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RELATIONSHIP OF CARDIOVASCULAR RISK MARKERS IN CHILDREN SGA AND AGA

Biochemistry

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ABSTRACT

INTRODUCTION: Children born preterm usually experience an initial growth restriction, suggested to be caused by the immature organs and an inadequate nutritional intake. After this initial growth faltering, healthy preterm born children, and especially those born after 32 gestational weeks, usually fall back to the reference growth curve, following that of term born babies. For children born SGA, 80 % will experience a relative catch-up growth within the first 6 months of life.

OBJECTIVE: Role of different risk profiles for children being born preterm vs being born SGA and early iron supplementation affect later cardiovascular risk

RESULT: In Placebo group, 4.6(0.5) patients had Fasting glucose (mmol/L), 2.9(2.3-3.5) patients had Fasting insulin(µU/mL), 0.59(0.4-0.7) patients had HOMA-IR, 4.5(0.7) patients had Cholesterol(mmol/L), 0.58(0.2) patients had Triglyceride(mmol/L), 2.8(0.6) patients had LDL(mmol/L), 1.5(0.3) patients had HDL(mmol/L), 0.63(0.4) patients had ApoB(g/L and 0.20(0.1-0.6) patients had hs-CRP(mg/L). In Iron supplements group, 4.4(0.5) patients had Fasting glucose(mmol/L), 2.7(2.0-3.8) patients had Fasting insulin(µU/mL), 0.54(0.4-0.8) patients had HOMA-IR, 4.3(0.8) patients had Cholesterol(mmol/L), 0.59(0.3) patients had Triglyceride(mmol/L), 2.8(0.6) patients had LDL(mmol/L), 1.5(0.4) patients had HDL(mmol/L), 0.61(0.3) patients had ApoB(g/L and 0.24(0.2-0.8) patients had hs-CRP(mg/L).

CONCLUSION: This literature showing that there is progression of these risk factors as children enter early adolescence. Further longer longitudinal studies are needed to elucidate the mechanisms responsible for progression of cardio-metabolic risk factors from infancy to adolescence in SGA and LGA subjects.

KEYWORDS

Cardiovascular Risk Markers, Initial Growth Restriction, Preterm Born Children

INTRODUCTION

Depending on intrauterine growth, children can be grouped according to being born small or appropriate for gestational age (SGA and AGA), mostly defined as having a birth weight of ≤-2 standard deviations (SD). Moreover, children born SGA can be further divided into intrauterine growth restricted (IUGR) children, or being constitutionally born SGA.[1,2] IUGR is more common and is a pathological condition caused by maternal, fetal or placental deficiencies during pregnancy.

Consequently, LBW children is a heterogeneous group, including a wide range of gestational ages and birth weights, which further on leads to a range of different long-term challenges. The last decades, research have mostly been focusing on extremely preterm birth or children born with very LBW. However, a vast majority (more than 60 %) of all LBW children born in Sweden today are born with a birth weight between 2000 and 2500 g. They have defined this group as marginally LBW children.[3] The long-term consequences these children encounter is not entirely known.

Children born preterm usually experience an initial growth restriction, suggested to be caused by the immature organs and an inadequate nutritional intake.[2,4] After this initial growth faltering, healthy preterm born children, and especially those born after 32 gestational weeks, usually fall back to the reference growth curve, following that of term born babies.[5] For children born SGA, 80 % will experience a relative catch-up growth within the first 6 months of life.[2] However, infants born SGA still have an increased risk of remaining growth restricted later in life, both in height and in weight.[6] In addition, the children born SGA who are also born preterm will have even more difficulties in catching up and will more likely remain short throughout adulthood.[2,6] Of particular interest in the matter of early growth research, is to determine how these growth traits can be affected by environmental factors, particularly nutrition. The goal is to find the ideal growth standards for each individual, to be able to give the newborn child the right preconditions to reach his or her optimal potential without increasing the risk for adverse events. This balance is a current challenge to pediatric research.

Short small for gestational age (SGA) children constitute a special group within the group of low birth weight children because they did not reach a normal height. An increased prevalence of cardiovascular risk factors in short SGA children has been described [7,8]. Some parents of short SGA children were born SGA themselves [9,10]. It is unknown whether an increased risk for CVD in a short SGA child can be predicted by the presence of risk factors in his/her parents. We hypothesized that parents of short SGA children have an increased risk for CVD. In addition, we hypothesized that a relative high percentage of parents was born SGA themselves and that anthropometric data and cardiovascular risk factors correlate between parents and children. We, therefore evaluated in parents of short SGA children anthropometry, blood pressure, fasting serum lipids, glucose, and insulin levels, which are regarded as predictors of CVD [11].

