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Original Research

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Key words: breast-feeding, catch-up growth, insulin resistance, insulin secretion, formula feeding, obesity

Objective: The aim of the present study was to evaluate the association between the type of early feeding and indices of insulin metabolism in 8-year-old overweight and obese children.

Methods: The sample included 350 overweight (body mass index [BMI] $\geq$1.036 standard deviation score [SDS]) and obese (BMI $\geq$1.645 SDS) children and 33 normal-weight control subjects who had been exclusively breast-fed or formula-fed for 4 months or longer. Parameters of insulin sensitivity and secretion were derived from 120-minute oral glucose tolerance tests.

Results: Overweight and obese formula-fed children (N = 165) were more insulin resistant than breast-fed individuals (N = 185; Whole-Body Insulin Sensitivity Index 5.1 $\pm$ 2.3 vs 6.6 $\pm$ 2; $p < 0.0001$) despite having the same degree of obesity (BMI z-score 1.8 $\pm$ 0.4 vs 1.7 $\pm$ 0.4 SDS; $p = 0.5$). They compensated for enhanced insulin resistance by augmenting insulin secretion (Insulinogenic Index 6.8 $\pm$ 3.6 vs 5.2 $\pm$ 2.5 μIU/mL $\times$ mg/mL^{-1}; $p < 0.0001$). Thus, they presented with a disposition index similar to that of breast-fed children (34.6 $\pm$ 15 vs 30.8 $\pm$ 19.2; $p = 0.4$), Formula feeding was associated with greater catch-up growth in the first month (odds ratio 2.49, 95% confidence interval 1.97 to 3.01; $p < 0.0001$) and between months 6 and 12 of life (odds ratio 4.62, 95% confidence interval 3.58 to 5.67; $p < 0.0001$).

Conclusions: In comparison with breast-feeding, formula feeding seems to be associated with reduced insulin sensitivity and increased insulin secretion in overweight and obese children.

INTRODUCTION

The perinatal window may be crucial for determining an individual's risk of developing metabolic abnormalities [1]. *In utero* growth [2], birth weight [3], and timing and rate of postnatal growth [4,5] have all been associated with the risk of obesity, insulin resistance, and type 2 diabetes mellitus (T2DM). The mechanisms of these associations are still unknown, although several hypotheses have been formulated. Barker [6] initially proposed that altered glucose metabolism associated with a low birth weight could be the result of impaired beta-cell function. Intrauterine undernutrition during a critical period of fetal life could lead to abnormal development of the endocrine organs, mainly the pancreas [6]. Successively, Barker also reported that a low birth weight confers an increased risk for insulin-resistance syndrome, which encompasses hyperinsulinemia that may or may not be associated with impaired glucose tolerance and T2DM, dyslipidemia, and hypertension. Thus, according to Barker's hypothesis, an adverse intrauterine environment causes permanent changes in insulin physiology and metabolism [6]. The "thrifty phenotype" hypothesis explains this phenom-

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Abbreviations:ALT = alanine aminotransferase, AST = aspartate aminotransferase, DI = Disposition Index, IGI = Insulinogenic Index, HIRI = Hepatic Insulin Resistance Index, HOMA-IR = Homeostasis Model Assessment of Insulin Resistance, OGTT = Oral Glucose Tolerance Test, WISI = Whole-Body Insulin Sensitivity Index.

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enon by suggesting that the fetal nutrient-conserving adaptations in response to intrauterine under nutrition are overwhelmed by nutrient abundance postnatally and manifest in adult metabolic diseases [7].

The increased risk of adult metabolic diseases in those who are born small at birth (small for gestational age [SGA]) can be further amplified by a diet-induced accelerated pattern of growth during childhood [5,8–10]. Early nutritional experience during this critical and specific period of development, which is also termed the "opportunity window," might result in a long-lasting, lifelong effect that predisposes to certain disease as well [1].

Breast-feeding represents one of the earliest nutritional experiences of newborns, giving continuity to intrauterine nutrition. Nutritional factors might play a pivotal role, modulating the patterns and timing of catch-up growth and probably influencing the hormonal milieu and the balance between hypertrophy and hyperplasia of the adipose tissue. Significant differences exist between human milk and formulas in terms of quantitative and qualitative intakes of calories, protein, carbohydrate, and fats [11], which may induce a different daily profile of systemic and gastrointestinal hormones. Whether breast-feeding protects against obesity later in life is a controversial topic. Some investigators have shown that breast-feeding has protective effects against childhood obesity [12–16]. Others have observed no association [17–20]. Meta-analyses of published observational studies have suggested either that breastfeeding is associated with a 13%–22% lower likelihood for overweight and obesity in adulthood, with a significant dose-related effect [21], or that patterns of such associations can be uncertain and are strongly influenced by a number of confounding factors [3,21,22].

