Human Milk Metabolic Hormones

Subjects: Endocrinology & Metabolism

Submitted by: Zoya Gridneva

Definition

Human milk (HM) contains a wide array of peptide hormones including leptin and adiponectin, which are involved in the regulation of infant growth and development. These essential hormones might play an important role in the regulation of metabolic reprogramming of the new-born infant. The protective activity of HM is thought to be due to the presence of bioactive molecules that are dynamic in response to maternal conditions and can positively modulate energy metabolism and inflammatory responses in infants and mothers. Hormones such as leptin, adiponectin, ghrelin, insulin, resistin, obestatin and apelin have been recently identified in HM.

1. Leptin

Leptin, a polypeptide hormone with an average of 167 amino acids (16.2 kDa), is mainly synthesised and secreted by adipocytes of white adipose tissue as a product of the obese (Ob) gene expression [1]. Leptin signals the amount of fat stored in the body; thus, plasma leptin concentration is positively correlated with body fat mass in adults [2][3]. Leptin modulates energy homeostasis; it induces energy consumption and reduces food intake by initiating a signal cascade beginning with leptin binding to the Ob receptor in the hypothalamus [4][5]. At birth, cord blood leptin concentrations are reported to correlate positively with neonatal fat mass index [6]. Two mechanisms contribute to the presence of leptin in HM. First, it is suggested that maternal plasma leptin enters HM via diffusion or receptor-mediated transport [7][8][9]. Second, mammary epithelial cells can produce small amounts of leptin [10]. HM leptin is present in a relatively high and variable concentration (range: 0.2 to 1.47 ng/mL), which generally decreases as the duration of lactation increases (**Table 1**).

Table 1. Studies examining human milk leptin.

Author	Year	Sample Size (n)	Sample Type	Sampling	Time of the Day (h)	Time Postpartum	Preparation	Method	Intra, Inter Assay (%CV)	LOD (ng/mL)	R (%)	Concentration (ng/mL)
Houseknecht et al. [11]	1997	14	-	12 h fast	08:00	-	SM and Wm	RIA	3.0, 12.6	0.3	SM: 90 WM: 82	WM, 10.1 ± 2.6; SM, 1.5 ± 0.87
Uçar et al. [12]	2000	18	C, M	pre- and post-feed	9:00–12:00	3–120 d	SM	RIA	-	0.5	-	(0.8–15) (range)
Lönnerdal and Havel [13]	2000	-	M	-	-	2–4 mo	SM and WM	RIA	-	-	-	WM, 32.7 ± 14.1 SM, 0.2 ± 0.1
Resto et al. [14]	2001	29	M	-	-	1–4 wk	M, added pancreatic lipase, $NaHCO_3$	RIA	-	-	-	5.28 (24.79)
Uysal et al. [15]	2002	50	M	2 h after last feed	8:00–10:00	1,2, 3 mo	SM	RIA	<6, -	0.1	-	Non-Ob, 0.37 ± 0.4 Ob, 0.27 ± 0.2
Bielicki et al. [16]	2004	33	C, M	1–3 h after breakfast	-	2–3, 4–5 d 4–6 wk	WM	RIA	<10, 9.7	0.25	97	Preterm, 0.63 ± 0.18 Term, 1.34 ± 0.14
Dundar et al. [17]	2005	47	M	pre-feed	10:00–11:00	15 d, 1, 2, 3 mo	WM	RIA	6.2, -	0.5	83 ± 4	15 d, AGA, 18.4 ± 2; LGA, 28.5 ± 4.4; SGA, 13.4 ± 2.2
Ilcol et al. [18]	2006	160	C, M	pre-feed, 3 h after breakfast	morning	2, 8, 25 d	WM	IRMA	<5, 7	0.1	-	2 d, 3.35 ± 0.25; 8 d, 2.65 ± 0.21; 25 d, 1.63 ± 0.18
Bronsky et al. [19]	2006	59	C	collected on EDTA and aprotinin	after 7:00	1–2 d	SM	ELISA	7.6, 9.1	0.05	-	0.50 (0.05) mean (SEM)
Miralles et al. [20]	2006	28	M	post-feed	morning	1, 3, 6, 9 mo	WM	ELISA	-	0.008	103.1 ± 1.4	1 mo, 0.156 ± 0.039
Weyermann et al. [8]	2006	766	M	pre-feed	-	6 wk, 6 mo	SM	ELISA	<7	-	-	12.8 ± 10.1
Weyermann et al. [21]	2007	767	M	-	-	6 wk	SM	ELISA	<7, -	-	-	0.175 (0–4.1) median (range)

