Prothrombotic State, Cardiovascular, and Metabolic Syndrome Risk Factors in Prepubertal Children Born Large for Gestational Age

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OBJECTIVE — To evaluate metabolic syndrome and cardiovascular disease risk factors in prepubertal children born large for gestational age (LGA) to nondiabetic, nonobese mothers.

RESEARCH DESIGN AND METHODS — At 6–7 years of age, the comparison of various factors was made between 31 LGA and 34 appropriate-for-gestational-age (AGA) children: fibrinogen, antithrombin III, protein C and S, fasting insulin, glucose, homeostasis assessment model of insulin resistance (HOMA-IR) index, adiponectin, leptin, visfatin, IGF-1, IGF-binding protein (IGFBP)-1, IGFBP-3, lipids, and the genetic factors V Leiden G1691A mutation, prothrombin 20210A/G polymorphism, and mutation in the enzyme 5,10-methylene tetrahydrofolate-reductase (MTHFR-C677T).

RESULTS — LGA children had higher levels of leptin (P < 0.001), fasting insulin (P < 0.001), and HOMA-IR (P < 0.01), but lower IGFBP-3 (P = 0.0001), fibrinogen (P = 0.0001), and lipoprotein(a) (P < 0.001) than AGA children. Significantly more LGA children were homozygous for the MTHFR-C677T mutation (P = 0.0016).

CONCLUSIONS — Being born LGA to nondiabetic, nonobese mothers is associated with diverse effects on cardiometabolic risk factors at prepuberty.

RESEARCH DESIGN AND METHODS — The study group consisted of 64 singleton Caucasian children, born at term: 31 (10 female, 21 male) were LGA (birth weight >95th percentile for gestational age), and 33 (12 female, 21 male) appropriate for gestational age (AGA) (birth weight 10th–90th percentile). No mother to standard methods (5). Lipids and IF levels were determined with functional methods and chromatometric assays. Genomic DNA was isolated from the leukocytes of peripheral whole-blood samples collected in EDTA-anticoagulant according to standard methods (5). Lipids and IF levels were determined with techniques previously described (1).

Data were analyzed by ANOVA and multiple regression analysis using the StatView software package of SAS Institute (Cary, NC).

RESULTS — The anthropometric and laboratory findings are depicted in Table 1. The significant differences in leptin, IF, and HOMA-IR between LGA and AGA children persisted after controlling for age, sex, and BMI.

Homoyzogosity for the MTHFR-C677T mutation was detected in 12 LGA and 2 AGA children (P = 0.002) and heterozogosity in 19 LGA and 8 AGA children (P = 0.003). Three LGA and none of the AGA children were heterozogous.
Table 1—Characteristics, anthropometric indices, and indices of the prothrombotic state and insulin resistance, components of the IGFs-axis, lipid profile, and adipocytokines (means ± SD) at prepuberty of children born LGA (birth weight ≥95th percentile) or AGA (birth weight 10th–90th percentile)

