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Can we do something in early life to reduce the risk of obesity?

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ABSTRACT

Background :Obesity usually results from a combination of several modifiable and non-modifiable contributing factors, such as genetics, race, and socioeconomic status. Other factors, including birth by cesarean section, perinatal antibiotics usage, and promotion of exclusive breastfeeding for six months, could be potentially prevented or modulated. However, one of the factors can be easily implemented through reduction of protein content in infant formulas for non-breastfed infants. High protein (HP) in infant formula is one of the causes of rapid weight gain, predisposing the neonates to later obesity.

This study was performed to evaluate the effect of HP formula on weight gain and resulting risks of later obesity. The samples (i.e., non-breastfed infants) were randomly divided into two groups of HP formula (2.9 and 4.4 g protein/100 kcal before and after five months of age, respectively) and LP formula (1.77 and 2.2 g protein/100 kcal before and after five months of age, respectively) in this study. At the age of two, weight-for-length z-score of the infants in the HP formula group was calculated at 0.20 (95%CI: 0.06, 0.34), which was higher compared to the LP group. Meanwhile, the latter group had results similar to the findings of the control group (breastfed). Body length of the infants was not affected by the extent of protein intake. A six-year follow-up of the subjects indicated a significantly lower body mass index (BMI) (0.51) in the LP formula group (95% CI: 0.13, 0.90; P=0.009). In addition, a 2.43 fold risk of later obesity (95% CI: 1.12, 5.27; P=0.024) was reported in the LP group, which was lower compared to the HP formula group. Given the role of HP formula as one of the contributing factors in the development of metabolic syndrome and obesity risks in infants, it is recommended that lower protein content formulas be used in non-breastfed neonates to prevent later obesity and other complications.

Keywords: Cesarean section, Infant formula, Low protein formula, Obesity, Predisposing factors for obesity

Introduction

To date, the factors that predispose an individual to obesity have been almost impossible to modify. Generally, polymorphisms of various genes control appetite and regulate metabolism and might predispose to obesity under certain dietary regimens. Genetics have been responsible for 6-85% of the obesity cases (depending on the sample population) around the world (1, 2). Among these genes, obesogenic and lactogenic genes play a pivotal role in promoting gain or loss in obese individuals (3).

Other factors, including race, ethnicity, and socioeconomic background, are not modifiable by the researchers. In general, information on house-hold socioeconomic status is limited to self-report by the parents and is associated with income level and educational status; therefore, it is difficult to make definite conclusions. According to the literature, an association has been observed between later obesity and factors including maternal obesity, caesarean birth, and early use of antibiotics. Maternal obesity is accompanied by an increased risk for developing weight gain and metabolic syndrome in neonates (4). However, weight loss during pregnancy is not easy to achieve. Evidence suggests that large-for-gestational-age neonates, exposed to maternal diabetes or obesity in utero, are at a high risk for developing metabolic syndrome.

According to the previous studies, a significant relationship was observed between cesarean birth and later adiposity and obesity of infants (3-5). A study was conducted on children born between 1991-1992 in Avon, UK, who were enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC). The obtained results indicated that among 10.219 studied neonates, 926 (9.06%) were delivered by cesarean section (4).

After making multiple adjustments for eliminating the influence of risk factors, cesarean section was

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consistently associated with increased adiposity, starting at six weeks of age (SD: +0.11, 95% CI: 0.03-0.18; P=0.005) through the age of 15 years (BMI z-score increment: +0.10 SD, 95% CI: 0.001-0.198; P=0.042). By the age of 11 years, the risk of overweight or obesity was 1.83 times higher among infants delivered by cesarean section (95% CI: 1.24-2.70; P=0.002), compared to those with vaginal childbirth. A meta-analysis in 2014 concluded that the overall pooled odds ratio (OR) of obesity for neonates delivered by cesarean section was 1.33 (95% CI: 1.19, 1.48; I (2): 63%), compared to those born vaginally. In this regard, the OR was 1.32 (1.15, 1.51) for infants, 1.24 (1.00, 1.54) for adolescents, and 1.50 (1.02, 2.20) for adults (5).

A study in Denmark was performed on 28,354 mother–child dyads to evaluate the relationship between delivery mode (vaginal birth vs. cesarean section), and contributing factors (e.g., maternal pre-pregnancy BMI and early exposure to antibiotics prior to six months of age) for increased risk for obesity at the age of seven (6). The results were indicative of no statistically significant relationship between the delivery mode and childhood obesity (OR: 1.18, 95% CI: 0.95–1.47). However, the use of antibiotics during the first six months of life was associated with an increased risk for obesity among the neonates of mothers with a normal weight (OR: 1.54, 95% CI: 1.09–2.17) and a decreased risk of weight gain among the infants of overweight mothers (OR: 0.54, 95% CI: 0.30–0.98).

In another study in Philadelphia, a significant association was found between cumulative exposure to antibiotics and later obesity in neonates (rate ratio [RR]: 1.11; 95% CI: 1.02-1.21 for ≥4 episodes). However, this side effect was mostly implied by broad-spectrum antibiotics (RR: 1.16; 95% CI: 1.06-1.29) (7). This finding highlighted the importance of the acquisition and maintenance of a normal gut macrobiota in neonates.