Author	Year	Sample Size (n)	Sample Type	Sampling	Time of the Day (h)	Time Postpartum	Preparation	Method	Intra, Inter Assay (%CV)	LOD (ng/mL)	R (%)	Concentration (ng/mL)
Aydin et al. [22]	2008	31	C, M	pre-feed, collected on aprotinin	9:00	2, 25 d	SM	ELISA	-	-	-	C, 2.01 ± 0.34; M, 2.04 ± 0.67
Savino et al. [23]	2010	36	-	-	-	<6 mo	SM	RIA	<5, 8	0.04	-	0.51 (0.34)
Bronsky et al. [24]	2011	72	C, M	collected on EDTA + protease inhibitor	-	1 d; 1, 3, 6, 12 mo	SM	ELISA	6, 9	0.5	-	1 d, 0.3 ± 0.04; 1 mo, 0.2 ± 0.03; 3 mo, 0.1 ± 0.01; 6 mo, 0.1 ± 0.02; 12 mo, 0.2 ± 0.04
Schuster et al. [25]	2011	23	C, M	-	-	1, 2, 3, 4 wk 2, 3, 4, 5, 6 mo	SM	RIA	-	0.01	70.2 ± 8.7	1 wk, 0.21 ± 0.19 6 mo, 0.18 ± 0.15
Eilers et al. [26]	2011	77	C, M	fasting 2 h prior sampling	16:00–20:00	3 d, 28 d	SM	RIA	5, 6	-	~94	Preterm, 3 d, 0.7 ± 0.79; 28 d, 0.5 ± 0.4; Term, 3 d, 0.65 ± 0.67; 28 d, 0.5 ± 0.4
Fields and Demerath [27]	2012	19	M	complete breast expression	8:00–10:00	~1 mo	SM	-	-	-	-	0.95 ± 0.73
Savino et al. [28]	2012	23	-	-	-	<6 mo	SM	ELISA	<5, 6.8	6	-	2.34 (5.73)
Schueler et al. [29]	2013	13	M	overnight fast, pre- and post-feed	7:00–10:00	29–38 d.	SM	RIA	9.4, -	-	-	pre, 0.9 ± 0.7 post, 1.0 ± 0.8
Chang et al. [30]	2013	-	-	-	-	3–4 mo	SM	ELISA	<5, 6	0.5	-	-
Ojeda et al. [31]	2013	-	-	-	-	2 mo	-	ECIs, & ELISA			+	ECIs, 2.6 ± 0.1 ELISA, 2.9 ± 0.5
Kon et al. [32]	2014	103	M	-	Morning	1, 2, 3 mo	SM	ELISA	3.7, -	0.42	-	LWG, 1 mo, 1.63 (0.27); 3 mo, 1.35 (0.31); NWG, 1 mo, 1.55 (0.17); 2 mo, 1.83 (0.23); 3 mo, 3.29 (0.70) HWG,1 mo: 1.53 (0.29); 2 mo, 2.20 (0.28); 3 mo, 3.57 (1.37) mean (SEM)
Brunner et al. [33]	2014	6 wk, 152 6 mo, 120	M	overnight fast	Morning	6 wk, 6 mo	SM	RIA	-	-	-	6 wk, 0.11 (0.19); 6 mo, 0.09 (0.18)
Khodabakhshi et al. [34]	2015	Ob, 40 NW, 40	M	overnight fast, 2 h after last breast feed	8:00–10:00	2–5 mo	SM	ELISA	-	-	-	NW, 1.81 (1.65–1.94) Ob, 1.78 (1.67–1.94)
Cannon et al. [35]	2015	19	M	pre- and post-feed	24 h milk collection	3–21 wk	SM	RIA	-, 9.9	0.017	98.4 ± 6.8	pre, 0.43 ± 0.10, post, 0.42 ± 0.11
Quinn et al. [36]	2015	113		mid-feed sampling	6:00–10:00	10 d–36 mo	SM	ELISA	-	-	-	0.3 ± 0.29