Conversely, few studies [23–26] have looked at the association between breast-feeding and incident T2DM. Breast-feeding was not found to be protective against the disease in one study that was recently performed in a cohort of overweight Latino youth with a positive history of T2DM [26].

Perinatal factors and feeding history can synergistically influence both sides of insulin metabolism, i.e., insulin sensitivity and insulin secretion, thus influencing the disposition index (DI) [27], namely, the product of insulin sensitivity per the insulin secretion. The DI estimates the ability of the beta cell to compensate for increased insulin resistance [28]. Studies performed in overweight and obese children with incident diabetes have found that reduced DI is one of the best predictors of the disease [28].

The aim of the present study was to investigate the association between the modality of early feeding—whether via breast milk or formula—and insulin dynamics in a large sample of overweight or obese children (N = 350) age 8–9 years born either SGA or with an appropriate weight for gestational age (AGA).

METHODS

Study Population

The sample included 390 children (age 8–9 years old) and was recruited from a retrospective cohort of children born either SGA or AGA (N = 199) along with a sample of patients (N = 191) recruited from the obesity ward in the same period with similar inclusion criteria. Children were admitted to the Liver Unit of the Bambino Gesù Paediatric Hospital, Rome, Italy, between January–June 2007 and July–November 2008.

The first sample (N = 199) included 159 overweight/obese children and 40 controls. For the purpose of the present study, 7 controls were excluded from the analysis, as they had familiarity for T2DM. Therefore, the controls were 33 normal-weight children born at term with an AGA and no familiarity for T2DM. Children from this cohort born in 1999–2000 at the San Pietro Hospital, Rome, Italy, were evaluated for associations among birth weight, rate of catch-up growth, modality of feeding in the first 4 months of life, and parameters of insulin metabolism.

The second sample included exclusively overweight and obese individuals from the obesity ward of the Bambino Gesù Hospital. Thus, the total studied population included 383 children.

The study was approved by the Bambino Gesù Hospital's Ethics Committee.

Eligibility criteria for the study included being born at term with an Apgar score ranging from 8 to 10, singleton, absence of endocrine or genetic diseases, and exclusive breastmilk or formula intake during the first 4 months of life or longer. Exclusion criteria were maternal overweight/obesity (body mass index [BMI] $\geq$24 kg/m^2) or weight gain during pregnancy $>$16 kg, maternal history of gestational diabetes, systemic diseases, smoking, alcohol abuse, or the use of any medication known to affect carbohydrate metabolism. Table 1 and Fig. 1 describe characteristics of the first cohort sample and how the sample was selected.

Research Protocol

Enrolled children were between the age of 8 and 9 when approached. All were of Caucasian ethnicity and had been born at term ($\geq$37 weeks).

Mothers were interviewed about the modality of early feeding through an ad hoc questionnaire to identify children suitable for the study; those who had received mixed feeding were excluded from participation. The mothers also provided information on weight gain during pregnancy. Birth weight, gestational age, Apgar score, feeding modalities, timing of introduction of formula and other food and beverages, and rate of growth were recorded and used in the statistical analysis. Family pediatricians were also asked to provide growth charts with anthropometric records according to the guidelines of the Italian Ministry of Health.

Table 1. First Sample of Patients: Characteristics of Eligible Children Participating or Not in the Cohort Study

	Excluded Children (N = 1960)	Enrolled Children (N = 199)	*P*
Male/female sex (%)	1010/950 (51/49)	106/93 (53/47)	0.7
Gestational age (wk)	41.02 ± 1.36	40.09 ± 1.44	0.6
Vaginal/caesarean delivery (%)	1296/664 (66/34)	135/64 (68/32)	0.7
Birth weight (kg)	3.396 ± 0.54	3.179 ± 0.69	0.4
Birth weight (SDS)	0.10 ± 1.41	−0.32 ± 1.24	0.3
Length (m)	0.50 ± 0.4	0.48 ± 0.3	0.4
Length (SDS)	−0.49 ± 1.19	−0.53 ± 1.09	0.5
AGA/SGA (%)	1917/43 (98/2)	98/101 (49/51)	<0.0001
Exclusively breast-fed versus formula-fed (%)	755/1201 (39/61)	102/97 (51/49)	0.0008
BMI (kg/m^2)	18.6 ± 2.9	23.09 ± 4.51	<0.0001
BMI (SDS)	0.45 ± 0.75	1.44 ± 0.89	0.001
Normal-weight subjects (%)	1333 (68)	40 (20)	<0.0001
Overweight subjects (%)	510 (26)	58 (29)	0.2
Obesity subjects (%)	117 (6)	101 (50)	<0.0001
Maternal age (y)	29.6 ± 7.5	30.3 ± 6.4	0.6
Maternal parity			
0	1137 (58)	111 (56)	0.3
1	436 (22)	42 (21)	0.4
2	233 (12)	28 (14)	0.2
≥3	154 (8)	18 (9)	0.3
Maternal weight gain (kg)	13.2 ± 2.4	12.9 ± 2.2	0.4
Socioeconomic status			
1	345 (18)	34 (17)	0.5
2	901 (46)	85 (43)	0.2
3	714 (36)	80 (40)	0.2

