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Review Article

Early Life Factors Influencing the Risk of Obesity

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The obesity epidemic is a worldwide problem. Factors predisposing to obesity include genetics, race, socioeconomic conditions, birth by cesarean section, and perinatal antibiotic use. High protein (HP) content in infant formulas has been identified as a potential culprit predisposing to rapid weight gain in the first few months of life and leading to later obesity. In a large multicountry study the effects of lower protein (LP) formula (1.77 and 2.2 g protein/100 kcal, before and after the 5th month, respectively) were compared to those of higher protein (2.9 and 4.4 g protein/100 kcal, respectively). Results indicated that at 24 months, the weight-for-length z score of infants in the LP formula group was 0.20 (0.06, 0.34) lower than that of the HP group and was similar to that of the breastfed reference group. The authors concluded that a HP content of infant formula is associated with higher weight in the first 2 years of life but has no effect on length. LP intake in infancy might diminish the later risk of overweight and obesity. At 6 years of age HP children had a significantly higher body mass index (by 0.51; 95% confidence interval [CI], 0.13-0.90; p=0.009) and a 2.43 (95% CI, 1.12-5.27; p=0.024) fold greater risk of becoming obese than those who received the LP. In conclusion, several factors may influence development of metabolic syndrome and obesity. Breastfeeding should always be encouraged. An overall reduction of protein intake in formula non breastfed infants seems to be an additional way to prevent obesity.

Key Words: Obesity, Infant formula, Low protein formula, Cesarean section

INTRODUCTION

An individual is considered to be overweight if their body mass index (BMI, kg/m^2) is between 25.0 to 29.9, while she/he will be considered as being obese if the BMI is 30.0 or higher. In 1960, in the Unites States, approximately 45% of adults were estimated to be overweight, including 13% who were considered to be obese. For younger Americans between the ages 6 to 17 years, the rate was 4%. Although obesity rates remained relatively unchanged for the next 20 years, between 1980 and 2000, rates doubled. In 2001, the Unites States surgeon general announced that obesity had reached "epidemic" proportions. Unfortunately the obesity rate continued to rise and seven years later, 68% of American adults were assessed as being overweight, while 34% were obese. This approximates to the fact

that one in three children and adolescents was overweight, while nearly one in five was obese. The problem has extended to almost the whole world. If there is one thing that could be considered positive from this worldwide serious health problem, is the incredible amount of research and new information that it has generated. In this review, we will look at several early life factors known to have long term impact leading to overweight and obesity.

PREDISPOSING FACTORS FOR OBESITY

Genetics

Although the ultimate cause for obesity is an excessive intake of calories compared to their utilization, obesity is the result of an interplay between genetic and environmental factors [1]. Polymorphisms in various genes controlling appetite and metabolism predispose to obesity under certain dietary conditions. Depending on the population examined, the percentage of obesity that can be attributed to genetics varies widely estimates ranging from 6% to 85% [2]. As of 2006, more than 41 sites on the human genome had been linked to the development of obesity when a favorable environment is present [3]. Some of these obesogenic or leptogenic genes may influence obese individual's response to weight loss or weight management [4].

Race, ethnicity and socioeconomic status

The Centers for Disease Control indicated that in 2000 the prevalence of obesity was 19% among non-Hispanic black children and 20% among Mexican American children, compared with 11% among non-Hispanic white children. Since 1980, the increase was especially evident among non-Hispanic, black and Mexican American adolescents. However, although the overall prevalence of childhood obesity continued to increase (14% in 2000 vs. 17% in 2004), the differences by race/ethnicity appear to have diminished, in part due to rapid increases in obesity in white children: in 2004 the prevalence of childhood obesity was 20% in non-Hispanic blacks, 19% in Mexican Americans, and 16% in non-Hispanic

whites, and prevalence was highest in Mexican American boys (22%) and African American girls (24%). The prevalence of obesity in Asian American boys and girls was 10 and 4%, respectively.