Author	Year	Sample Size (n)	Sample Type	Sampling	Time of the Day (h)	Time Postpartum	Preparation	Method	Intra, Inter Assay (%CV)	LOD (ng/mL)	R (%)	Concentration (ng/mL)
Andreas et al. [37]	2016	120	-	1 h fast prior sampling, pre- and post-feed, on protease inhibitors	10:00–13:00	1 wk, 3 mo	SM	Multiplex assay	3, -	3.1	-	1 wk, pre 541.7 (161.2); post 614.4 (172.1) 3 mo, pre 684.8 (117.4); post 464.3 (125.1) mean (SEM)
Gridneva et al. [38]	2016	27	M	pre- and post-feed	09:30–11:30	2–5 mo	SM and WM	ELISA	-, <7.2	-	97.7 ± 9.7	WM, 0.51 ± 0.18 [0.23–1.10] SM, 0.28 ± 0.12 [0.20–0.84]
Kugananthan et al. [39]	2016	61	M	pre- and post-feed	11:00	2, 5, 9, 12 mo	SM and WM	ELISA	<5, 7.2	-	97.7 ± 9.7	WM, 2 mo, 0.50 ± 0.16; 5 mo, 0.48 ± 0.16; 9 mo, 0.56 ± 0.11; 12 mo, 0.54 ± 0.14 SM, 2 mo, 0.32 ± 0.16; 5 mo, 0.26 ± 0.07; 9 mo, 0.22 ± 0.03; 12 mo, 0.21 ± 0.02
De Luca et al. [40]	2016	100	M	over-feed	9:00–11:00	1 mo	SM	RIA	<10, -	0.5	+	Non-Ob, 2.5 [2.1–3.0] Ob, 4.8 [4.1–5.6] mean (95% CI)
Savino et al. [41]	2016	58	-	collected on protease inhibitor	7:00–9:00	-	SM	RIA	-	0.04	-	0.89 (1.32)
Fields et al. [42]	2017	37	M	complete breast expression	8:00–10:00	1, 6 mo	SM	-	-	-	-	1 mo (n = 37), 0.589 (0.353–1.45) 6 mo (n = 30), 0.426 (0.145–940)
Meyer et al. [43]	2017	147	M	overnight fast	-	6 wk, 4 mo	-	RIA	-	-	-	-
Quinn and Childs [44]	2017	116	-	mid-feed	6:00–10:00	-	SM	ELISA	17.8, -	-	-	0.27 ± 0.25
Nunes et al. [45]	2017	69	C, M	-	-	1, 2, 30 d	SM	ELISA	-	-	-	SGA, M, 0.377 (0.36–0.41) GDM, M, 0.460 (0.45–0.70) CTL, M, 0.715 (0.48–0.9)
Cannon et al. [46]	2017	20	-	pre- and post-feed	24 h milk collection	6–32 wk	SM	ELISA	-, 9.9	0.017	98.4 ± 6.8	0.51 ± 0.16 (0.42–1.15)
Kugananthan et al. [9]	2017	59	M	pre- and post-feed	9:30–11:30	2, 5, 9, 12 mo	SM and WM	ELISA	-, <7.2	0.05	SM, 96.3 ± 1.2 WM, 97.1 ± 9.1	WM, 0.53 ± 0.19 (0.20–2.24) 2 mo, 0.55 ± 0.29; 5 mo, 050 ± 0.17; 9 mo, 0.53 ± 0.15; 12 mo, 0.54 ± 0.13 SM, 0.28 ± 0.12 (0.19–1.46) 2 mo, 0.34 ± 0.21; 5 mo, 0.27 ± 0.07; 9 mo, 0.26 ± 0.09; 12 mo, 0.26 ± 0.08