One hundred ninety-nine patients were first studied, but 44 controls were excluded from the data analysis, as they were born small for gestational age (SGA) and/or they had familiarity for type 2 diabetes mellitus. Data are presented as mean ± SD or number of cases (%). Statistical significance at the Mann-Whitney *U* test or χ^2 test. Data were obtained either by clinical charts or recalled by telephone. The body mass index (BMI) was calculated on available data self-reported during the interview over the telephone. Socioeconomic status: 1 = blue-collar workers, 2 = white-collar workers, 3 = professional. AGA = appropriate weight for gestational age, SDS = standard deviation score.

Any family history of T2DM, cardiovascular disease, hypertension, and/or dyslipidemia in first- and second-degree relatives was recorded.

The research protocol consisted of anthropometrics, clinical evaluation, routine laboratory assays, and oral glucose tolerance test (OGTT). Weight and height were measured barefoot using standard procedures: height was assessed using a right-angle ruler placed on the head against a tape measure secured to the wall, and weight was measured without clothes using an electronic scale. The BMI was calculated as (weight [kg] divided by height squared [m^2]). The z-scores for BMI, weight, and height as standard deviation scores (SDS) were calculated according to the Centers for Disease Control growth charts for infants to 36 months and those for children aged 2 to 20 years using a public software package (Epi Info version 3.5.1, release date August 18, 2008). Overweight was defined as BMI ≥85th (1.036 SDS) and <95th (1.645 SDS) percentiles and obesity was defined as BMI ≥95th (1.645 SDS) percentile for gender and age, as was done previously [29].

Waist circumference was measured at the highest point of the iliac crest with subjects standing. A large waist was defined as waist ≥90th percentile for age and gender [30].

Blood pressure was measured after 5 minutes of rest with an aneroid sphygmomanometer (Taylor Instruments, Asheville, NC) and the average of 3 measurements was recorded. Hypertension was defined as average systolic and/or diastolic blood pressure ≥95th percentile for age, gender, and height [31]. Glucose tolerance was classified according to the American Diabetes Association classification [32].

Pubertal stage was estimated separately by two experienced endocrinologists (M.M., P.C.) according to Tanner [33].

Children were defined as SGA when their weight at birth was ≤10th percentile, corrected for gestational age and gender [34]. They were defined as AGA when the weight at birth was between the 10th and 89th percentiles according to Italian references [35].

Parameters of insulin sensitivity (whole-body insulin sensitivity [WISI] [36]) and secretion (insulinogenic index [IGI] [37]) were derived from a 2-hour OGTT with glucose and insulin determinations every 30 minutes. Beta cell ability to adapt insulin secretion to changes in insulin sensitivity was assessed by the DI (DI = WISI × IGI) [27].

Serum glucose, triglycerides, cholesterol, and high-density lipoprotein cholesterol were measured using standard labora-