OBJECTIVES

The objectives of the present thesis were to answer the following research questions:

- Are the risk profiles different for children being born preterm vs being born SGA?
- How does early iron supplementation affect later cardiovascular risk?

MATERIALS AND METHODS

This study was hospital based comparative study.

Statistical Analysis:

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or

unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests. A chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.

Explicit expressions that can be used to carry out various *t*-tests are given below. In each case, the formula for a test statistic that either exactly follows or closely approximates a *t*-distribution under the null hypothesis is given. Also, the appropriate degrees of freedom are given in each case. Each of these statistics can be used to carry out either a one-tailed test or a two-tailed test.

Once a *t* value is determined, a *p*-value can be found using a table of values from Student's t-distribution. If the calculated *p*-value is below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01 level), then the null hypothesis is rejected in favour of the alternative hypothesis.

p-value ≤ 0.05 was considered for statistically significant.

Table 1. Anthropometrics, body composition and laboratory cardiovascular risk markers in marginally LBW children born SGA and AGA compared to controls.

Marginally LBW subgroups			
	SGA	**AGA**	**Controls**
Anthropometrics			
Weight(kg)	23.1(3.6)**	23.2(3.6)	24.3(3.6)
Height(cm)	131.2(5.1)**	123.3(5.5)*	124.9(5.6)
BMI(kg/m^2)	16.0(1.5)*	15.2(1.7)	15.5(1.5)
WC(cm)	52.7(5.4)	54.7(4.8)	55.2(5.7)
FMI(kg/m^2)	2.5(1.3)*	2.6(1.3)	2.8(1.3)
FFMI(kg/m^2)	12.3(0.8)*	12.5(0.9)	12.6(0.9)
Fatmass(kg)	3.6(2.4)*	4.0(2.1)	2.5(2.1)
Fatmass(%)	15.5(5.6)*	16.5(6.2)	17.6(5.9)
Truncaladiposetissue(%)	14.3(8.1)	14.9(7.1)	15.8(6.6)
Laboratorymarkers			
Fastingglucose(mmol/L)	4.7(0.5)*†	4.5(0.5)	4.5(0.5)
Fastinginsulin(µU/mL)	2.10(2.2-4.2)	2.3(2.1-3.6)	2.8(LD-3.5)
HOMA-IR	0.63(0.4-0.9)	0.52(0.2-0.4)	0.60(LD-
Cholesterol(mmol/L)	4.4(0.7)	4.4(0.8)	4.5(0.8)
Triglycerides(mmol/L)	0.59(0.3)	0.61(0.3)	0.57(0.2)
LDL(mmol/L)	2.7 (0.8)	2.7(0.6)	2.8(0.7)
HDL(mmol/L)	1.6(0.5)	1.5(0.4)	1.4(0.3)
ApoB(mg/L)	0.81(0.3)	0.94(0.2)	0.81(0.2)
ApoA1(mg/L)	1.5(0.3)	1.2(0.3)	1.4(0.2)
hs-CRP(mg/L)	0.22(0.1-0.7)	0.14(0.1-0.8)	0.19(0.1-

Table 2. Anthropometrics, body composition, BP and laboratory markers of cardiovascular risk in marginally LBW children receiving placebo or iron between 6weeks and 6months of age

	Placebo	**Iron supplements**
Weight(kg)	23.0(3.2)	23.0(3.7)
Height(cm)	121.6(5.4)	122.5(5.5)
BMI(kg/m^2)	14.8(1.6)	15.2(1.6)
Waist circumference(cm)	53.5(4.9)	54.6(4.10)
FMI(kg/m^2)	2.4(1.3)	2.5(1.3)
FFMI(kg/m^2)	12.2(0.8)	12.6(0.4)
Heart rate(beats/min)	82(12)	83(10)
Systolic blood pressure(mmHg)	103.0(8)	101.2(8)†
Diastolic blood pressure(mmHg)	63.0(5)	62.9(5)
Fasting glucose(mmol/L)	4.6(0.5)	4.4(0.5)
Fasting insulin(µU/mL)	2.9(2.3-3.5)	2.7(2.0-3.8)
HOMA-IR	0.59(0.4-0.7)	0.54(0.4-0.8)
Cholesterol(mmol/L)	4.5(0.7)	4.3(0.8)
Triglyceride(mmol/L)	0.58(0.2)	0.59(0.3)
LDL(mmol/L)	2.8(0.6)	2.8(0.6)
HDL(mmol/L)	1.5(0.3)	1.5(0.4)
ApoB/ApoA1	0.63(0.4)	0.61(0.3)
hs-CRP(mg/L)	0.20(0.1-0.6)	0.24(0.2-0.8)

