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# Intrauterine growth restriction is associated with persistent aortic wall thickening and glomerular proteinuria during infancy

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Low birth weight, caused either by preterm birth or by intrauterine growth restriction, has recently been associated with increased rates of adult renal and cardiovascular disease. Since aortic intima-media thickening is a noninvasive marker of preclinical vascular disease, we compared abdominal aortic intima-media thickness among intrauterine growth restricted and equivalent gestational age fetuses *in utero* and at 18 months of age. The relationship between intrauterine growth restriction, fetal aortic thickening, and glomerular function during infancy was measured by enrolling 44 mothers with single-fetus pregnancies at 32 weeks gestation: 23 growth restricted and 21 of appropriate gestational age as controls. Abdominal aortic intima-media thickness was measured by ultrasound at enrollment and again at 18 months of age. Fetuses with intrauterine growth restriction had significantly higher abdominal aortic intima-media thickness compared with age controls when measured both *in utero* and at 18 months. At 18 months, the median urinary microalbumin and median albumin-creatinine ratio were significantly higher in those infants who experienced intrauterine growth restriction compared to the controls. Our results show that intrauterine growth restriction is associated with persistent aortic wall thickening and significantly higher microalbuminuria during infancy.

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Low birth weight, caused either by preterm birth or by intrauterine growth restriction (IUGR), has recently been shown to be associated with increased rates of renal and cardiovascular disease in adult life.<sup>1–3</sup> The fetal origins hypothesis proposes that these diseases originate through metabolic or endocrine adaptations when the fetus is undernourished and result in permanent changes of the structure and function of the body.<sup>4,5</sup>

Early endothelial dysfunction, impaired arterial vasodilation, and aortic wall intima-media thickening (aIMT) occurring *in utero* may have an important role in premature *in-utero* stiffening of the aortic vessels and may predispose these individuals to hypertension, nephropathies, and the metabolic syndrome.<sup>6</sup> Moreover, the developing kidneys appear to be extremely susceptible to IUGR and are often found to be small in proportion to body weight.<sup>7,8</sup> Several studies in animals and humans have described a reduced number of nephrons after IUGR.<sup>9–11</sup> The reduced number of nephrons results in a decreased glomerular filtration surface area, while renal blood flow per glomerulus is increased in an attempt to maintain a normal overall glomerular filtration rate. According to Brenner's hyperfiltration hypothesis, this leads to glomerular hypertension and hypertrophy, which ultimately results in glomerulosclerosis and albuminuria.<sup>12–14</sup> These findings clearly indicate that IUGR may have an adverse affect on the integrity and function of blood vessels and on glomerulogenesis during fetal life. Whether the finding of fetal aortic wall thickening predicts glomerular damage and microalbuminuria during infancy is not known.

During a recent longitudinal prospective study to evaluate aortic wall thickness in intrauterine growth-restricted fetuses and infants,<sup>15</sup> we planned additional analyses to determine if aortic thickening was predictive of precocious renal damage during infancy. Therefore, the aims of the present study were to (1) compare abdominal aortic intima-media thickness (aIMT) among IUGR and appropriate for gestational age (AGA) fetuses *in utero* and at 18 months of age, and (2) to assess the relationship between IUGR, fetal aortic thickening, and glomerular function during infancy.

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## RESULTS

Fifty fetuses initially met our inclusion criteria for the study, but only data on 44 subjects ( $n=23$  IUGR,  $n=21$  AGA) were included in our final statistical analysis. Six subjects were excluded (two IUGR and four AGA) because they did not provide urine samples. Anthropometric and clinical characteristics of the study population are shown in Table 1.

