; p < 0.01 and p < 0.05), while diastolic blood pressure did not differ between the groups. Of note, weight and BMI were strongly correlated with small vessel compliance (p < 0.0001 for both).

Discussion

In our study, small vessel compliance (C₂) was significantly increased in obese and diabetic subjects compared to lean subjects matched for age and sexual maturation. Among diabetic subjects, C₂ was significantly greater in patients on antihypertensive medications as compared to antihypertensive naïve diabetic subjects.

In adults, obesity is positively correlated with CVD mortality and arterial stiffness [9], a recognized early marker of CVD. Obesity-related reductions in arterial compliance have been reported in adults [10–12]. However, data on arterial compliance in normal or obese children are conflicting; several studies have reported decreased arterial compliance in obese adoles-

cents [13, 14] most of which evaluated large vessel compliance only. Our findings are consistent with the recent observations of Chalmers et al. [15] who reported an increase in small arterial compliance in obese pubertal children using radial artery pulse wave contour analysis. Dangardt et al. [16] also reported decreased pulse wave velocity at radial artery (and hence increased compliance) in obese adolescent girls compared to lean controls despite increased radial intimal thickness. Obesity raises insulin concentrations and promotes relative insulin resistance [16, 17]. Elevated circulating insulin levels may increase vascular compliance through chronic smooth muscle relaxation and vasodilatation as a result of enhanced nitric oxide (NO) production from stimulation of NO synthase activity via the PI3 kinase pathway and enhancement of adiponectin release from visceral fat [18]. Plasma insulin and insulin resistance were noted to be high in our obese and T2DM subjects. In addition, puberty is also associated with decreased insulin sensitivity [19, 20]. Although a trend toward slightly more advanced Tanner stages in our obese and T2DM subjects compared to the lean subjects may have contributed to the increased insulin levels and insulin resistance, the differences were not significant. Since most prior studies reporting reduced compliance in childhood obesity measured carotid artery stiffness [13, 14, 21], varying results may represent differences between central aortic and peripheral blood pressure, as reported in the CAFÉ substudy of the ASCOT trial [22]. Large arteries that contain relatively more elastin and collagen and less smooth muscle and endothelium are more sensitive to changes in pressure, whereas thinner walled vessels of the microcirculation, in which endothelium and smooth muscle predominate, respond more to endothelial cell release of NO [23].

Cross-sectional studies of vascular compliance in adult patients with diabetes indicate that arterial stiffness is increased in patients with diabetes and tends to worsen with longer duration of disease, increasing levels of blood glucose, advancing age, higher blood pressures, progressive decline in endothelial function, and deterioration of vascular structure [24]. Reports defining vascular function in childhood T2DM, a relatively recent phenomenon in children, are limited. In the present study, small artery compliance (a measure of microvascular function) was greater in the T2DM group than in the lean group but similar to that of the Ob, while large vessel compliance was not significantly different between the three groups. This is in contrast to several prior studies performed in adults, which have reported decreased vascular compliance with diabetes. In most of these studies, patients either had diabetes for many years or duration of diabetes was not reported [14, 25]. However, Tryggstad et al. [26] have recently reported that arterial compliance was increased in T2DM children compared with normal weight peers. Others have shown that both C_1 and C_2 increase in healthy children, adolescents, and young adults, peak near the age of 30, and then gradually decline in adults free of CVD and risk factors beyond 30 years of age [27, 28]. It has been estimated that untreated diabetes mellitus reduces longevity by 10–15 years owing to changes in the structure and function of arteries [29]. The shorter duration of T2DM (mean of 23 ± 5 months) and the mean age of 15 years could account for increased C_2 in our study group, indicating that the subjects were still in the phase of vascular maturation prior to reaching the plateau phase.

The increase in vascular compliance in our diabetic subjects receiving antihypertensive drug therapy compared with those not receiving antihypertensive therapy is consistent with the improvement observed in studies of ACE inhibitors, angiotensin receptor blockers, and other antihypertensive agents [30, 31]. ACE inhibitors have been shown to increase vascular compliance by blocking the effect of angiotensin II in promoting vascular smooth muscle and cardiomyocyte growth and remodeling. The relatively smaller changes in C_1 and C_2 in diabetic patients not receiving antihypertensive drugs compared to lean subjects may reflect the relatively short duration of diabetes (mean of 23 ± 5 months). This finding is consistent with data from the Diabetes Control and Complications Trial [32, 33] which showed that in both the

entire cohort and in the subset of adolescents with type 1 diabetes, intensive diabetes therapy delayed the onset and slowed the progression of diabetic retinopathy, microalbuminuria, and neuropathy compared to conventional treatment, differences which became apparent only after 3–5 years of treatment. It is also possible that metformin treatment of T2DM patients may have had a salutary role in reducing insulin resistance and glucose output by the liver [34].

Limitations of our study include the use of an African-Caribbean population, which might potentially prevent the extrapolation of the results to the general population and the cross-sectional design, which precludes acquisition of outcome data. In addition, our study did not include estimates of central aortic blood pressure, which could potentially affect measurement of vascular compliance in young obese and T2DM subjects.

Conclusion

Small artery compliance is increased in children with T2DM and in those with obesity compared to their normal lean peers. Large artery compliance in children with T2DM did not differ between groups. In adults, CVD is known to correlate with decreased vascular compliance. This paradoxical increased vascular compliance in obese and T2DM children suggests early vascular maturation heralding early aging and premature CVD-related morbidity and mortality. Larger prospective studies with long-term follow-up are required to understand this phenomenon better.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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