RESULT AND DISCUSSION

We found that in Marginally LBW SGA group, 23.1(3.6) patients had Weight(kg),131.2(5.1) patients had Height(cm),16.0(1.5) patients had BMI(kg/m^2),52.7(5.4) patients had WC(cm),2.5(1.3) patients had FMI(kg/m^2),12.3(0.8) patients had FFMI(kg/m^2),3.6(2.4) patients had Fatmass(kg),15.5(5.6) patients had Fatmass(%)and 14.3(8.1) patients had Truncaladiposetissue(%). In Marginally LBW AGA group, 23.2(3.6) patients had Weight(kg),123.3(5.5) patients had Height(cm),15.2(1.7) patients had BMI(kg/m^2),54.7(4.8) patients had WC(cm),2.6(1.3) patients had FMI(kg/m^2),12.5(0.9) patients had FFMI(kg/m^2),4.0(2.1) patients had Fatmass(kg),16.5(6.2) patients had Fatmass(%)and 14.9(7.1) patients had Truncaladiposetissue(%). In Marginally LBW Controls group, 24.3(3.6) patients had Weight(kg),124.9(5.6) patients had Height(cm),15.5(1.5) patients had BMI(kg/m^2),55.2(5.7) patients had WC(cm),2.8(1.3) patients had FMI(kg/m^2),12.6(0.9) patients had FFMI(kg/m^2),2.5(2.1) patients had Fatmass(kg),17.6(5.9) patients had Fatmass(%)and 15.8(6.6) patients had Truncaladiposetissue(%).

Chiavaroli V et al[12] (2014) found that fasting insulin and HOMA-IR were higher in SGA and LGA than AGA subjects both during childhood (all P<0.01) and adolescence (all P<0.01). Similarly, the clustered cardio-metabolic risk score was higher in SGA and LGA than AGA children (both P<0.05), and these differences among groups increased during adolescence (both P<0.05). Of note, a progression of the clustered cardio-metabolic risk score was observed from childhood to adolescence within SGA and within LGA subjects (both P<0.05).

Skilton MR et al [13](2011) showed that carotid intima-media thickness, brachial flow-mediated dilatation and cardiovascular risk factors were compared between young adults (24–45 years) born at term with impaired fetal growth (birth weight <10th percentile; n=207), born preterm (<37 weeks' gestation; n=253), and a control group born at term with normal fetal growth (birth weight 50–90th percentile; n=835), in the Cardiovascular Risk in Young Finns study. Compared with controls, those with impaired fetal growth had elevated triglycerides (P=0.006), C-reactive protein (P=0.004), low-density lipoprotein cholesterol, systolic blood pressure (both P=0.06), and intima-media thickness and impaired flow-mediated dilatation (both P=0.02), the latter partially mediated by systolic blood pressure, C-reactive protein, and triglycerides. Those born preterm had higher intima-media thickness (P=0.005) and lower flow-mediated dilatation (P=0.03) compared with controls, although this was restricted to those with concurrent fetal growth restriction.

Ramírez-Vélez R et al[14] (2017) found that preterm SGA group had a greater risk for having elevated fasting glucose and metabolic syndrome (total sample and in boys) compared with term AGA group (p<0.05). For other cardiovascular risk factors, no significant relationships were observed based on birth characteristics.