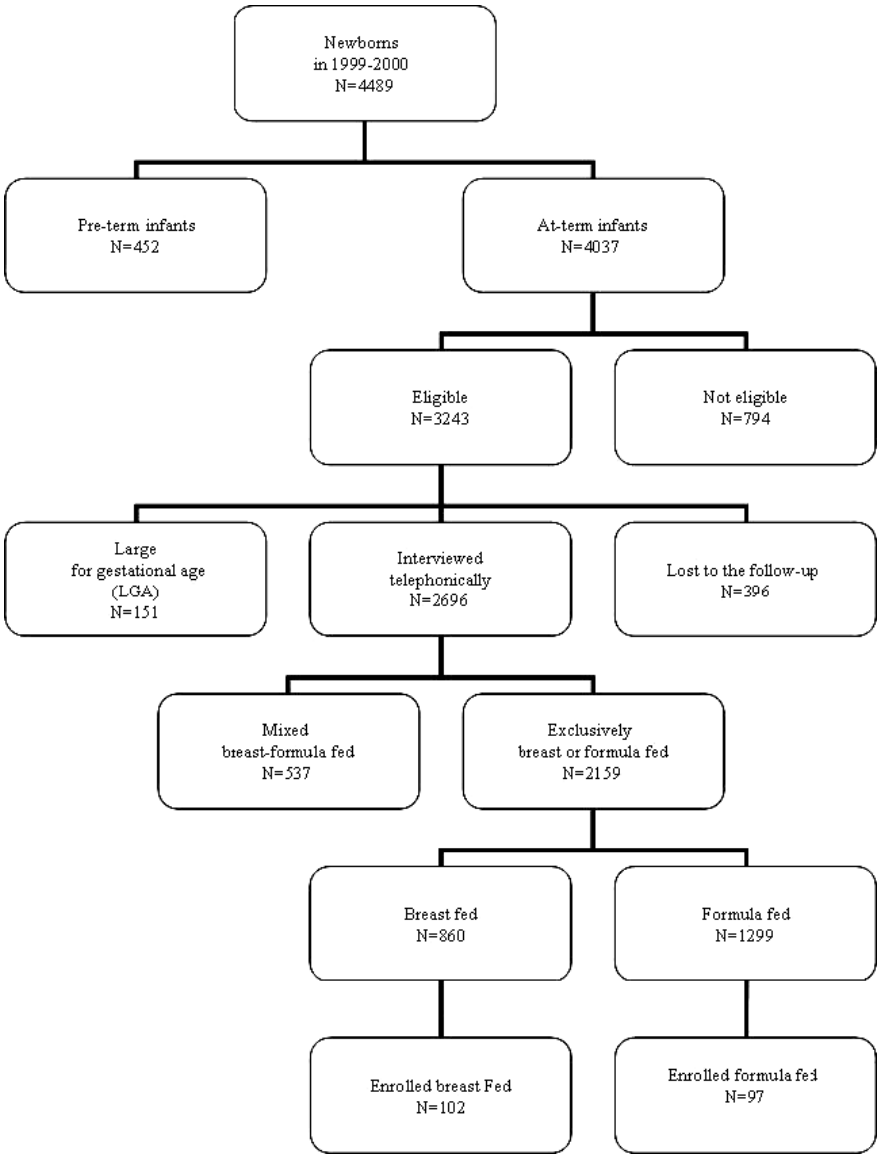

Fig. 1. Of the initial cohort of 4489 children, 4037 were born at term. Seven hundred ninety-four did not meet eligibility criteria. Three hundred ninety-six children were lost to follow-up. Seven hundred ninety-four children were excluded as they were not eligible (e.g., born of diabetic mothers or with genetic disease). One hundred one children were excluded as they had a birth weight that was high for gestational age. Of the 2847 eligible newborns, the families of 2696 children were interviewed by telephone. Five hundred thirty-seven children were not eligible, as they received both breast milk and formula. For the initial purpose of the study, we excluded children born with a high-for-gestational-age birth weight and we selected children who had been fed exclusively breast milk (BF) or formula (FF) for >4 months.

tory methods. Insulin was measured by radioimmunoassay (MYRIA Technogenetics, Milan, Italy) with a lower limit of sensitivity of 0.3 μU/ml and interassay coefficient of variations ranging from 2.9% to 4.8%.

Dietary and Physical Activity Recall

Dietary habits were assessed by a validated food frequency questionnaire [38]. Mothers were interviewed for approximately 50 minutes, and each meal was analyzed to determine which foods were eaten and how often. The nutrient content of all food items was calculated by using computerized tables (Food Processor II, Hesha Research, Salem, OR, modified according to the food tables of the National Institute of Nutrition, Rome, Italy). The energy content of food was computed as follows: 4.3 kcal/g for protein, 4.2 g for starch (or starch equivalent), and 9.3 kcal/g for fat.

Physical activity was investigated by means of a 7-day diary recall. The numbers of hours spent at school, watching television, using a computer or playing videogames (sedentary activities), participating in sports (sporting activities), and

playing outdoors with other children (leisure activities) were recorded [39]. The jobs of the parents were used as a surrogate measure of socioeconomic status (1 = low, 2 = medium, 3 = high), as was done in a previous study investigating physical activity and socioeconomic status in obese Italian adolescents [40].

Statistical Analysis

Continuous variables were given as means ± standard deviations (SDs), unless otherwise indicated. Comparisons among groups were performed using the analysis of variance and the Bonferroni post hoc test for the comparisons between obese formula-fed and breast-fed groups. The χ^2 test was used as appropriate. The Mann-Whitney *U* test was used to compare duration of breast-feeding in controls and overweight/obese children.

Correlation analyses between duration of breast-feeding and continuous variables (including anthropometrics, WISI, and IGI) were performed using the Spearman rho test. Univariate analyses were run to determine the relationship between WISI and IGI and modality of feeding, degree of education, and family history of cardiovascular and metabolic disease. Only significant correlations are reported in the results section. Stepwise linear regression analyses were performed to find predictors of WISI and IGI among duration of breast-feeding, birth weight z-score, BMI-z score upon enrollment, waist circumference, triglycerides, and catch-up growth at 1 month and between 6 and 12 months. In the 2 models, adjustments were made for gestational age, gender, and height whenever appropriate. A dummy variable was introduced to account for differences from the first sample and the second sample. Furthermore, birth weight z-score and breast-feeding were modeled as continuous variables.

