Milk and Linear Growth:
Programming of the IGF-1 Axis and Implication for Health in Adulthood

Richard M. Martin, Jeff M.P. Holly and David Gunnell

There is increasing awareness that childhood circumstances influence disease risk in adulthood. As well as being strongly influenced by genes/genetic factors, stature acts as a marker for early-life exposures, such as diet, and is associated with risk of several chronic diseases in adulthood [1]. Stature is also a marker for levels of insulin-like growth factor (IGF)-I in childhood. Levels of IGF-I are nutritionally regulated and are therefore modifiable.

Circulating IGF-I in childhood is raised in response to some aspects of diet, particularly cow’s milk and dairy product intake [2], and raised childhood IGF-I in turn leads to greater subsequent growth in stature [3]. Studies conducted by our team and others, however, indicate that the effect of milk is complicated because consumption in childhood appears to have long-term, programming effects which are opposite to the immediate effects of consuming milk. Specifically, studies suggest that the long-term effect of higher levels of milk intake in early childhood is opposite to the expected short-term effect, because milk intake in early life is inversely associated with IGF-I levels throughout adult life (table 1). The most important evidence supporting the long-term programming of the IGF system comes from a randomized controlled trial of milk supplements provided to pregnant women and their offspring up to 5 years of age [4]. In a long-term follow-up of the offspring of the mothers originally recruited to the trial, circulating levels of IGF-I were measured at age 25 years. Those offspring who received milk supplements up to age 5 years had markedly lower serum IGF-I levels when measured 20 years later (fig. 1). The findings are opposite to the likely immediate responses to milk supplementation, which would have been to increase hepatic production of IGF-I [2].
We have hypothesized that a relatively high IGF-I level at the time of supplementation could cause a resetting of the pituitary due to greater feedback on the growth hormone axis from the prevailing circulating IGF-I during a sensitive period of life. This long-term resetting of the pituitary to raise the threshold for stimulating growth hormone release would result in relatively lower hepatic IGF-I production and serum levels in later life. The reverse effect would occur in response to lower nutritional intake in early life (for example, in response to breastfeeding), which would be expected to lower IGF-I levels in early life but may program, via pituitary resetting, higher observed levels in later life [5]. Such a programming effect of milk intake in early life could potentially have implications for cancer and ischemic heart disease risk many years later.

**Table 1.** Interrelationships between diet and IGF at various points in life course

<table>
<thead>
<tr>
<th>High milk/protein intake</th>
<th>IGF-I levels</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>infancy</td>
<td>childhood</td>
<td>adulthood</td>
</tr>
<tr>
<td>In infancy (bottle feeding)</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>In childhood</td>
<td>+</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>In adulthood</td>
<td></td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

+ = Positive association; – = inverse association.

**Fig. 1.** Serum IGF-I levels at age 25 years following intervention with milk supplementation versus no milk supplementation up to age 5 years (the Barry-Caerphilly growth cohort; n = 663). From Ben Shlomo et al. [4].
References