Socioeconomic factors are likely to play an important influence on health, although there are conflicting views on their relation with childhood obesity. Information on household socioeconomic status is often limited to self-reported parents' education and income. The percentage of poverty and the poverty-to-income ratio have been used as well to stratify survey participants by income groups. However, these two indexes of parental education and household income levels, fail to completely cover the complexities of socioeconomic and social class.

Gestational diabetes, maternal obesity, cesarean section and early antibiotic use

Multiple studies point to an associations between maternal obesity, birth by cesarean section and early antibiotic use and offspring obesity. A study has shown that large for gestational age offspring of diabetic mothers were at significant greater risk of developing metabolic syndrome in childhood [5]. The study also found that children exposed to maternal obesity were at increased risk of developing metabolic syndrome, which suggests that obese mothers who do not fulfill the clinical criteria for gestational diabetes mellitus may still have metabolic factors that affect fetal growth and postnatal outcomes. Children who are large for gestational age at birth and exposed to an intrauterine environment of either diabetes or maternal obesity and are at increased risk of developing metabolic syndrome.

Several studies have shown an association of cesarean delivery with child adiposity and obesity. One of such study included children born in 1991-1992 in Avon, United Kingdom who participated in the Avon Longitudinal Study of Parents and Children (ALSPAC) [6]. Of the 10,219 children, 926 (9.06%) were delivered by cesarean section. In mixed multivariable models adjusting for birth weight, gender, parental body mass, family sociodemographics, gestational factors and infant feeding patterns, cesarean deliv-

ery was consistently associated with increased adiposity, starting at 6 weeks (+0.11 standard deviation [SD] units; 95% confidence interval [CI], 0.03-0.18; p=0.005), through age 15 years (BMI z-score increment +0.10 SD units; 95% CI, 0.001-0.198; p=0.042). By age 11 years, cesarean-delivered children had 1.83 times the odds of being overweight or obese (95% CI, 1.24-2.70; p=0.002) than vaginally-delivered ones. When the sample was stratified by maternal pre-pregnancy weight, the association among children born to overweight/obese mothers was strong and long-lasting. Several other studies support this finding [7-9].

A 2014 meta-analysis concluded that the overall pooled odds ratio (OR) of overweight/obesity for offspring delivered by cesarean section compared with those born vaginally was 1.33 (95% CI, 1.19-1.48; I^2=63%); the OR was 1.32 (1.15, 1.51) for children, 1.24 (1.00, 1.54) for adolescents and 1.50 (1.02, 2.20) for adults [10]. In subgroup analysis, the overall pooled OR was 1.18 (1.09, 1.27; I^2=29%) for high-quality studies and 1.78 (1.43, 2.22; I^2=24%) for medium-quality (p for interaction=0.0005); no low-quality studies were identified. The ORs for children, adolescents and adults all tended to be lower for high-quality studies compared with medium-quality studies. Results indicated that cesarean section was moderately associated with offspring overweight and obesity.

The purpose of a Danish study was to investigate whether the delivery mode (vaginal versus cesarean section), maternal pre-pregnancy BMI and early exposure to antibiotics (<6 months of age) influenced the child's risk of being overweight at the age of 7 years, and in such way, supporting the hypothesis that environmental factors which influence the establishment and diversity of the intestinal microbiota may be associated with later risk of being overweight [11]. The study was longitudinal, prospective with measure of exposures in infancy and follow-up at age of 7 years and included a total of 28,354 mother-child dyads. In that study, however, delivery mode was not significantly associated with childhood overweight (OR, 1.18; 95% CI, 0.95-1.47) but

