Characteristics and Potential Functions of Human Milk Adiponectin

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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 octodecamer (18 mer). 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 breast-fed 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 breast-feeding. 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 breast-fed infant to modify infant metabolic processes. Transmission of information from mother to infant through milk may allow adaptation to fluctuating environmental conditions. *(J Pediatr 2010;156:S41-6)*.

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 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 3-protein unit whose peptide chains assemble as a collagen helix. The high-molecular-weight (HMW) form is mostly 18 mer, the intermediate weights are 6 and 12 mer, and the low-molecular-weight forms are the 3 mer, 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 HMW 18 mer 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 suggests 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 to 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% to 6% with each month of lactation (**Figure 2**).

BMI	Body mass index
HMW	High molecular weight
SDS-PAGE	Sodium dodecyl sulfate–polyacrylamide gel electrophoresis

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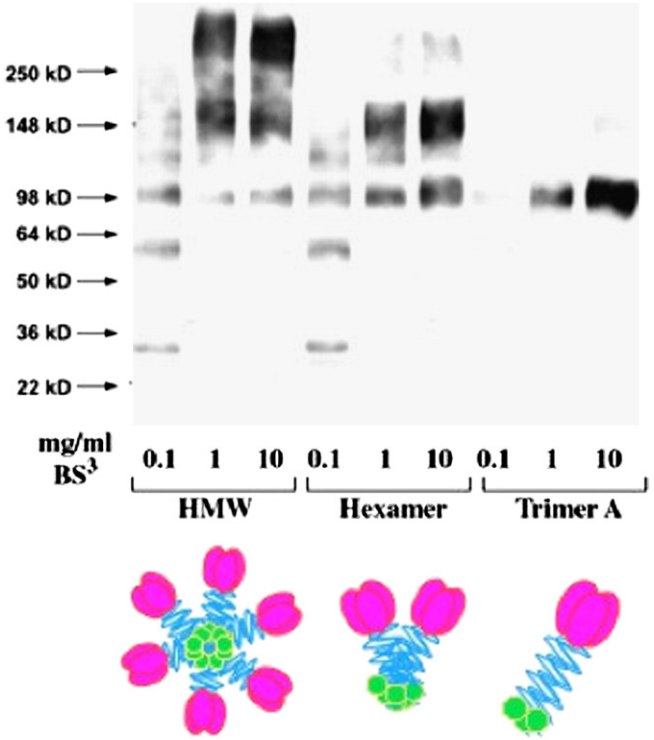

Figure 1. Adiponectin oligomers. Adapted from Tsao et al. J Biol Chem 2002;277:29359. Reprinted with permission. © 2002 The American Society for Biochemistry and Molecular Biology. All rights reserved.

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 postpregnancy body mass index (Figure 3). The solid line represents the regression line predicted from the repeated-measures analysis of maternal body mass index (BMI) and the natural log of milk adiponectin concentrations when two women whose milk adiponectin concentrations exceeded 50 ng/mL ($\beta \pm$ SE: 0.08 $\pm$ 0.02) were excluded. The dashed line represents the predicted regression line when these two women were included ($\beta \pm$ SE: 0.10 $\pm$ 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 because of 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]

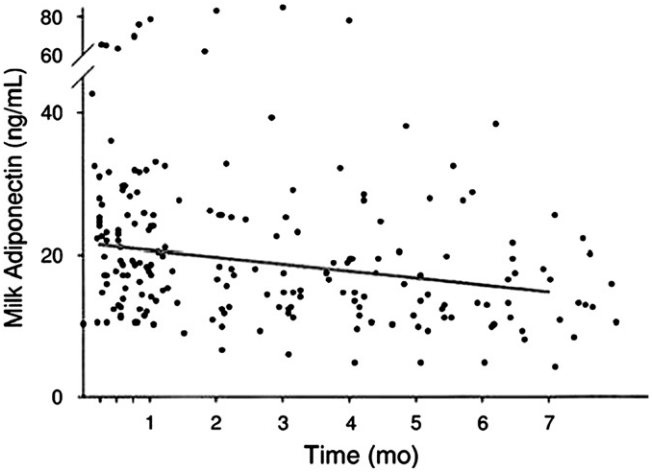

Figure 2. Concentration of adiponectin in human milk over the course of lactation. From Martin et al. Am J Clin Nutr 2006;83:1106. Reprinted with permission. © 2006 American Society for Nutrition. All rights reserved.

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.

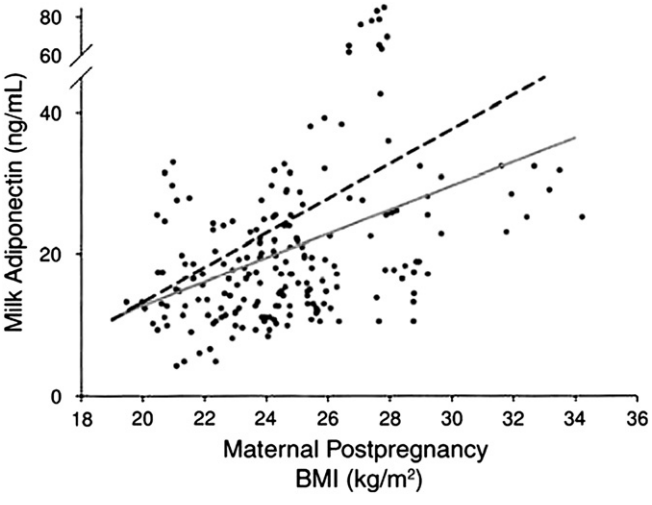

Figure 3. Concentration of adiponectin in human milk as a function of maternal body mass index (BMI). From Martin et al. Am J Clin Nutr 2006;83:1106. Reprinted with permission. © 2006 American Society for Nutrition. All rights reserved.