Insulin in Human Milk and the Use of Hormones in Infant Formulas

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Introduction

Breastfeeding is the ‘natural and advisable way of supporting the healthy growth and development of young children’ [1]. Most advantages of breastfeeding can be attributed to human milk which contains cytokines, antibodies, enzymes, many hormones and growth factors (table 1). Studies in animal models show that some of these peptides (e.g. insulin, IGF-1, EGF) have an effect on the small intestine after orogastric administration.

We detail the rationale, evidence and plans for adding one of these hormones (insulin) to infant formulas.

Insulin in Human Milk

Insulin taken orally affects gut maturation and mucosal enzyme expression in newborn animal models [2]. Human milk contains significant amount of insulin, about 4-fold higher than amounts found in fresh pooled cow’s milk. Also, insulin is present in milk of mothers who gave birth to pre-mature infants as well as in milk of breastfeeding mothers for 15 months [3].

Insulin and Gut Maturation

Intestinal receptors for insulin were documented in mammalians in fetal life, during the suckling period, after weaning and in adults [3]. Insulin given orally to rats or piglets results in increased intestinal mRNA, protein, various intestinal enzymes’ activities and enhanced maturation of the pancreas.

Insulin is a macromolecule that is usually not absorbed in the gut and its effect may be local and limited to the suckling period [3]. However, we were able to demonstrate, in a rat model, that the trophic effects of oral insulin on the intestine are observed 6 weeks after weaning.

In a rat model of short bowel syndrome (75% small intestinal resection), oral insulin significantly increased mucosal adaptation [4]. Furthermore,
oral insulin given to premature infants and children with short bowel syndrome or chronic intestinal failure provided clinical benefit in 3/6 premature infants and one child on home parenteral nutrition [4]. Also in humans, Shulman [5] demonstrated that oral insulin (8 preterm infants) increased lactase activity, reduced gastric residuals and shortened time to full feeds in treated infants compared to historic controls [5]. Oral insulin also influences intestinal permeability and has systemic indirect effects [3].

**Insulin in Infant Formulas**

*Safety*

No adverse events including hypoglycemia and production of autoantibodies were reported in premature infants [4, 5]. In the DPT-1 trial, which aimed to test whether oral insulin can prevent type 1 diabetes in children at risk of developing type 1 diabetes within 5 years [6], rates of hypoglycemia were similar in insulin-treated children compared to controls.

*Adding Insulin to Infant Formulas*

In order to add insulin to infant formula, a product was designed containing a dry powder composed of bioactive insulin microencapsulated within a matrix of maltodextrin and vitamin C. The microencapsulation process enables insulin bioactivity protection until its immersion and consumption within infant formula.
In a preliminary study providing oral insulin (InsuMeal, Nutrinia, Israel) or placebo added to liquid infant formula (final insulin concentration of 400 μU/ml), 8 preterm infants were enrolled (table 2). The results suggest that preterm infants in the treatment group gained more weight during the first month (p < 0.02) with a trend of arriving earlier at full oral feeding (p < 0.09). However, the sample size is minimal and can only serve as guidance to a properly sized prospective study. Indeed, such a study is currently ongoing.

If the addition of insulin to preterm infant formulas results in better growth and accelerated intestinal maturation, future studies will need to address insulin supplementation in term infants and assess the efficacy of such supplementation in enhancing gut maturation and preventing non-communicable diseases such as allergy, autoimmune diseases and obesity.

### Table 2. Weight gain and time to full feeds

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight at day 1, g</th>
<th>Gained weight, g</th>
<th>Time to full feeds, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>805</td>
<td>475</td>
<td>11</td>
</tr>
<tr>
<td>Control</td>
<td>930</td>
<td>560</td>
<td>16</td>
</tr>
<tr>
<td>Control</td>
<td>1,480</td>
<td>610</td>
<td>6</td>
</tr>
<tr>
<td>Control</td>
<td>1,665</td>
<td>680</td>
<td>16</td>
</tr>
<tr>
<td>Treatment</td>
<td>1,040</td>
<td>725</td>
<td>7</td>
</tr>
<tr>
<td>Treatment</td>
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<td>3</td>
</tr>
<tr>
<td>Treatment</td>
<td>1,460</td>
<td>760</td>
<td>5</td>
</tr>
<tr>
<td>Treatment</td>
<td>1,606</td>
<td>834</td>
<td>8</td>
</tr>
</tbody>
</table>

Weight gain and time to full feeds in 8 preterm infants fed with control formula and a formula with added insulin during days 1–28 after birth.

References