| Characteristics and parameters | LGA group | AGA group | P value |
|-------------------------------|-----------|-----------|---------|
| n                             | 31        | 33        | —       |
| Age (years)                   | 6.5 ± 0.5 | 6.4 ± 0.6 | ns      |
| Body weight (kg)              | 32 ± 8    | 24 ± 6    | <0.01   |
| Body height (cm)              | 126 ± 8   | 119 ± 9   | 0.08    |
| Waist circumference z score   | 0.80 ± 0.98 | 0.06 ± 1.3 | 0.05 |
| BMI z score                   | 0.80 ± 0.80 | −0.20 ± 0.8 | <0.001 |
| Systolic BP z score           | 0.49 ± 0.41 | 0.41 ± 0.43 | ns |
| Diastolic BP z score          | 0.71 ± 0.35 | 0.51 ± 0.5   | ns      |
| Prothrombin time (s)          | 13.29 ± 0.53 | 13.2 ± 0.52 | ns      |
| APTT (s)                      | 37.04 ± 22 | 38.64 ± 24 | ns      |
| Fibrinogen (µmol/l)           | 7.67 ± 0.9 | 10.05 ± 2.3 | ≤0.0001 |
| Antithrombin III (%)          | 104 ± 50  | 107 ± 69  | ns      |
| Protein C (%)                 | 99 ± 11   | 97 ± 18   | ns      |
| Protein S (%)                 | 69 ± 24   | 70 ± 19   | ns      |
| Fasting glucose (mmol/l)      | 5.1 ± 0.5 | 4.9 ± 0.6  | ns      |
| Fasting insulin (pmol/l)      | 48.6 ± 20.1 | 27 ± 24.3  | <0.01   |
| FGIR                          | 0.11 ± 0.05 | 0.25 ± 0.11 | ≤0.0001 |
| HOMA-IR                       | 1.5 ± 0.6 | 0.8 ± 0.7  | <0.01   |
| IFG-1 (µg/l)                  | 189 ± 115 | 140 ± 84  | 0.06    |
| IGFBP-1 (µg/l)                | 84 ± 33   | 88 ± 31   | ns      |
| IGFBP-3 (mg/l)                | 2.6 ± 1.1 | 3.9 ± 0.8  | ≤0.0001 |
| t cholesterol (mmol/l)        | 4.53 ± 0.6 | 4.45 ± 0.6  | ns      |
| HDL (mmol/l)                  | 1.41 ± 0.2 | 1.45 ± 0.2  | ns      |
| Triglycerides (mmol/l)        | 0.65 ± 0.1 | 0.71 ± 0.2  | ns      |
| Lipoprotein(a) (µmol/l)       | 0.09 ± 0.1 | 0.3 ± 0.2   | <0.001  |
| Adiponectin (mg/l)            | 16.3 ± 6  | 14.7 ± 5   | ns      |
| Leptin (µg/l)                 | 52 ± 23   | 31 ± 19    | ≤0.01   |
| Visfatin (µg/l)               | 13.3 ± 6  | 13 ± 5     | ns      |

APTT, activated partial thromboplastin time; FGIR, fasting glucose-to-insulin ratio; ns, not significant (P > 0.05).

eérozygous for the PT G20210A mutation (P = 0.06). One LGA but no AGA child was heterozygous for the Factor V Leiden (FVL) G1691A mutation. No child was homozygous for the prothrombin (PT) G20210A mutation or FVL polymorphism.

**Correlation studies**

On pooled data for LGA and AGA children, multiple regression analysis revealed negative correlation between birth weight z score and fibrinogen level (t = −3.8, P < 0.01), Lp(a) level (t = −3.4, P < 0.01), and IGFBP-3 level (t = −2.5, P = 0.01), and positive correlation between birth weight z score and IGF level (t = 2.8, P = 0.01) and HOMA-IR (t = 2.9, P < 0.001), independent of BMI or waist circumference z score.

**Incidence of components of the MetS and other CVD risk factors**

Of the LGA group, 9.7% fulfilled the criteria for MetS (≥3 components: waist circumference ≥90th percentile for age and sex for Greek children; BP ≥95th percentile for age, sex, and height; G_F >100 mg/dl; triglycerides >95th percentile; and HDL <5th percentile) (6,7), while no AGA child presented three components. In the AGA group, 54.5% of the children were completely free of components of MetS or risk factors for CVD (BP ≥90th percentile, I_F >15 µU/ml, fasting glucose-to-insulin ratio <7, HOMA-IR >2.83, or BMI >85th percentile) (6,8), while only 22.6% of the LGA children were free of components or risk factors (P = 0.008).

**CONCLUSIONS**— Children born LGA at term to nondiabetic, nonobese mothers are at significant risk of developing MetS. Diverse effects on CVD risk factors were observed in this group.

LGA children had significantly higher indexes of insulin resistance (I_F and HOMA-IR), independent of BMI or waist circumference z scores. The higher incidence of obesity, such as BMI and waist circumference found in this group may be attributed to earlier adiposity rebound (4,9).

Diverse effects on CVD risk factors were observed in this group. They also had a higher trend toward higher IGF-1 levels. This may indicate a possible protective mechanism against development of insulin resistance (13).

In summary, diverse effects on CVD risk factors were observed in term LGA children at prepuberty. They had higher insulin resistance indexes and anthropometric obesity markers, but lower fibrinogen and Lp(a) levels than matched AGA children. They also had a higher prevalence of the MTHFR-C677T mutation. LGA offspring of nondiabetic, nonobese mothers warrant careful monitoring for evidence of MetS precursors throughout childhood and beyond.
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