The median estimated fetal weight (EFW) at the time of the initial aIMT measurement was 1750 g (<5th percentile) in the IUGR group, and 2200 g (50th percentile) in the AGA group.<sup>16,17</sup> The median maternal age at the time of delivery was 30.5 years in the IUGR group and 31.2 years in the AGA group. Nine (39%) women in the IUGR group had a vaginal delivery, while 14 (61%) underwent cesarean section. In the AGA group, there were 14 (77%) vaginal deliveries and 7 (33%) cesarean sections. The median birth weight of the 23 children born IUGR was 1850 g (<5th percentile) at a median gestational age of 33 weeks. Neonates that were AGA had a median gestational duration of 38 weeks, with a median birth weight of 2975 g (50th percentile). In addition, no gender disparity was encountered on comparing IUGR and AGA children. The median fetal aIMT was significantly different between IUGR and AGA fetuses (IUGR 2.0 mm vs AGA 1.05 mm;  $P<0.001$ ).

At the 18-month follow-up evaluation, there was no statistically significant difference in median weight in the IUGR and AGA groups (12.3 vs 12.5 kg,  $P=0.23$ ). The aIMT, however, remained significantly larger among infants in the IUGR group compared with those in the AGA group (2.1 vs 1.05 mm;  $P<0.001$ ). IUGR infants had a higher systolic blood pressure (SBP) compared with AGA infants ( $P<0.001$ ). In addition, median urinary microalbumin (11.1 vs 4.4 mg/l;  $P=0.001$ ) and the albumin/creatinine

ratio (A/CR) (26 vs 14.6 mg/l;  $P=0.001$ ) (Figure 1) were higher in the IUGR infants compared with AGA infants.

Univariate analysis defined the following variables as being related to aIMT in fetuses: IUGR ( $P<0.001$ ) and estimated fetal weight ( $P<0.001$ ), and the following in infants: IUGR ( $P<0.001$ ), microalbuminuria ( $P<0.001$ ), systolic blood pressure ( $P<0.001$ ), and albumin/creatinine ratio ( $P<0.001$ ) (Table 2).

In addition, a positive association was observed between the prenatal aIMT values and 18-month postnatal aIMT (regression coefficient 0.86, standard error 0.24;  $P=0.001$  and regression coefficient 0.46, standard error 0.22;  $P=0.04$ , respectively) within the children born with IUGR, a phenomenon not observed among AGA children. Among IUGR infants, SBP was also positively associated with the post-natal aIMT (regression coefficient 0.02, standard error 0.009;  $P=0.04$ ) (Table 3).

## DISCUSSION

The present study highlights that aortic wall thickness and microalbuminuria are significantly higher in IUGR compared with AGA infants at a mean age of 18 months.

Although the exact mechanisms that underlie these associations remain unclear, these data, indicating early glomerular damage, extend the findings of our previous study on the natural course of aIMT among IUGR fetuses<sup>15</sup> and other studies in intrauterine fetal growth-restricted children, adolescents, and young adults at risk for premature cardiovascular and kidney diseases.<sup>11,12,18–21</sup>

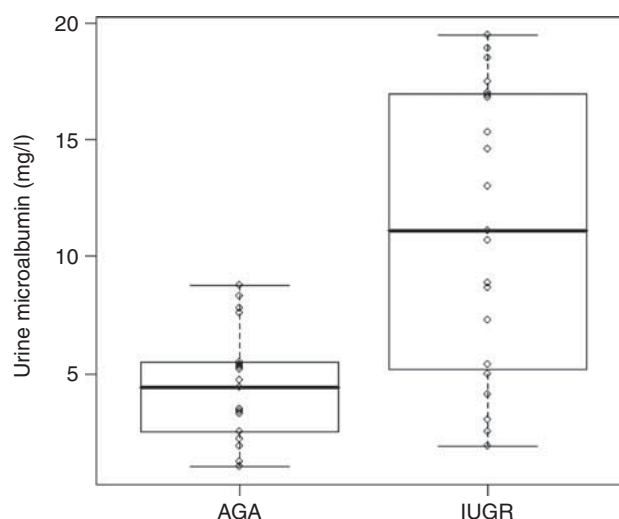
Aortic intima-media thickening is the best currently available non-invasive marker of preclinical atherosclerosis. Evidence from non-invasive ultrasound studies of the neonatal aorta, combined with fetal and early childhood