A p value less than 0.05 was considered significant. Analysis was performed using SPSS statistical software (SPSS V12.0, Inc., Chicago, IL).

RESULTS

Characteristics of the Samples

A total of 350 overweight and obese children, aged 8–9, and 33 controls with an AGA birth weight and with no familiar history of T2DM were enrolled. Among the overweight/obese children, 165 individuals were exclusively formula-fed and 185 were breast-fed; among controls, 20 were breast-fed and 13 were formula-fed. Differences were observed between the 2 samples of overweight/obese individuals from the first study (N = 159) and those from the second sample (N = 191) in gender (M/F 50/100 vs 100/128; $p = 0.01$), in prevalence of formula-fed vs breast-fed children (94/61 vs 84/144 children, respectively; $p < 0.0001$), and in the prevalence of SGA children (87 in the first sample and 9 in the second sample; $p < 0.0001$). Thus, the 2 groups differed significantly in birth weight z-score (0.68 ± 0.24 vs −0.14 ± 1.2 SDS; $p > 0.0001$) and birth length z-score (−0.25 ± 1.1 vs −0.51 ± 1 SDS; $p = 0.012$). There was a trend for children to present with a different height at enrollment (0.9 ± 1.6 m vs 0.4 ± 2.2 m; $p = 0.06$).

Anthropometrics and rate of catch-up growth of the 2 groups are reported in Table 2. Maternal weight gain, parity, rates of vaginal delivery vs caesarean section, education, and family history of T2DM, hypertension, and cardiovascular disease in first-degree ancestors were similar among breast- and formula-fed obese children. No differences in postnatal complications and hospital stay were observed between them.

No differences were found in daily calorie intake and composition of nutrients between obese groups.

All children were prepubertal. None of the subjects had hypertension, dyslipidemia, or diabetes. Liver function tests were within the range of normality. All subjects had received prophylaxis for hepatitis B, and markers of hepatitis C were negative.

Insulin Metabolism in Breast-Fed Versus Formula-Fed Children

Parameters of insulin metabolism are displayed in Table 3. All the children had normal glucose tolerance.

Univariate analysis showed that formula feeding was associated with reduced insulin sensitivity (odds ratio [OR] −1.42, 95% confidence interval [95%CI] −1.86 to −0.98; $p < 0.0001$), faster growth in the first month of life (OR 2.49, 95%CI 1.97 to 3.01, $p < 0.0001$), and faster growth between 6 and 12 months of life (OR 4.62, 95%CI 3.58 to 5.67, $p < 0.0001$).

WISI was associated with birth weight z-score ($r_o = 0.138$; $p = 0.007$), catch-up growth at 1 month ($r_o = -0.103$; p = 0.04), and catch-up growth between 6 and 12 months ($r_o = -0.164$; $p = 0.001$).

DI was associated with body weight z-score at the time of enrollment ($r_o = 0.106$; $p = 0.05$), catch-up growth in the first month ($r_o = -0.122$; $p = 0.02$), catch-up growth in the first 6 months ($r_o = -0.217$; $p < 0.0001$), and values of high-density lipoprotein cholesterol ($r_o = 0.192$; $p < 0.0001$).

The birth weight z-score was associated with fasting insulin ($r_o = -0.178$; $p = 0.002$) and $\text{insulin}_{120\ \text{min}}$ ($r_o = -0.157$; $p = 0.002$).

In the group of breast-fed children, duration of breast-feeding was correlated with waist circumference ($r_o = -0.420$; $p < 0.0001$), BMI ($r_o = -0.157$; $p < 0.02$), BMI z-score ($r_o = 0.172$; $p = 0.01$), fasting insulin ($r_o = -0.205$; $p = 0.003$), insulin secretion (IGI $r_o = 0.137$; $p = 0.05$), triglycerides ($r_o = -0.229$; $p = 0.001$), and DI ($r_o = 0.157$; $p = 0.02$). No correlation was found with WISI ($r_o = 0.03$; $p = 0.6$).

