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Characteristics and potential functions of human milk adiponectin

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Abstract

Adiponectin is a protein hormone produced by adipose tissue whose circulating levels are inversely related to adiposity and inflammation. Adiponectin circulates as oligomers, from the low molecular weight trimer to the high molecular weight octadecamer (18mer). Each oligomer has distinct biological activities, which include enhancement of insulin sensitivity and metabolic control, and suppression of inflammation. Adiponectin occurs in human milk at higher concentrations than leptin. The adiponectin in human milk is almost entirely of the high molecular weight form, the form with the highest activity in controlling many types of metabolic processes. Human adiponectin fed to infant mice is transported across the intestinal mucosa into the serum. An inverse relationship between adiponectin levels in milk and adiposity (weight-for-height) of the breastfed infant was observed, and could be due to modulation of infant metabolism by milk adiponectin, and may be related to the observed protection against obesity by breastfeeding. Human milk may be a medium whereby the hormonal milieu (in response to internal factors and the environment) of the mother can be used to communicate with the breastfed infant to modify infant metabolic processes. Transmission of information from mother to infant through milk may allow adaptation to fluctuating environmental conditions.

Keywords

infant development; body weight; BMI; adiposity

Adiponectin

Obesity in children has reached epidemic proportions, with obesity-related disorders that had typically been diseases of adults now occurring in children. Several reports describe an association between feeding human milk and reduced obesity later in life. Likewise, inflammatory bowel diseases are an increasingly important problem in pediatrics, and there is evidence of protection by human milk. The mechanisms by which human milk could provide

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Author Disclosures

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protection against obesity and inflammatory bowel conditions are unclear, but bioactive factors in human milk provide a promising explanation.

Adiponectin, a protein produced in adipose tissue, is a potent metabolic mediator that controls processes associated with obesity and inflammation. Serum adiponectin improves insulin sensitivity and fatty acid metabolism (1,2); low levels are associated with obesity, type 2 diabetes, dyslipidemia, and cardiovascular disease (3-6). Serum adiponectin has strong anti-inflammatory properties in the vascular endothelium, pancreas, and intestinal mucosal epithelial cells. Although total adiponectin concentrations play an important role in adult and childhood metabolic dysfunction, recent studies have highlighted the differing activities of specific adiponectin oligomers.

Adiponectin occurs naturally as oligomers that are multiples of the three-protein unit whose peptide chains assemble as a collagen helix. The high molecular weight form is mostly 18mer, the intermediate weights are 6 and 12mers, and the low molecular weight forms are the 3mers, and there are free globular heads. Different forms of adiponectin can display different, and sometimes opposing, activities. The ratio of these forms may be an important determinant of insulin sensitivity and response to insulin-sensitizing drugs (7,8). The high molecular weight 18mer is highly active in controlling insulin sensitive metabolic processes (Figure 1).

Adiponectin in milk

Human milk varies in composition within and between lactating women. Variation in composition of milk proteins over the course of lactation is due primarily to programmed changes in protein expression (9-11). Variability in milk protein concentrations among individuals has been attributed to genetic variation (12,13), maternal adiposity (14), and other factors. Adipose tissue is the primary source of adiponectin. The large quantity of adipose tissue in the human breast suggested that adiponectin could occur in milk. Moreover, the concentration of this protein hormone in milk could be anticipated to vary over the course of lactation, among individual women within a population, or between populations.

The concentration of adiponectin in cross-sectional and longitudinal human milk samples was quantified in lactating women residing in the United States and Mexico. In human milk, the concentration of adiponectin (range 4–88 ng/mL) is more than 40 times that of other major adipokines of milk such as leptin or ghrelin, (15,16). The average quantity of adiponectin in human milk was approximately 19 ng/mL.

In mice, adiponectin in milk decreases over the course of lactation. Human milk adiponectin concentrations decrease approximately 5% – 6% with each month of lactation (Figure 2).