**Table 1 | Anthropometric, sonographic, and clinical measurements among IUGR and AGA fetuses and infants**

	IUGR (n=23)	AGA (n=21)	P
<i>Prenatal measurements</i>			
Gestational age (weeks)	32.1 (29.9–33.7)	32 (30–34)	0.99
Estimated fetal weight (g)	1750 (1450–2050)	2200 (1930–2470)	<0.001
Fetal aIMT (mm)	2.00 (1.78–2.23)	1.05 (0.95–1.15)	0.001
<i>Neonatal measurements</i>			
Gestational age (weeks)	33 (31–36)	38 (35–41)	0.001
Birth weight (g)	1850 (1850–2200)	2975 (2700–3250)	0.001
Gender: male	12 (52.1)	10 (47.6)	0.87
<i>Postnatal measurements</i>			
Corrected postnatal age (months)	18 (12.8–25.2)	19 (13.3–26.7)	0.48
Body weight (kg)	12.3 (11.2–13.4)	12.5 (11.3–14)	0.23
Length (cm)	87 (80–90)	86.5 (79–92)	0.34
Infant aIMT (mm)	2.1 (1.4–3.0)	1.05 (0.95–1.25)	<0.001
Systolic BP (mm Hg)	123 (107–139)	103 (95.5–112.5)	<0.001
Diastolic BP (mm Hg)	65 (57.6–72.4)	64 (59–71)	0.99
Urine microalbumin (mg/l)	11.1 (1.9–19.5)	4.4 (0.0–8.8)	0.001
A/CR (mg/g)	26 (9.8–41.4)	14.6 (8.2–21.2)	0.001

Abbreviations: A/CR, albumin/creatinine ratio; AGA, appropriate for gestational age; aIMT, aortic intima-media thickness; BP, blood pressure; IUGR, intrauterine growth restriction.

Values are shown as number (%) or as median (IQR).



**Figure 1 | Urine microalbumin in intrauterine growth restricted (IUGR) and appropriate for gestational age (AGA) infants. Median (interquartile range). Urinary microalbumin was significantly higher in the IUGR infants compared with the AGA group (11.1 vs 4.4 mg/l;  $P<0.001$ ).**

**Table 2 | Aortic intima-media thickness and associated anthropometric and clinical characteristics of fetuses and infants (univariate analysis)**

	aIMT: median (IQR)	P-value
<b>Fetuses</b>		
Group		< 0.001
AGA	1.05 (0.95–1.15)	
IUGR	2.00 (1.78–2.23)	
Sex		0.71
F	1.63 (1.09–2.06)	
M	1.35 (1.04–2.00)	
Gestational age	0.07 <sup>a</sup>	0.65
EFW	−0.72 <sup>a</sup>	< 0.001
<b>Infants</b>		
Group		< 0.001
AGA	1.05 (1.00–1.10)	
IUGR	2.10 (1.65–2.55)	
Sex		0.50
F	1.50 (1.10–2.13)	
M	1.34 (1.00–2.03)	
Corrected postnatal age	−0.11 <sup>a</sup>	0.46
Weight	−0.02 <sup>a</sup>	0.89
Microalbuminuria	0.53 <sup>a</sup>	0.001
SBP	0.81 <sup>a</sup>	< 0.001
DBP	0.09 <sup>a</sup>	0.58
A/CR	0.65 <sup>a</sup>	< 0.001

Abbreviations: A/CR, albumin/creatinine ratio; AGA, appropriate for gestational age; aIMT, aortic intima-media thickness; DBP, diastolic blood pressure; EFW, estimated fetal weight; F, female; IQR, interquartile range; IUGR, intrauterine growth restriction; M, male; SBP, systolic blood pressure.