Table 2. Anthropometrics and Growth Parameters of Controls and Breast- and Formula-Fed Overweight/Obese Children

	Control Subjects (N = 33)	Overweight/Obese Subjects: Formula-Fed (N = 165)	Overweight/Obese Subjects: Breast-Fed (N = 185)	*P* (Comparison of All Groups)	*P* (Comparison of Obese Groups)
Sex (M/F)	13/20	56/109	81/104	0.2	-
Gestational age (wk)	40 ± 1.6	40 ± 1.4	40 ± 1.5	0.6	0.9
Vaginal/caesarean delivery	17/16	114/51	127/58	0.2	-
Birth weight (g)	3668 ± 258	3501 ± 535	3398 ± 604	0.02	0.2
Birth weight (SDS)	0.71 ± 0.2	0.22 ± 1	0.07 ± 1.1	0.004	0.5
Length (cm)	47 ± 3	49 ± 2.6	48.5 ± 2.3	0.0001	0.2
Length (SDS)	−1.0 ± 1.3	−0.23 ± 1.1	−0.46 ± 0.9	0.0001	0.1
AGA/SGA	33/0	127/38	136/49	0.0001	0.3
Maternal weight gain (kg)	13.7 ± 1.4	12.8 ± 2.3	12.9 ± 2.2	0.08	0.9
Maternal age (y)	34.4 ± 4.3	29 ± 6.3	31.1 ± 6.2	0.0001	0.005
Maternal parity (0/1/2/≥3)	18/9/3/3	90/36/20/16	106/42/27/9	0.4	-
Breast-feeding duration (mo)*	7.7 ± 1.6	-	6.9 ± 1.8	0.5	-
Weaning time (mo)	4.1 ± 0.5	4 ± 0.5	4 ± 0.5	0.7	0.9
Weight gain 0–1 mo (g)	1280 ± 156	1419 ± 304	1170 ± 184	0.0001	0.0001
Weight gain 1–6 mo (g)	2230 ± 467	2413 ± 370	2359 ± 758	0.2	0.9
Weight gain 6–12 mo (g)	4850 ± 310	5118 ± 348	4655 ± 599	0.0001	0.0001
Weight gain 12–24 mo (g)	2450 ± 248	2510 ± 224	2453 ± 434	0.3	0.4
Weight gain 24–36 mo (g)	610 ± 189	658 ± 161	684 ± 153	0.02	0.4
Body weight (kg)	32.7 ± 3.6	39.7 ± 9.4	39.9 ± 8.4	0.0001	0.9
Body weight (SDS)	0.9 ± 0.6	1.5 ± 1.1	1.6 ± 1	0.003	0.9
Height (cm)	133 ± 6.9	128 ± 15	128 ± 14	0.09	0.9
Height (SDS)	1.4 ± 0.8	0.4 ± 2.4	07 ± 1.8	0.02	0.5
BMI (kg/m^2)	18.4 ± 2	24.2 ± 4	24.3 ± 4	0.0001	0.9
BMI SDS	0.4 ± 0.5	1.8 ± 0.4	1.7 ± 0.4	0.0001	0.5
Waist circumference (cm)	64 ± 6.4	68 ± 6	68 ± 6	0.001	0.9
Energy intake (kcal/d)	2122 ± 456	2263 ± 543	2159 ± 333	0.5	-
Sporting activities (h/wk)	2.1 ± 1.9	2.3 ± 2.2	2.4 ± 2.2	0.7	0.9
Leisure activities (h/wk)	5.7 ± 1.4	5.8 ± 2	5.7 ± 1.9	0.9	0.9
Sedentary activities (h/d)	3.5 ± 1	3.5 ± 0.9	3.4 ± 0.9	0.4	0.6

Data are presented as mean ± SD or number of cases (%). Statistical significance is reported in the left column for the analysis of variance, and significance according to the Bonferroni post hoc test for the obese groups is reported in the right column.

SDS = standard deviation score, AGA = appropriate weight for gestational age, SGA = small for gestational age, BMI = Body Mass Index.

* Duration of breast-feeding was calculated in 20 of 33 controls. Comparison with obese breast-fed children was performed using the Mann-Whitney *U* test.

Table 4 shows the results from stepwise linear regression models investigating predictors of insulin dynamics.

DISCUSSION

The findings of the present study suggest that in overweight and obese children aged 8–9 years, consumption of formula is associated with reduced insulin sensitivity. In stepwise regression models, birth weight, duration of breast-feeding, and waist circumference (negatively) predicted insulin sensitivity, while waist circumference and rate of weight gain in the first semester were associated with enhanced insulin secretion. Conversely, children born SGA might have reduced insulin release (Table 4). Furthermore, formula feeding was associated with a more rapid weight gain during the first month of life and from 6 to 12 months of age.