Adiponectin levels circulating in the bloodstream are inversely related to the adiposity of the individual. Mammary tissue is embedded in adipose tissue. However, mammary tissue is isolated from other tissues by a barrier composed of tight junctions, and many of the components of milk, including proteins, are known to be exclusively of mammary origin. In contrast to serum adiponectin levels, human milk adiponectin levels increase with maternal post-pregnancy body mass index (Figure 3). The solid line represents the regression line predicted from the repeated-measures analysis of maternal BMI and the natural log of milk adiponectin concentrations when 2 women whose milk adiponectin concentrations exceeded 50 ng/mL ($\beta \pm \text{SE}$: 0.08 ± 0.02) were excluded. The dashed line represents the predicted regression line when these 2 women were included ($\beta \pm \text{SE}$: 0.10 ± 0.02).

This increase in human milk adiponectin with increasing adiposity is the inverse of the relationship between serum adiponectin levels and adiposity and thus raises questions regarding its biological relevance and potential function. Several arguments suggest that the

adiponectin in human milk could be biologically relevant. The proteins of human milk may be resistant to degradation in the stomach due to the low acidity of the infant stomach (17) and the protective environment that forms from milk components as they enter the stomach (18), resulting in limited gastric proteolysis (19). Oral insulin is not degraded and stimulates gut maturation (18,20,21), and adiponectin increases insulin sensitivity (1,2). The presence of adiponectin receptor 1 in fetal small intestine (22) suggests that a direct role of oral adiponectin in the neonate is possible.

The potential biological activity of orally consumed human milk adiponectin could be addressed experimentally in two ways: The first is to determine the distribution of oligomeric forms of human milk adiponectin. The different oligomeric forms of adiponectin have different metabolic control functions. The results of analyzing human milk adiponectin by western blot are shown in Figure 4:

SDS PAGE, milk (M) or serum (S; 1:60) was applied to each well of a 4% – 12% gel (Figure 4, A). Both human serum adiponectin and human milk adiponectin reduce to a single band whose weight is consistent with a stable monomer, confirming that the structures of both milk and serum adiponectin are similarly constructed from adiponectin monomers.

Native PAGE, 13 (13 μ L), 10 (10.4 μ L) of milk, or serum (13 μ L of a 1:60 dilution) was applied to each well of a native PAGE 3% – 12% Bis-Tris gel (Figure 4, B). Bands were blotted, incubated with anti-adiponectin antibody, anti-rabbit secondary antibody, and overlain photographic film developed to visualize adiponectin bands. Human milk adiponectin is found as the 18mer, a form associated with highest activity for controlling many metabolic processes.

The second question is whether these high molecular forms of adiponectin are absorbed. If the adiponectin were absorbed from the lumen of the gut into the circulation, it could have potential influence on the control of metabolism of the breastfeeding infant. If not absorbed, adiponectin could act only at a local level, where it might act to suppress inflammation of the intestinal mucosa.

The ability of adiponectin to be absorbed through the infant intestinal mucosa was tested in two ways. The first was to put human adiponectin into the lumen of the gut of an infant mouse and measure the appearance of human adiponectin into the circulation of the mouse. As seen below, the highest absorption of adiponectin occurs 2 hours after its administration into the stomach through oro-gastric intubation, and less is absorbed after 4 and 6 hours, consistent with physiological absorption of adiponectin (Figure 5).

In a second test of the ability of adiponectin to be absorbed into the circulation, we tested the serum adiponectin levels in the breastfed infants of our cohort. If human adiponectin were similarly absorbed across the intestinal mucosa of human infants, there should be a direct relationship between the concentration of adiponectin in individual human milks and the level of adiponectin in the serum of the breastfeeding infants consuming these milks. To test this, adiponectin in human milk samples and infant serum samples were measured 3 months postpartum in 77 breastfeeding mother-infant pairs from Mexico City. Even after adjustment for the infant's sex, birth weight, weight-for-age Z-score at 3 months, and the proportion of the infant's diet consisting of human milk (1.23 ± 0.50 μ g/mL increase per quartile, $P = 0.017$), increasing quartiles of adiponectin concentration in human milk related to increases in the infant's serum adiponectin ($\beta \pm$ SE for trend: 1.10 ± 0.50 μ g/mL increase per quartile, $P = 0.03$).