Author	Year	Sample Size (n)	Sample Type	Sampling	Time of the Day (h)	Time Postpartum	Preparation	Method	Intra, Inter Assay (%CV)	LOD (ng/mL)	R (%)	Concentration (ng/mL)
Gridneva et al. [47]	2018	20	M	pre- and post-fed	24 h milk collection	2, 5, 9, 12 mo	SM and WM	ELISA	-, <7.2	0.05	97.1 ± 9.1	WM, 2 mo, 0.50 ± 0.18; 5 mo, 0.49 ± 0.17; 9 mo, 0.56 ± 0.11; 12 mo, 0.50 ± 0.11 SM, 2 mo, 0.34 ± 0.20; 5 mo, 0.26 ± 0.08; 9 mo, 0.21 ± 0.02; 12 mo, 0.21 ± 0.03
Chan et al. [48]	2018	430	M	pooled 24 h milk collection	24 h milk collection	4 mo	SM	ELISA	-	0.137	_	349 (186–689)
Yu et al. [49]	2018	96	C, M	pre- and post-feed for mature milk	3 d, 8:00–9:00 42, 90 d, 14:00–16:00	3, 42, 90 d	SM	ELISA	<7.4, 9.3	-	-	GDM (n = 48), 3 d, 1.28 (0.87–2.63); Healthy (n = 48), 3 d, 1.49 (0.56–3.25)
Sadr Dadres et al. [50]	2019	135	M	2 h after feeding	10:00–12:00	1, 3 mo	SM	ELISA	<6, 6	0.008	90–94	1 mo, 0.640 ± 0.606 3 mo, 0.484 ± 0.672
Zamanillo et al. [51]	2019	59	M	-	9:00–14:00	30, 60, 90 d	WM	ELISA	-	-	-	1 mo, 0.376 ± 0.353; 2 mo, 0.341 ± 0.314; 3 mo, 0.346 ± 0.333
Logan et al. [52]	2019	SPATZ, 1090 UBCS, 1006	M	1 h after last feed	9:00–12:00	6 wk, 6 mo	SM	ELISA	<7.0, -	-	-	SPATZ, 6 wk, 266.5 (152.0–498.0); UBCS, 6 wk, 175.0 (79.8–350.0)
Larrosa Haro et al. [53]	2019	131	M	pre- and post-feed	-	8, 16 wk	SM	ELISA	-	0.01	-	8 wk, pre, 0.316 (0.50); post, 0.317 (0.57); 16 wk, pre, 0.447 (0.48); post, 0.411 (0.64)
Logan et al. [54]	2019	694	M	1 h after last feed	9:00–12:00	6 wk, 6 mo, 12 mo	SM	ELISA	-, 5.8	-	-	6 wk (n = 668), 388.8 ± 398.1; 6 mo (n = 445), 269.6 ± 305.3; 12 mo (n = 69), 320.4 ± 345.2

Author	Year	Sample Size (n)	Sample Type	Sampling	Time of the Day (h)	Time Postpartum	Preparation	Method	Intra, Inter Assay (%CV)	LOD (ng/mL)	R (%)	Concentration (ng/mL)
Kocaadam et al. [55]	2019	65	M	pre-feed, ~2 h fast prior, ~2 h after last feed, on EDTA and aprotinin	8:00–11:00	15–30 d	SM	ELISA	-	-	-	preterm, (n = 31), 2.0 (2.5) term, (n = 34), 0.0 (2.3)
Schneider-Worthington et al. [56]	2020	25	M	-	-	1 mo	SM	ELISA	4.48, 13.56	-	-	0.47 (0.94)
Dal Bello et al. [57]	2020	-	-	-	-	-	-	nano-HPLC-HRMS	-	27	-	6.70
Galante et al. [58]	2020	501	-	pre-feed	10:00–24:00	2–3 mo	SM	ELISA	4, 8	-	-	0.116 ± 0.112, ng/mg (raw values corrected per mg of protein per mL)
Joung et al. [59]	2021	50	C, M	post-feed, 24 h pooled	-	7, 14, 21 and 28 d	WM	ELISA	10	0.01	-	-

Data reported as mean ± SD or median (IQR) unless specified. AGA, appropriate age for gestational age; C, colostrum milk; CTL, control group; CI, confidence interval; CV, coefficient variation; d, day; ECIs, electrochemical immunosensor; EDTA, ethylenediaminetetraacetic acid; ELISA, enzyme-linked immunosorbent assay; GDM, gestational diabetes mellitus; IRMA, immunoradiometric assay; LGA, large for gestational age; LOD, limit of detection; M, mature milk; mo, month; Non-Ob, without obesity; Ob, with obesity; R, recovery of analyte; RIA, radioimmunoassay; SGA, small for gestational age; SM, skim milk; SPATZ, Ulm SPARTZ health study; UBCS, Ulm birth cohort study; wk, week; WM, whole milk; y, year.

2. Adiponectin

Adiponectin, the most abundant adipokine, consists of 247-amino acids (27 kDa). Three circulating oligomers of adiponectin have been identified in the blood (low-, medium- and high- molecular weight), each with discrete biological activities. The high molecular weight oligomer is the more active and prevalent form of adiponectin in intracellular spaces, whereas low-molecular-weight adiponectin dominates the blood circulation [60]. Adiponectin is involved in the regulation of lipid and glucose metabolism and the stimulation of food intake, as well as the reduction of energy expenditure and regulation of the inflammatory response [61][62]. Although adiponectin is mainly synthesised by adipocytes, some evidence suggests that it also may be synthesised by the mammary epithelial cells [63]. Adiponectin is also the most abundant adipokine in HM, with a concentration range of ~4.2–78.9 ng/mL [47][64][65]. HM is dominated by the more biologically active high-molecular-weight adiponectin [66] that may enhance insulin sensitivity and metabolic control and suppresses inflammation [64].