Despite a similar degree of obesity, children who were breast-fed presented with significantly greater insulin sensitivity and reduced insulin secretion (Table 2). Because the DI was not different between the 2 groups of overweight/obese children, it can be speculated that formula-fed children maintained the same DI by increasing insulin secretion to compensate for reduced insulin sensitivity. Independent of the modality of feeding, children who grew more rapidly in the first month of life and in the first semester had a lower DI, a finding that is in agreement with the possible negative effect of accelerated early growth. It is widely accepted that reduced DI is the best predictor of diabetes in both childhood [28] and adulthood [41]. Accordingly, formula feeding may favor the development of impaired glucose metabolism in those individuals who are genetically prone to diabetes, since their beta cell function may be unable to compensate for the increased insulin demand [42]. Conversely, the duration of breast-feeding seems to positively influence the first-phase response of beta cells, since it was correlated inversely with fasting insulin and positively with the IGI. In our series, breast-feeding was associated with a better DI. Breast-feeding duration was also associated with a more "healthy" phenotype

Table 3. Lipid Profile, Liver Enzymes, and OGTT-Derived Parameters of Insulin Metabolism

	Control Subjects (N = 33)	Overweight/Obese Subjects: Formula-Fed (N = 165)	Overweight/Obese Subjects: Breast-Fed (N = 185)	*P* (Comparison of All Groups)	*P* (Comparison of Obese Groups)
Fasting glucose (mg/dl)	77 ± 6.4	80 ± 7.7	79 ± 7.6	0.1	0.6
Fasting insulin (uUI/ml)	8.9 ± 3.1	11.7 ± 5.3	9.0 ± 3.4	0.0001	0.0001
ALT (IU/L)	27 ± 5.8	27 ± 6.4	28 ± 6.2	0.02	0.02
AST (IU/L)	28 ± 5.2	25 ± 5.9	26 ± 6.7	0.08	0.9
γ-GT (IU/L)	22 ± 15	25 ± 11	26 ± 15	0.0001	0.9
Cholesterol (mg/dl)	141 ± 17	145 ± 17	145 ± 17	0.4	0.9
HDL cholesterol (mg/dl)	43 ± 5	42 ± 3.9	40 ± 3.2	0.0001	0.0001
Triglycerides (mg/dl)	76 ± 18	84 ± 21	88 ± 19	0.007	0.3
$Glucose_{120\ min}$ (mg/dl)	93 ± 10	90 ± 15	89 ± 16	0.3	0.9
$Insulin_{120\ min}$ (uUI /dl)	9.1 ± 2.4	19.6 ± 19.6	9 ± 3.8	0.0001	0.0001
WISI	7.3 ± 2	5.1 ± 2.3	6.6 ± 2	0.0001	0.0001
IGI ($\mu IU/ml \times mg/ml^{-1}$)	4.9 ± 2.6	6.8 ± 3.6	5.2 ± 2.5	0.0001	0.0001
DI	34.4 ± 17	34.6 ± 15	30.8 ± 19.2	0.1	0.14

Data are presented as means ± SDs. Statistical significance is reported in the left column for the analysis of variance, while significance according to the Bonferroni post hoc test for the obese groups is reported in the right column.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, γ-GT = gamma glutamyl transferase, HDL = high-density lipoprotein, IGI = insulinogenic index, OGTT = oral glucose tolerance test, WISI = whole-body insulin sensitivity index.

of obesity, characterized by reduced waist circumference and levels of triglycerides [43].

Although the sample size was not large enough to determine the synergistic effect of birth weight and nutrition on insulin dynamics, children with an appropriate birth weight were more insulin sensitive and showed a preserved beta cell function. The degree of insulin sensitivity was predicted by slower catch-up growth in the first year of life, but this variable did not enter the stepwise regression model.

An earlier study, performed in 720 Pima Indians aged 10–39 years, found that exclusive breast-feeding for at least 2 months was associated with a lower rate of type 2 diabetes, as measured by OGTT [25]. Young et al. [23] conducted a case-control study of 138 native Canadian youngsters (10–17 years of age) and determined that prolonged breast-feeding (>6 months) served as a strong protector against the risk of type 2 diabetes. Furthermore, an inverse association between length of breast-feeding and fasting glucose levels has been observed in young children [44]. A recent study [26] assessed the protective effects of breast-feeding on T2DM risk factors in a cohort of overweight/obese Latino youth. The investigators used both the OGTT and the frequently sampled intravenous glucose tolerance test. The association between breast-feeding and T2DM risk factors was controlled for precise adiposity measures at baseline or across pubertal transitions. The study was strong in its methodology, but no information was provided on birth weight and early catch-up growth. Moreover, it was conducted in a sample of individuals at increased risk for insulin resistance and around the age when puberty begins.

It could be argued that the high percentage of SGA children in our sample may account for the difference in the association between breast-feeding and impaired insulin metabolism, with