<sup>a</sup>Spearman's rank correlation.

postmortem studies, indicates that impaired fetal growth, *in utero* exposure to maternal hypercholesterolemia, and diabetic macrosomia might all be important risk factors for vascular changes consistent with the earliest physical signs of atherosclerosis.<sup>21–23</sup> These changes first develop in the intima of the aorta by both native and oxidized LDL and macrophage infiltration.<sup>24</sup>

IUGR has also been associated with oligonephropathy. According to the hyperfiltration hypothesis, the decreased glomerular filtration surface leads to glomerular hypertension and hypertrophy, which causes systemic hypertension and glomerular damage, and ultimately results in glomerulosclerosis and albuminuria later in life.<sup>12–14</sup> However, whether fetal intima-media thickening and early endothelial dysfunction among IUGR infants are significant contributors to later atherosclerosis and glomerulosclerosis is not yet known.<sup>25,26</sup>

It is now possible to measure aortic wall thickness accurately and reproducibly *in vivo* during fetal and postnatal life with external ultrasonography. Ultrasound-based measurement of aIMT in IUGR children was found to be a sensitive marker of hypertension in young IUGR children and of atherosclerosis risk in adult life,<sup>26,27</sup> supporting the epidemiological link between impaired fetal growth and later cardiovascular disease. In addition, Singh and Hoy<sup>28</sup> described an association between low birth weight, kidney size, and albuminuria in aboriginal subjects between 4 to 72 years of age. Recently, Keijzer-Veen's<sup>18</sup> prospective follow-up study showed an association between the severity of IUGR

**Table 3 | Aortic intima-media thickness and associated anthropometric and clinical characteristics of fetuses and infants (multivariate analysis)**

aIMT	Regression coefficient	Standard error	P-value
<b>Fetuses</b>			
Group: IUGR	0.86	0.24	0.001
Sex: male	−0.003	0.04	0.95
Gestational age	0.006	0.08	0.94
EFW	−0.001	0.0004	0.49
<b>Infants</b>			
Group: IUGR	0.46	0.22	0.04
Sex: male	−0.02	0.11	0.86
Corrected postnatal age	0.005	0.004	0.24
Weight	0	0.0001	0.99
Microalbuminuria	0.03	0.02	0.24
SBP	0.02	0.009	0.04
DBP	0.01	0.01	0.33
A/CR	0.009	0.01	0.35

Abbreviations: A/CR, albumin/creatinine ratio; aIMT, aortic intima-media thickness; DBP, diastolic blood pressure; EFW, estimated fetal weight; IUGR, intrauterine growth restriction; SBP, systolic blood pressure.

and renal function in young adults born very prematurely. On average, their low birth weight subjects had lower glomerular filtration rates (GFRs), higher serum creatinine concentrations, and higher microalbumin secretion at the age of 19 years. More recently, Puddu *et al.*<sup>29</sup> reported high levels of microalbuminuria in a group of very low birth weight infants.

Microalbuminuria is one of the first symptoms of developing renal disease and precedes a decrease in GFR. The higher risk of aortic intima-media thickening and microalbuminuria may have clinical implications for IUGR infants at 18 months of age. Early endothelial dysfunction and intima-media thickening could be significant contributors to premature stiffening of the arterial tree, which ultimately might predispose these individuals to systemic hypertension and increased cardiovascular risk.<sup>22–24,27,28</sup>

Our results are in agreement with previous studies that correlate low birth weight with endothelial damage that may influence arterial function and the overall incidence of cardiovascular events.<sup>6,9,22</sup> Unlike these studies, which focused on aortic wall thickness in term IUGR infants and in high-risk children and young adults, we evaluated the natural course of this marker of endothelial dysfunction in fetuses with IUGR and severe Doppler abnormalities, both *in utero* and at 18 months of age. These results suggest that, in addition to other pathogenic mechanisms, higher arterial thickness is already present in IUGR fetuses during intrauterine life and this, together with factors such as impaired nephrogenesis and glomerulosclerosis, could have a role in programming adult disease, as previously suggested.<sup>12–14,24,26</sup>

There are limitations to our study that must be considered in the interpretation of these results. First of all, the markedly greater range in ultrasound aIMT measurements and the wide pattern of Doppler abnormalities of IUGR fetuses limited the possibility of making comparisons with other

studies, performed with different equipment (7–12 MHz probe), in both term growth-restricted neonates and in high-risk children and young adults. Second, the follow-up is limited to the second year of life. Third, we are unable to establish whether renal function will decrease more rapidly with age compared with aortic wall thickening. It is also not known whether screening for microalbuminuria and aIMT will help to prevent the loss of renal function, atherosclerosis, and hypertension at an early stage.