3. Ghrelin

Ghrelin is a small polypeptide hormone comprising 28-amino acids (33.7 kDa) and is predominantly synthesised by the stomach, with smaller amounts produced by other organs, including the pancreas, kidneys and placenta [67]. Two different isoforms of ghrelin exist in the circulation: acetylated ghrelin (active) and deacylated ghrelin (restricted activity). Ghrelin is an appetite-stimulant hormone; it acts in a positive feedback loop that signals feeding behaviour to the hypothalamus, inducing food intake and controlling energy homeostasis. Further, in humans active ghrelin induces growth hormone (GH) secretion through binding and activation of GH secretagogue receptor 1a (GHS-R 1a) [68]. Ghrelin is present in HM, and there are two potential sources, maternal circulating ghrelin [22][69][70] and mammary epithelial cell expression [71][72].

4. Insulin

The β cells of the pancreas synthesise insulin, a glucose controlling hormone that consists of 51 amino acids (5.8 kDa) [73]. Insulin is present in HM, with the primary source being maternal blood. The detection of artificial insulin in HM of women with type 1 diabetes suggests an active transport mechanism of HM insulin from the maternal circulation [74]. However, some evidence suggests that mammary epithelial cells can also produce insulin [75]. Colostrum concentrations of insulin are substantial (114–306 mU/L) and rapidly decrease so HM concentrations match that of maternal blood by day 5 postpartum [74].

5. Resistin

Resistin is a 12.5 kDa cysteine-rich polypeptide hormones consisting of 114 amino acids. First discovered in rodents as an adipose-secreted hormone, resistin plays a physiological role as a subclinical inflammatory mediator between obesity and diabetes. Serum resistin concentrations are higher in obese and diabetic mice, and mouse models with diet-induced obesity [76]. Resistin antagonises insulin action and induces glucose intolerance in vivo [76]. In humans, the primary source of resistin is macrophages, therefore it is strongly related to inflammatory conditions [77]. Resistin gene expression has been reported in human placental tissue with its prominence in the chorionic villi during the first trimester suggesting a role in modulating insulin sensitivity during pregnancy [78]. Concentrations of resistin in HM are lower than that of maternal and infant serum, and decrease throughout the lactation period [79].

6. Obestatin

Obestatin is a 23 amino acid peptide, discovered in 2003 as a carboxyl-terminal fragment of pro-ghrelin (C-ghrelin) [80]. Obestatin is encoded by the ghrelin gene and is derived from the carboxy-terminal part of proghrelin; ghrelin is derived from the N-terminal part of the same

precursor preproghrelin. Obestatin is considered an antagonist to ghrelin as it inhibits feeding and digestive motility by binding to the orphan G protein-coupled receptor GPR39 [80][81]. Gronberg et al. [71] reported the subcellular localisation of obestatin and that obestatin immunoreactive cells were present in the gastrointestinal tract, pancreatic islets and mammary glands. Obestatin appears to be involved in many physiological functions, cell proliferation, decreasing food intake, reducing body weight gain, increasing the secretion of pancreatic enzymes, and inhibiting glucose-induced insulin secretion [82]. HM obestatin concentrations are 538.90 ± 46.21 pg/mL and 528.5 ± 39.00 pg/mL in HM colostrum and mature milk, respectively [22]. HM obestatin concentrations are almost twice higher than in maternal serum; indicating it is an important component for the infant that may be synthesised by the mammary gland.