A remaining question is whether the human milk adiponectin, when absorbed, is degraded as it is absorbed from the lumen of the gut to the circulation, or, rather, is transported to its target organs in a form that remains biologically active. The highly variable content of adiponectin among mothers within a population that we observed, and differences observed between

adiponectin levels in the Mexican and US cohort, provided a tool to test this question. If the human milk adiponectin remains intact and functional after traversing the intestinal mucosa and entering the circulation, we might expect differences in adiponectin consumption to influence processes that are closely related to metabolic control, such as growth and adiposity. These parameters are best measured as the cumulative manifestation of metabolic processes in rapidly growing infants, such as weight-for-age and weight-for-length, measures of adiposity, and length-for-age, a measure of growth *per se*. Therefore, the relationship between adiponectin in milk and weight-for-age, weight-for-length, and length-for-age in breastfeeding infants were investigated.

Infants from Mexico had younger and less educated mothers (both $P < 0.0001$), and were shorter ($P < 0.0001$) and lighter ($P = 0.0003$) than their counterparts from Cincinnati. Overall, baseline milk adiponectin was $24.0 \pm 8.6 \mu\text{g/L}$ and did not differ by cohort ($P = 0.18$). At the outset of the study, weight-for-length Z-scores did not differ between the Mexican and Cincinnati cohorts ($P \geq 0.16$) (Figure 6).

The concentration of adiponectin in milk was associated with lower infant weight-for-age Z-score ($\beta \pm \text{SE}$: -0.20 ± 0.04 Z-score units, $P < 0.0001$), adjusting for the standard covariates plus length. This association was found in both the Cincinnati (-0.12 ± 0.05 units, $P = 0.009$) and Mexico cohorts (-0.25 ± 0.06 units, $P < 0.0001$). This result is consistent with the adiponectin in milk having a cumulative effect on the adiposity of the breastfed infants (Figure 7).

Further, milk adiponectin concentration was associated with lower weight-for-length Z-score ($\beta \pm \text{SE}$: -0.29 ± 0.08 units, $P = 0.0002$), adjusting for the standard covariates plus cohort (Figure 8). This result is also consistent with the adiponectin in milk having a cumulative effect on the adiposity of the breastfed infants.

Infant weight was added to the models for weight-for-length Z-score to test whether the relationship of milk adiponectin concentrations with weight-for-length Z-score could be explained by its association with infant weight (data not shown). The effect of milk adiponectin on weight-for-length Z was attenuated but remained significant (-0.13 ± 0.06 units, $P = 0.04$), suggesting an effect of milk adiponectin on body proportionality independent of infant weight.

Moreover, milk adiponectin was not significantly associated with infant length ($\beta \pm \text{SE}$: 0.19 ± 0.11 cm, $P = 0.08$) or length-for-age Z-score (0.09 ± 0.06 units, $P = 0.09$) in mixed models, adjusting for covariates. These data suggest that adiponectin in milk is having a significant influence on the dispensation of extra energy-containing nutrients beyond that required for growth, but does not influence the processes related to growth rate *per se*.

Discussion

Adiponectin is found in human milk in concentrations that are high relative to those of many other hormones, including the other known adipokines such as ghrelin and leptin. In both mouse and human milk, the concentration of adiponectin decays over the course of lactation.

The presence of human milk adiponectin as HMW octadecamers is consistent with its functional relevance to the infant. Circulating HMW adiponectin is recognized as the form most biologically active in many aspects of metabolic control. HMW adiponectin is more strongly correlated with weight loss and circulating high density lipoprotein cholesterol than total adiponectin (23), and better predicts response to the insulin-sensitizing drugs thiazolidinediones (8). Many milk proteins, including adiponectin, are highly glycosylated, aiding their protection against proteolytic degradation (24,25). The HMW form of adiponectin is the most highly glycosylated form, and this glycosylation is necessary for activation of

downstream pathways (26). Adiponectin in cord blood is predominantly in the HMW form (27). Thus, the predominance of human milk adiponectin in the HMW form is consistent with both resistance to digestion and high biological activity in the infant.

The adiponectin of milk is absorbed from the lumen of the gut into the circulation in mice. In breastfed infants, serum adiponectin is significantly related to the adiponectin concentrations in the milk being consumed, suggesting transport across the human intestinal mucosa. The biological relevance of human milk adiponectin is evident by the significant inverse relationship between concentrations of milk adiponectin and adiposity of the infant. This inverse relationship between adiponectin ingestion and adiposity may contribute to the association between breastfeeding and reduced risk of adiposity in later life that has been reported.