Table 4. Predictors of Insulin Dynamics

	β	*P*	95%CI
Model 1: WISI			
Birth weight z-score (SDS)	0.754	**<0.0001**	0.392 to 1.116
Waist circumference (cm)	−0.071	**0.045**	−0.141 to −0.001
BMI z-score (SDS)	−0.031	0.688	-
Weight gain 0–1 mo (g)	0.078	0.311	-
Weight gain 1–6 mo (g)	−0.094	0.173	-
Weight gain 6–12 mo (g)	−0.094	0.173	-
Weight gain 12–24 mo (g)	−0.028	0.347	-
Weight gain 24–36 mo (g)	0.014	0.454	-
Duration of breast-feeding (mo)	0.171	**0.005**	0.052 to 0.290
Triglycerides (mg/dl)	0.107	0.113	-
Model 2: IGI ($\mu IU/ml \times mg/ml^{-1}$)			
Birth weight z-score (SDS)	−0.025	**0.013**	−0.045 to −0.005
Waist circumference (cm)	0.005	**0.02**	0.001 to 0.008
BMI z-score (SDS)	0.035	0.662	-
Weight gain 0–1 mo (g)	0.009	0.910	
Weight gain 1–6 mo (g)	0.061	**0.009**	0.015 to 0.107
Weight gain 6–12 mo (g)	0.038	0.6	-
Weight gain 12–24 mo (g)	0.018	0.792	-
Weight gain 24–36 mo (g)	−0.013	0.850	-
Duration of breast-feeding (mo)	−0.103	0.138	-
Triglycerides (mg/dl)	−0.02	0.77	-

In model 1, birth weight z-score, waist circumference, and duration of breast-feeding were predictors of whole-body insulin sensitivity index (WISI) ($R = 0.357$; $F = 9.401$; $p < 0.0001$). In model 2, predictors of insulinogenic index (IGI) ($R = 0.282$; $F = 5.557$; $p = 0.001$) were birth weight z-score, weight gain in the first semester of life, and waist circumference. 95%CI = 95% confidence interval, SDS = standard deviation score.

long-term breast-feeding being particularly beneficial in children born SGA.

Several bioactive factors are found in the human milk, such as growth hormones and growth factors, insulin, adrenal steroids, T3 and T4 [45], and gastrointestinal hormones [46], which are actively involved in the modulation of beta-cell activity. Lucas et al. [11] observed different endocrine responses to the release of pancreatic and intestinal hormones among breast-fed and formula-fed newborns, even in the first days of life. Moreover, the higher content of proteins in formula could be one of the factors responsible for alteration in insulin and insulin growth factor-1 metabolism [47]. Finally, a different content of polyunsaturated fatty acids may also play a pivotal role in this framework of metabolic programming.

According to our observations, the effect of the early type of feeding on insulin metabolism could be mediated by timing and rate of first-year growth. Hyperinsulinemia, promoted by formula feeding, might induce preferential catch-up of fat compared to lean tissue [48,49], with a subsequent redistribution of insulin-mediated glucose utilization from muscle to adipose tissue [50].

The observed differences in the last semester might suggest a different mode or ability to metabolize nutrients in children previously fed formula, but no data were collected on differences in solid food introduction. This critical temporal window for the development of metabolic abnormalities has also been identified in the first year of life by other studies [6,51–53]. A recent study, conducted in a sample of 217 young healthy individuals, including subjects born SGA, found an inverse association between weight gain in the first 3 months of life and the risk of T2DM [5].

Several caveats affect our study. Selection and recall bias are of potential concern. First, we put together 2 samples that differed in modalities of feeding and of children born SGA. However, such differences were taken into account in the data analysis. Thus, selection bias is unlikely to have a major impact on our findings. Second, in our sample, children exposed during intrauterine life to factors known to influence fetal growth were excluded. In particular, maternal obesity [54], T2DM [54], and high-for-gestational-age birth weight [55] are important determinants of insulin dynamics. Indeed, a recent meta-analysis of 30 observational published studies of a total sample of 152,084 individuals has suggested that the association between birth weight and T2DM is U-shaped. One extreme of the "U" is represented by children who were born SGA, but the other one is represented by children with a high birth weight [55]. Nevertheless, we are aware that other environmental factors may have affected growth and development of insulin resistance during an 8- to 9-year life span. Both dietary intake and physical activity are difficult to assess and tend to change over days, weeks, and seasons, but this possible bias was randomly distributed among participants. Third, concern can be raised about the use of an OGTT-derived formula to determine insulin resistance. However, this formula has been validated against clamp in children and adolescents [56,57]. Finally, concern may derive from the fact that the study was initially designed to investigate the effect of birth weight, early feeding, and catch-up growth in a general population. The working hypothesis of the cohort study was that SGA children have an increased risk of developing abnormalities of the insulin metabolism, mostly when they are fed formula, and that, conversely, breast-feeding can be protective. Considering both the potential compliance of families of otherwise normal infants and ethical reasons, we focused our research on overweight and/or obese children.

CONCLUSION

The present study further contributes to the thesis that early breast-feeding is associated with better insulin dynamics in overweight/obese children. Our findings support the hypothesis that reasons other than more rapid catch-up growth may mediate this association. The biological mechanisms leading to differences in regulation of insulin homeostasis are still unclear. It may be useful to encourage breast-feeding in populations at high risk for metabolic abnormalities.

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