rather, use of antibiotics during the first 6 months of life led was linked to increased risk of overweight among children of normal weight mothers (OR, 1.54; 95% CI, 1.09-2.17) and a decreased risk of overweight among children of overweight mothers (OR, 0.54; 95% CI, 0.30-0.98). The same tendency was observed among children of obese mothers (OR, 0.85; 95% CI, 0.41-1.76). In another study, exposure to antibiotics during the first 6 months of life was found to be associated with consistent increases in body mass from 10 months to 38 months [12]. Exposures later in infancy (6-14 months, 15-23 months), however, were not consistently found to be associated with increased body mass. The authors commented that although effects of early exposures were modest at the individual level, they could have substantial consequences for population health. Similarly, a study in Philadelphia showed that cumulative exposure to antibiotics was associated with later obesity (rate ratio [RR], 1.11; 95% CI, 1.02-1.21 for ≥4 episodes); this effect was stronger for broad-spectrum antibiotics (RR, 1.16; 95% CI, 1.06-1.29) [13]. Early exposure to broad-spectrum antibiotics was also associated with obesity (RR, 1.11; 95% CI, 1.03-1.19 at 0-5 months of age and RR, 1.09; 95% CI, 1.04-1.14 at 6-11 months of age) but narrow-spectrum drugs were not at any age or frequency. These findings point to the important role that establishment and maintenance of normal intestinal microbiota plays in the regulation of energy metabolism. Alterations of the microbiota by mode of delivery and/or perinatal antibiotic use, predisposes the infant to later obesity.

Protein content of infant formula

Protein intake, both quantity and quality, during the first 2 years of life has important effects on growth, neurodevelopment, and long-term health [14]. Although protein deficiency has always been a nutritional concern, particularly in infants from less affluent environments, there is mounting evidence that a high protein (HP) intake in early life may have negative long-term effects on health [15]. The percentages of energy contributed by protein are 5, 7-9,

and 20% for breast milk, infant formula, and whole cow milk, respectively. As a result, formula-fed infants ingest 0.5 g/kg/day more protein than breastfed babies, and a total of 14 and 18 g/day versus 9 and 10 g/day at ages 3 and 6 months, respectively [16].

One of the best predictors of later obesity risk is weight gain during the first year of life [17-19]. It has been shown that formula fed infants gain weight more rapidly than those who are breastfed. There is data from different countries such as Australia, Canada, Finland, Sweden, United Kingdom, and United States, that show that growth of breast-fed infants does not parallel available reference data [20-26]; however, some studies have failed to show these differences [27-29]. Investigators have looked at factors in infant formula that may play a role in attenuating both early weight gain and later obesity [30]. Because certain aminoacids stimulate insulin-like growth factor (IGF)-1 secretion, alike glucose, it was hypothesized that the HP content existing in infant formulas could be responsible for rapid weight gain in the first few months of life. Therefore, a lower protein (LP) content formula was developed in recent years as new dairy technologies have made it possible to improve the biological quality of formula protein, reducing its concentration but maintaining desirable levels of essential and non-essential aminoacids.

A large multicountry study (European Childhood Obesity Program [CHOP]) investigated the effects of early protein intake on growth and adiposity [31]. In that study, 1,138 healthy, formula-fed infants were randomly assigned to receive cow-milk-based infant and follow-on formulas with LP (1.77 and 2.2 g protein/100 kcal, before and after the 5th month, respectively) or HP (2.9 and 4.4 g protein/100 kcal, before and after the 5th month, respectively) content for the first year. An exclusively breastfed group was also included for comparison. The composition of all study formulas complied with the 1991 European Union Directive on Infant and Follow-on Formulae, and protein contents represented approximately the lowest and highest amounts, respectively, of the range accepted in this Directive. The relative con-