7. Apelin

Apelin is a small peptide that results from a cleavage of pre-proprotein of 77 amino acids into a signal peptide from the N-terminal region and 55 amino acids apelin precursor called proprotein. The proprotein precursor produces a group of active peptides that includes apelin-36, apelin-17, apelin-13 and apelin-12 [83][84]. Apelin peptides are endogenous ligands of the apelin receptor (APJ), this APJ is a class A G-protein-coupled receptor that is widely distributed in several tissues such as the heart, lung, brain, kidney, adipose tissue, vascular epithelium, gastrointestinal tract and mammary gland [85]. Habata et al. [86] reported the highest expression of apelin mRNA in the mammary gland of pregnant rats, and this biologically active apelin and its mRNA increased substantially during pregnancy and lactation [86]. Immunohistochemistry techniques have detected apelin immunoreactivity in the ductal and lobular epithelial cells and vascular endothelial cells of human mammary gland [87]. Apelin has been demonstrated to be involved in the regulation of cardiovascular and fluid homeostasis, food intake, cell proliferation, angiogenesis and most importantly, glucose and lipid metabolism. Apelin also appears to possess anti-obesity and anti-diabetic properties [88].

References

1. Zhang, Y.; Proenca, R.; Maffei, M.; Barone, M.; Leopold, L.; Friedman, J.M. Positional cloning of the mouse obese gene and its human homologue. Nature 1994, 372, 425–432.
2. de Graaf, C.; Blom, W.A.; Smeets, P.A.; Stafleu, A.; Hendriks, H.F. Biomarkers of satiation and satiety. Am. J. Clin. Nutr. 2004, 79, 946–961.
3. Savino, F.; Liguori, S.A. Update on breast milk hormones: Leptin, ghrelin and adiponectin. Clin. Nutr. 2008, 27, 42–47.
4. Schwartz, M.W.; Woods, S.C.; Porte, D., Jr.; Seeley, R.J.; Baskin, D.G. Central nervous system control of food intake. Nature 2000, 404, 661.
5. Savino, F.; Liguori, S.A.; Lupica, M.M. Adipokines in breast milk and preterm infants. Early Hum. Dev. 2010, 86 (Suppl. 1), 77–80.
6. Chaoimh, C.N.; Murray, D.M.; Kenny, L.C.; Irvine, A.D.; Hourihane, J.O.; Kiely, M. Cord blood leptin and gains in body weight and fat mass during infancy. Eur. J. Endocrinol. 2016, 175, 403–410.
7. Casabiell, X.; Piñeiro, V.; Tomé, M.A.; Peinó, R.; Diéguez, C.; Casanueva, F.F. Presence of leptin in colostrum and/or breast milk from lactating mothers: A potential role in the regulation of neonatal food intake. J. Clin. Endocrinol. Metab. 1997, 82, 4270–4273.
8. Weyermann, M.; Beermann, C.; Brenner, H.; Rothenbacher, D. Adiponectin and leptin in maternal serum, cord blood, and breast milk. Clin. Chem. 2006, 52, 2095–2102.
9. Kugananthan, S.; Gridneva, Z.; Lai, C.T.; Hepworth, A.R.; Mark, P.J.; Kakulas, F.; Geddes, D.T. Associations between Maternal Body Composition and Appetite Hormones and Macronutrients in Human Milk. Nutrients 2017, 9, 252.
10. Smith-Kirwin, S.M.; O'Connor, D.M.; De Johnston, J.; Lancey, E.D.; Hassink, S.G.; Funanage, V.L. Leptin expression in human mammary epithelial cells and breast milk. J. Clin. Endocrinol. Metab. 1998, 83, 1810–1813.
11. Houseknecht, K.L.; McGuire, M.K.; Portocarrero, C.P.; McGuire, M.A.; Beerman, K. Leptin is present in human milk and is related to maternal plasma leptin concentration and adiposity. Biochem. Biophys. Res. Commun. 1997, 240, 742–747.
12. Uçar, B.; Kirel, B.; Bör, O.; Kiliç, F.S.; Doğruel, N.; Aydoğdu, S.D.; Tekin, N. Breast milk leptin concentrations in initial and terminal milk samples: Relationships to maternal and infant plasma leptin concentrations, adiposity, serum glucose, insulin, lipid and lipoprotein levels. J. Pediatr. Endocrinol. Metab. JPEM 2000, 13, 149–156.