Our study showed that in Marginally LBW SGA group, 4.7(0.5) patients had Fasting glucose(mmol/L), 2.10(2.2-4.2) patients had Fasting insulin(µU/mL), 0.63(0.4-0.9) patients had HOMA-IR,4.4(0.7) patients had Cholesterol(mmol/L), 0.59(0.3) patients had Triglycerides(mmol/L), 2.7 (0.8) patients had LDL(mmol/L), 1.6(0.5) patients had HDL(mmol/L), 0.81(0.3) patients had ApoB(mg/L),1.5(0.3) patients had ApoA1(mg/L) and 0.22(0.1-0.7)patients had hs-CRP(mg/L). In Marginally LBW AGA group, 4.5(0.5) patients had Fasting glucose(mmol/L), 2.3(2.1-3.6) patients had Fasting insulin(µU/mL), 0.52(0.2-0.4) patients had HOMA-IR,4.4(0.8) patients had Cholesterol(mmol/L), 0.61(0.3) patients had Triglycerides(mmol/L), 2.7(0.6) patients had LDL(mmol/L), 1.5(0.4) patients had HDL(mmol/L), 0.94(0.2) patients had ApoB(mg/L),1.2(0.3) patients had ApoA1(mg/L) and 0.14(0.1-0.8) patients had hs-CRP(mg/L). In Marginally LBW Controls group, 4.5(0.5) patients had Fasting glucose(mmol/L), 2.8(LD-3.5) patients had Fasting insulin(µU/mL), 0.60(LD-0.7) patients had HOMA-IR,4.5(0.8) patients had Cholesterol(mmol/L), 0.57(0.2)patients had Triglycerides(mmol/L), 2.8(0.7) patients had LDL(mmol/L), 1.4(0.3) patients had HDL(mmol/L), 0.81(0.3) patients had ApoB(mg/L),1.4(0.2) patients had ApoA1(mg/L) and 0.19(0.1-0.5) patients had hs-CRP(mg/L).

Epidemiological studies with regard to iron intake and later BP have been conducted. In a review by Lapice et al, the authors found associations between ID and increased risk of CVD, although concluded that data so far are inconsistent.[15] Interestingly, treatment with intravenous iron has recently been recommended to patients with congestive heart failure and ID. In a double-blinded randomized trial, those who received iron supplements had improved 6-min-walk-test,

reduced risk of hospitalizations due to heart failure, improved quality of life and improved NYHA (New York Heart Association) class, with an effect lasting until 52 weeks after treatment.[16]

It was found that in Placebo group, 23.0(3.2) patients had Weight(kg), 121.6(5.4) patients had Height(cm), 14.8(1.6) patients had BMI(kg/m^2), 53.5(4.9) patients had Waist circumference (cm), 2.4(1.3) patients had FMI(kg/m^2), 12.2(0.8) patients had FFMI(kg/m^2), 82(12) patients had Heartrate(beats/min),103.0(8) patients had Systolic blood pressure (mmHg),63.0(5) patients had Diastolic blood pressure (mmHg),4.6(0.5) patients had Fasting glucose (mmol/L), 2.9(2.3-3.5) patients had Fasting insulin(μU/mL), 0.59(0.4-0.7) patients had HOMA-IR, 4.5(0.7) patients had Cholesterol(mmol/L), 0.58(0.2) patients had Triglyceride(mmol/L), 2.8(0.6) patients had LDL(mmol/L), 1.5(0.3) patients had HDL(mmol/L), 0.63(0.4) patients had ApoB(g/L and 0.20(0.1-0.6) patients had hs-CRP(mg/L). In Iron supplements group, 23.0(3.7) patients had Weight(kg), 122.5(5.5) patients had Height(cm), 15.2(1.6) patients had BMI(kg/m^2), 54.6(4.10) patients had Waist circumference(cm), 2.5(1.3) patients had FMI(kg/m^2), 12.6(0.4) patients had FFMI(kg/m^2), 83(10) patients had Heart rate(beats/min),101.2(8) patients had Systolic blood pressure (mmHg),62.9(5) patients had Diastolic blood pressure(mmHg),4.4(0.5) patients had Fasting glucose(mmol/L), 2.7(2.0-3.8) patients had Fasting insulin(μU/mL), 0.54(0.4-0.8) patients had HOMA-IR, 4.3(0.8) patients had Cholesterol(mmol/L), 0.59(0.3) patients had Triglyceride(mmol/L), 2.8(0.6) patients had LDL(mmol/L), 1.5(0.4) patients had HDL(mmol/L), 0.61(0.3) patients had ApoB(g/L and 0.24(0.2-0.8) patients had hs-CRP(mg/L).

CONCLUSION

While the anthropometric outcomes and the laboratory risk markers did not depend on the early iron intervention, this study showed that the children who received iron supplementation between 6 weeks and 6 months of age had approximately 2 mmHg lower systolic BP at 7 years of age, and their odds of having a high systolic BP was reduced by 68 %. This suggests that marginally LBW children may be at risk of high BP but that this risk is reversed with iron supplements. Furthermore, it suggests that iron might have a mechanistic role in the adverse metabolic programming, in this and other settings. SGA and LGA populations are known to have increased cardio-metabolic risk factors in childhood and adulthood. This literature showing that there is progression of these risk factors as children enter early adolescence. Further longer longitudinal studies are needed to elucidate the mechanisms responsible for progression of cardio-metabolic risk factors from infancy to adolescence in SGA and LGA subjects.

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