tents of amino acids did not differ between all 4 formulas. An exception was the LP infant formula, which was supplemented with small amounts of arginine and tryptophan. Six hundred and thirty-six children in the LP (n=313) and HP (n=323) formula groups and 298 children in the breastfed group were followed until 24 months of age. Length was not different between randomized groups at any time. At 24 months, the weight-for-length z score of infants in the LP formula group was 0.20 (0.06, 0.34) lower than that of the HP group and did not differ from that of the breastfed reference group. The authors concluded that a HP content of infant formula is associated with higher weight in the first 2 years of life but has no effect on length. LP intake in infancy might diminish the later risk of overweight and obesity. At 6 months of age, essential amino acids, especially branched-chain aminoacids, IGF-1, and urinary C-peptide:creatinine ratio, were significantly (p=0.001) higher in the HP group than in the LP group, whereas IGF-binding protein (IGF-BP) 2 was lower and IGF-BP3 did not differ significantly [32]. The median IGF-1 total serum concentration was 48.4 ng/mL (25th, 75th percentile: 27.2, 81.8 ng/mL) in the HP group and 34.7 ng/mL (17.7, 57.5 ng/mL) in the LP group; the urine C-peptide:creatinine ratios were 140.6 ng/mg (80.0, 203.8 ng/mg) and 107.3 ng/mg (65.2, 194.7 ng/mg), respectively. Most essential amino acids, IGF-1, C-peptide, and urea increased significantly in both the LP and HP groups compared with the breastfed group. Total IGF-1 was significantly associated with growth until 6 months but not thereafter. The authors concluded that HP intake stimulates the IGF-1 axis and insulin release in infancy and that IGF-1 enhances growth during the first 6 months of life.

In another study, a formula with a LP content of 1.61 g/100 kcal was compared to a standard infant formula with a HP content of 2.15 g/100 kcal [33] fed to infants born to overweight and obese mothers. Infants fed the LP formula gained less weight between 3 and 6 months (-1.77 g/day, p=0.024) than infants fed the HP formula. In the subgroup of infants of mothers with BMI $>$ 30 kg/m^2, the difference

was −4.21 g/day (p=0.017). Weight (p=0.011) and BMI (p=0.027) of LP infants remained lower than that of HP infants until 2 years but were similar to that of breast-fed infants. Blood urea nitrogen, IGF-1, and insulinogenic amino acids at 6 months were significantly lower in LP compared with HP. A similar study in infants of normal (as opposed to overweight) mothers showed a milder effect on growth after 3 months of a LP formula [34]. Importantly, however, it also showed that the low-protein formula supported normal growth, suggesting that the protein content of formulas could safely be reduced, thereby contributing to a reduction of overall HP intakes in late infancy and bringing protein intakes closer to those of breast-fed infants.

In a long term follow-up of the Koletzko et al.'s study [31], the investigators measured the weight and height of 448 (41%) formula-fed children at 6 years of age [35]. BMI was the primary outcome. HP children had a significantly higher BMI (by 0.51 kg/m^2; 95% CI, 0.13-0.90; p=0.009) at 6 years of age. The risk of becoming obese in the HP group was 2.43 (95% CI, 1.12-5.27; p=0.024) times than in the LP group. There was a tendency for a higher weight in HP children (0.67 kg; 95% CI, 20.04-1.39 kg; p=0.064) but no difference in height between the intervention groups. Anthropometric measurements were similar in the LP and breastfed groups. The authors concluded that infant formula with a LP content reduces BMI and obesity risk at school age.

A recent systematic review of studies that enrolled healthy full-term infants and evaluated LP or lower-energy formula, reported anthropometric outcomes including weight and length, and followed infants for at least 6 months [36]. The authors found six studies that were eligible for inclusion. These studies varied in the content of nutrients provided in the intervention and control groups, by additional dietary components in the study groups, and the timing and length of the intervention, which limit their usefulness for interpreting newly introduced LP and low energy formulas in the United States. Results from these studies suggest adequate growth during infancy and early childhood with infant formulas with concentrations of protein and energy slightly below historical standards in the United States. Further long-term research was recommended to assess the impact of the use of LP and/or lower-energy products, especially for nutritionally at-risk populations such as preterm infants and infants who are born small for gestational age.

CONCLUSION

Among several factors that may influence development of metabolic syndrome and obesity, such as genetics, and in most cases, birth by cesarean section, cannot be modified. Breastfeeding should always be encouraged for many more reasons than just reducing the risk of obesity. Judicious use of antibiotics is also important. For infants who will not be breastfed, the obesogenic potential of HP intakes has been identified. An overall reduction of protein intake seems to be an additional way to prevent obesity. Reduction of formula protein content to 1.8 g/100 kcal offers a safe and simple manner to prevent obesity, at a time when the window of intervention for metabolic imprinting is still open.

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