13. Lönnerdal, B.; Havel, P.J. Serum leptin concentrations in infants: Effects of diet, sex, and adiposity. Am. J. Clin. Nutr. 2000, 72, 484–489.
14. Resto, M.; O'Connor, D.; Leef, K.; Funanage, V.; Spear, M.; Locke, R. Leptin levels in preterm human breast milk and infant formula. Pediatrics 2001, 108, E15.
15. Uysal, F.K.; Onal, E.E.; Aral, Y.Z.; Adam, B.; Dilmen, U.; Ardiçolu, Y. Breast milk leptin: Its relationship to maternal and infant adiposity. Clin. Nutr. 2002, 21, 157–160.
16. Bielicki, J.; Huch, R.; von Mandach, U. Time-course of leptin levels in term and preterm human milk. Eur. J. Endocrinol. 2004, 151, 271–276.
17. Dundar, N.O.; Anal, O.; Dundar, B.; Ozkan, H.; Caliskan, S.; Büyükgebiz, A. Longitudinal investigation of the relationship between breast milk leptin levels and growth in breast-fed infants. J. Pediatr. Endocrinol. Metab. JPEM 2005, 18, 181–187.
18. Ilcol, Y.O.; Hizli, Z.B.; Ozkan, T. Leptin concentration in breast milk and its relationship to duration of lactation and hormonal status. Int. Breastfeed. J. 2006, 1, 21.
19. Bronsky, J.; Karpísek, M.; Bronská, E.; Pechová, M.; Jancíková, B.; Kotolová, H.; Stejskal, D.; Prusa, R.; Nevoral, J. Adiponectin, adipocyte fatty acid binding protein, and epidermal fatty acid binding protein: Proteins newly identified in human breast milk. Clin. Chem. 2006, 52, 1763–1770.
20. Miralles, O.; Sánchez, J.; Palou, A.; Picó, C. A physiological role of breast milk leptin in body weight control in developing infants. Obesity 2006, 14, 1371–1377.
21. Weyermann, M.; Brenner, H.; Rothenbacher, D. Adipokines in human milk and risk of overweight in early childhood: A prospective cohort study. Epidemiology 2007, 18, 722–729.
22. Aydin, S.; Ozkan, Y.; Erman, F.; Gurates, B.; Kilic, N.; Colak, R.; Gundogan, T.; Catak, Z.; Bozkurt, M.; Akin, O.; et al. Presence of obestatin in breast milk: Relationship among obestatin, ghrelin, and leptin in lactating women. Nutrition 2008, 24, 689–693.
23. Savino, F.; Liguori, S.A.; Petrucci, E.; Lupica, M.M.; Fissore, M.F.; Oggero, R.; Silvestro, L. Evaluation of leptin in breast milk, lactating mothers and their infants. Eur. J. Clin. Nutr. 2010, 64, 972–977.
24. Bronsky, J.; Mitrova, K.; Karpisek, M.; Mazoch, J.; Durilova, M.; Fisarkova, B.; Stechova, K.; Prusa, R.; Nevoral, J. Adiponectin, AFABP, and leptin in human breast milk during 12 months of lactation. J. Pediatr. Gastroenterol. Nutr. 2011, 52, 474–477.
25. Schuster, S.; Hechler, C.; Gebauer, C.; Kiess, W.; Kratzsch, J. Leptin in maternal serum and breast milk: Association with infants' body weight gain in a longitudinal study over 6 months of lactation. Pediatr. Res. 2011, 70, 633–637.
26. Eilers, E.; Ziska, T.; Harder, T.; Plagemann, A.; Obladen, M.; Loui, A. Leptin determination in colostrum and early human milk from mothers of preterm and term infants. Early Hum. Dev. 2011, 87, 415–419.
27. Fields, D.A.; Demerath, E.W. Relationship of insulin, glucose, leptin, IL-6 and TNF-alpha in human breast milk with infant growth and body composition. Pediatr. Obes. 2012, 7, 304–312.
28. Savino, F.; Sorrenti, M.; Benetti, S.; Lupica, M.M.; Liguori, S.A.; Oggero, R. Resistin and leptin in breast milk and infants in early life. Early Hum. Dev. 2012, 88, 779–782.
29. Schueler, J.; Alexander, B.; Hart, A.M.; Austin, K.; Larson-Meyer, D.E. Presence and dynamics of leptin, GLP-1, and PYY in human breast milk at early postpartum. Obesity 2013, 21, 1451–1458.
30. Chang, J.C.; Chen, C.H.; Fang, L.J.; Tsai, C.R.; Chang, Y.C.; Wang, T.M. Influence of prolonged storage process, pasteurization, and heat treatment on biologically-active human milk proteins. Pediatr. Neonatol. 2013, 54, 360–366.