Quantity and quality of protein intake during the first two years of life have an important effect on growth, neurodevelopment, and long-term health of the infants (8). Evidence suggests that a high protein intake during the first two years of life might actually have a long-term negative effect on overall health (9). Protein contribution to energy varies depending on the mode of feeding (breast milk: 5%, infant formula: 7–9%, and whole cow milk: 20%). Consequently, formula-fed infants received more protein content (0.5 g/d) compared to the breastfed neonates. Total protein content for formula-fed infants was 14 and 18 g/d, while it was 9 and 10 g/d for breastfed neonates at three and six months of age, respectively (10).

Weight gain during the first 12 months of life is one of the most important predictors of risk for later obesity (11, 12). Previous research demonstrated that breastfed infants gained weight more slowly compared to formula-fed neonates. However, there is a discrepancy between this finding and the actual growth of breastfed neonates (13-19). In fact, some studies have not demonstrated such differences (20-22). Different aspects of infant formula feeding are involved in evaluation of rapid weight gain, including the amount of feeding per day (23). However, this might not be the only explanation in this regard. Similar to glucose, certain amino acids are able to stimulate the secretion of IGF-1.

It has been hypothesized that the HP content of infant formulas could be a factor for rapid weight gain in the first few months of life. The hypothesis was formulated that a lower-protein (LP) content formula could alter that course. New dairy technologies have been able to allow for a lower protein content formula. As a result, sufficient levels of essential and non-essential amino acids could be maintained by a reduction in protein concentration.

The European Childhood Obesity Program (CHOP) developed a study to investigate the effects of early protein intake on growth and adiposity (24). In total, 1138 healthy non-breastfed infants were randomly selected to receive cow milk and follow-on formulas with HP content (2.9 and 4.4 g protein/100 kcal before and after the fifth month, respectively) or LP (1.77 and 2.2 g protein/100 kcal before and after the fifth month, respectively) during the first year. An exclusively breastfed group was also included in the mentioned study for comparison.

In the aforementioned study, the composition of all formulas was in line with the 1991 European Union Directive on Infant and Follow-on Formulae. In addition, the protein contents in this study represented approximately the lowest and highest endpoints of the accepted range in this directive. The relative contents of amino acids did not differ between the four formulas. The LP infant formula was supplemented with small amounts of arginine and tryptophan.

In the mentioned research, the study population consisted of 636 children, allocated to LP (n=313), HP (n=323), and breastfed or control (n=298) groups. Children were followed-up until the age of 24 months. The obtained results indicated that the

groups were homogenous in terms of the length of infants. Although no significant difference was observed between the z-scores (weight-for-length) of the LP formula and breastfed groups at the age of 24 months, the scores were 0.20 (range: 0.06-0.34) lower than the HP group.

As represented in this study, the content of HP in infant formula was associated with increased weight in the first two years of life; however, the HP content had no effect on the length of the neonates. Therefore, consumption of LP formula in infancy might reduce the risk of future obesity in neonates born to overweight mothers.

At the age of six months, some of the essential amino acids (e.g., branched chain amino acids, IGF-I, and urinary C-peptide creatinine ratio) were significantly higher in the HP group compared to the LP group (P=0.001). On the other hand, IGF–binding protein (IGFBP-2) was lower in the HP group, and no significant difference was observed in the amount of IGFBP-3 in both groups (25). The median serum concentration of total IGF-1 was 48.4 ng/mL (25th and 75th percentiles: 27.2 and 81.8 ng/mL, respectively) in the HP group and 34.7 ng/mL (17.7, 57.5 ng/mL) in the LP group. It is less likely that lower IGF-1 levels are accompanied with weight gain and later obesity.

In a study by Koletzko et al. (24), the samples were followed-up until the age of six months (26). According to the results, a significant relation-ship was observed between the BMI of infants and the protein content of the formula they received, which was higher (by 0.51) in the HP group compared to the LP group (95% CI: 0.13, 0.90; P=0.009). The risk of becoming obese in the HP group was 2.43 (95% CI: 1.12, 5.27; P=0.024) times higher compared to the LP group. There was a tendency for a higher weight gain in the subjects of HP group (0.67 kg; 95% CI: 20.04, 1.39 kg; P=0.064), while no difference in height was observed between the intervention groups. Both LP and breastfed groups were homogeneous regarding anthro-pometric measurements of the samples. It was concluded that infant formula with a lower protein content reduced BMI and obesity risk at school age.

In this study, a systematic review of the literature was performed. Studies conducted on healthy term neonates that evaluated lower-protein and –energy formulas, reported anthropometric outcomes (e.g., weight and length), and follow-up of the infants for at least six months were included in this study (27). In total, six studies met the mentioned inclusion criteria. The results were indicative of an adequate growth percentile resulted from the use of infant formulas (with protein and energy concentration slightly below the standards of the formulas sold in the United States).

Conclusion

Metabolic syndrome and obesity could be triggered by numerous modifiable and non-modifiable factors. Extended and exclusive breastfeeding should be encouraged for various reasons; for instance, to reduce the risk of obesity. According to the results, the potential of HP infant formula increases the risk of rapid weight gain and later obesity in non-breastfed infants. Therefore, it is recommended that the protein content of formulas be reduced to 1.8 g/100 Kcal in order to decrease the risk of obesity in neonates.

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