In conclusion, these findings indicate that IUGR children have a higher risk of both aortic wall thickening and glomerular proteinuria, which may contribute to cardiovascular and renal disease in later life. Follow-up studies are needed to confirm the prognostic role of these markers of atherosclerosis and renal disease.

## PATIENTS AND METHODS

Subjects were recruited from the Obstetrics and Gynaecology clinics at the University Hospital of Padua (Italy) between January 2006 and August 2008. Written informed consent was obtained from each woman before enrolment and the project was approved by the University Hospital Committee for Research on Human Subjects. Some of the subjects had been recruited as part of a separate multicenter study.<sup>16</sup> Data concerning women and their pregnancies were recorded according to the routine practice of the Department of Obstetrics and Gynaecology. Inclusion criteria at admission were single pregnancy, gestational age determined from known last maternal menstrual period and/or ultrasound dating before 20 weeks of gestation, and women originating from the Veneto region (Italy). Exclusion criteria were twin pregnancy, major congenital anomalies, pregnancies complicated by maternal history of cardiovascular disease or endocrine disorders such as diabetes, hypercholesterolemia, pre-eclampsia, thyroid or adrenal problems, and clinical chorioamnionitis. Women who received alcohol, nicotine, or medications such as ritodrine and corticosteroids (except for fetal lung maturation) were excluded.

Fetuses were classified as IUGR if the estimated fetal weight (EFW) was <10th percentile and the umbilical artery pulsatility index (PI) >2 standard deviations (s.d.) above the mean, and AGA if the EFW was between 10th and 90th percentiles.<sup>16,17</sup> All fetuses had at least three ultrasound and Doppler examinations during pregnancy. In each enrolled IUGR and AGA fetus, EFW and antenatal testing were available, despite no indications or guidelines recommending the use of Doppler ultrasonography in uncomplicated pregnancies.

Fetal aIMT was measured in each IUGR and AGA subject at a median gestational age of 32 weeks (interquartile range (IQR) 30–34 weeks) by high-resolution ultrasound scan (Antares, Siemens Medical Solutions, Mountain View, CA) using a 3.5–5 MHz linear array transducer, as previously reported.<sup>15</sup> Fetal examination required no more than 20 min, with about 40 min required for the children. A single, skilled practitioner performed all ultrasound studies, in both fetuses and children, using the same equipment, unaware of their clinical course and outcomes.

The follow-up examination was performed at a median corrected postnatal age of 18 months (IQR 15–21 months) and included aIMT, growth parameters, blood pressure, and a urine sample.

Blood pressure measurements were performed using a standard Doppler sphygmomanometer (Philip Medical System Monitor,

Agilent, M3046A model, M4, Boeblingen, Germany) using a cuff size appropriate for the subject's right arm circumference. Three independent measurements for each child were taken and the arithmetic mean was used for the study, as recommended by the current guidelines.<sup>30</sup>

Urine microalbumin was assayed using an immunonephelometric method (BN™II, Siemens Medical Solutions). Urine creatinine was tested by a colorimetric Jaffé method (Roche Diagnostics, Monza, Italy).

Data are presented as median (IQR). Differences between groups were tested using the Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables. As previously reported, intra-observer and inter-observer aIMT correlation coefficients were 0.876 and 0.856, respectively.<sup>15</sup> The association between aIMT and continuous variables was tested with Spearman's rank correlation. Multivariate analysis by median regression was performed to identify the independent effect of IUGR/AGA on fetal and infant aIMT after controlling for potential confounders (sex, gestational and corrected postnatal age, estimated fetal weight, body weight, systolic and diastolic blood pressure, microalbuminuria, and A/CR). A *P* < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 17 software package (SPSS, Chicago, IL) and R 2.5 statistical language.

## DISCLOSURE

All the authors declared no competing interests.

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