This interpretation is consistent with the finding in children that circulating adiponectin is inversely associated with obesity (28,29). Milk adiponectin appears to be associated with lower infant weight in the first six months of life, but a follow-up study of our cohorts is necessary to determine if this relationship persists after two years of life.

The biological role of an increase in adiponectin in milk with increased BMI of the mother is more challenging to interpret. It runs counter to insulin, where increased adiposity of the mother results in increased circulating insulin prenatally, and increased circulating insulin results in increased growth of the fetus. Taken at face value, the increase in adiponectin concentrations in milk with increasing maternal adiposity could induce a compensatory postnatal reduction in adipose accrual that would limit the processes whereby obese infants result from obese mothers. This phenomenon requires further data for more comprehensive understanding.

Milk adiponectin was not associated with infant length. By the end of 6 months, the prevalence of overweight and underweight were low in our cohorts, so the impact of milk adiponectin appears to occur largely within the range of normal variation of infant growth during this period. These data suggest that adiponectin in milk is having a significant influence on the dispensation of extra energy-containing nutrients beyond that required for growth, but does not appear related to growth rate *per se*.

Human milk has a powerful immunosuppressive activity that has never been fully accounted for by the anti-inflammatory molecules that have been identified (30). Clinically, human milk feeding has been shown to be associated with a reduction in inflammatory processes in infants of all stages of maturity and with significantly reduced risk of necrotizing enterocolitis in premature infants.

Our data suggest an important physiologic role for milk adiponectin in the early growth and development of breastfed infants. However, it is possible that the effects observed to be associated with milk adiponectin could be caused by other related factors, such as other milk proteins whose synthesis is inked with that of adiponectin, or adiponectin in combination with other factors. Nevertheless, our observations add to the growing body of evidence that the complement of human milk hormones are a means whereby the mother is able to communicate metabolic information or even social cues to the infant directly through her milk in order to help the infant adapt to the prevailing variable nutritional and environmental conditions.

In summary, higher adiponectin concentrations in human milk are associated with significantly lower weight and leaner body proportionality over the first 6 months of life in breastfed infants. These data, in conjunction with the occurrence of human milk adiponectin predominantly in the HMW biologically active form, suggest a significant role for milk adiponectin in early regulation of neonatal weight gain. The predominance of HMW adiponectin in milk also suggests a possible role in the attenuation of inflammatory processes, especially those of the

intestinal mucosa. Thus, a component of human milk, adiponectin, may contribute toward the low risk of obesity and inflammatory disorders when infants are breastfed.

Acknowledgments

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List of Abbreviations

SDS PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
BMI	body mass index
HMW	high molecular weight

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Figure 1.

Adiponectin oligomers. [Adapted from Tsao et al. J. Biol. Chem. 2002;277:29359. Reprinted with permission. © 2002 The American Society for Biochemistry and Molecular Biology. All rights reserved.]

Figure 2. Concentration of adiponectin in human milk over the course of lactation. [From Martin et al. Am J Clin Nutr 2006;83:1106. Reprinted with permission. © 2006 American Society for Nutrition. All rights reserved.]

Figure 3. Concentration of adiponectin in human milk as a function of maternal body mass index (BMI). [From Martin et al. Am J Clin Nutr 2006;83:1106. Reprinted with permission. © 2006 American Society for Nutrition. All rights reserved.]

Figure 4.

A) Western blot of milk and serum adiponectin following reduction and separation and SDS PAGE; B) Western blot of native human milk and serum adiponectin. [From Woo et al. *Breastfeeding Med.* 2009;4:101. Reprinted with permission. © 2009 Mary Ann Liebert, Inc. All rights reserved.]

Figure 5.
Appearance of adiponectin in the serum of infant mice after orogastric milk adiponectin administration of human adiponectin.

Figure 6.
Adiponectin in milk from the Mexico and Cincinnati cohort at the onset of the study.

Figure 7.

Infant weight-for-age relative to adiponectin concentrations of the milk being consumed. [From Woo et al. *Breastfeeding Med.* 2009;4:101. Reprinted with permission. © 2009 Mary Ann Liebert, Inc. All rights reserved.]

Figure 8.

Infant weight-for-length relative to adiponectin concentrations of the milk being consumed.
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