31. Ojeda, I.; Moreno-Guzmán, M.; González-Cortés, A.; Yáñez-Sedeño, P.; Pingarrón, J.M. A disposable electrochemical immunosensor for the determination of leptin in serum and breast milk. Analyst 2013, 138, 4284–4291.
32. Kon, I.Y.; Shilina, N.M.; Gmoshinskaya, M.V.; Ivanushkina, T.A. The study of breast milk IGF-1, leptin, ghrelin and adiponectin levels as possible reasons of high weight gain in breast-fed infants. Ann. Nutr. Metab. 2014, 65, 317–323.
33. Brunner, S.; Schmid, D.; Zang, K.; Much, D.; Knoeferl, B.; Kratzsch, J.; Amann-Gassner, U.; Bader, B.L.; Hauner, H. Breast milk leptin and adiponectin in relation to infant body composition up to 2 years. Pediatr. Obes. 2014, 10, 67–73.
34. Khodabakhshi, A.; Ghayour-Mobarhan, M.; Rooki, H.; Vakili, R.; Hashemy, S.I.; Mirhafez, S.R.; Shakeri, M.T.; Kashanifar, R.; Pourbafarani, R.; Mirzaei, H.; et al. Comparative measurement of ghrelin, leptin, adiponectin, EGF and IGF-1 in breast milk of mothers with overweight/obese and normal-weight infants. Eur. J. Clin. Nutr. 2015, 69, 614–618.
35. Cannon, A.M.; Kakulas, F.; Hepworth, A.R.; Lai, C.T.; Hartmann, P.E.; Geddes, D.T. The Effects of Leptin on Breastfeeding Behaviour. Int. J. Environ. Res. Public Health 2015, 12, 12340–12355.
36. Quinn, E.A.; Largado, F.; Borja, J.B.; Kuzawa, C.W. Maternal characteristics associated with milk leptin content in a sample of Filipino women and associations with infant weight for age. J. Hum. Lact. 2015, 31, 273–281.
37. Andreas, N.J.; Hyde, M.J.; Herbert, B.R.; Jeffries, S.; Santhakumaran, S.; Mandalia, S.; Holmes, E.; Modi, N. Impact of maternal BMI and sampling strategy on the concentration of leptin, insulin, ghrelin and resistin in breast milk across a single feed: A longitudinal cohort study. BMJ Open 2016, 6, e010778.
38. Gridneva, Z.; Kugananthan, S.; Hepworth, A.R.; Tie, W.J.; Lai, C.T.; Ward, L.C.; Hartmann, P.E.; Geddes, D.T. Effect of Human Milk Appetite Hormones, Macronutrients, and Infant Characteristics on Gastric Emptying and Breastfeeding Patterns of Term Fully Breastfed Infants. Nutrients 2016, 9, 15.
39. Kugananthan, S.; Lai, C.T.; Gridneva, Z.; Mark, P.J.; Geddes, D.T.; Kakulas, F. Leptin Levels Are Higher in Whole Compared to Skim Human Milk, Supporting a Cellular Contribution. Nutrients 2016, 8, 711.
40. De Luca, A.; Frasquet-Darrieux, M.; Gaud, M.A.; Christin, P.; Boquien, C.Y.; Millet, C.; Herviou, M.; Darmaun, D.; Robins, R.J.; Ingrand, P.; et al. Higher Leptin but Not Human Milk Macronutrient Concentration Distinguishes Normal-Weight from Obese Mothers at 1-Month Postpartum. PLoS ONE 2016, 11, e0168568.
41. Savino, F.; Sardo, A.; Rossi, L.; Benetti, S.; Savino, A.; Silvestro, L. Mother and Infant Body Mass Index, Breast Milk Leptin and Their Serum Leptin Values. Nutrients 2016, 8, 383.
42. Fields, D.A.; George, B.; Williams, M.; Whitaker, K.; Allison, D.B.; Teague, A.; Demerath, E.W. Associations between human breast milk hormones and adipocytokines and infant growth and body composition in the first 6 months of life. Pediatr. Obes. 2017, 12 (Suppl. 1), 78–85.
43. Meyer, D.M.; Brei, C.; Stecher, L.; Much, D.; Brunner, S.; Hauner, H. The relationship between breast milk leptin and adiponectin with child body composition from 3 to 5 years: A follow-up study. Pediatr. Obes. 2017, 12 (Suppl. 1), 125–129.
44. Quinn, E.A.; Childs, G. Ecological pressures and milk metabolic hormones of ethnic Tibetans living at different altitudes. Ann. Hum. Biol. 2017, 44, 34–45.
45. Nunes, M.; da Silva, C.H.; Bosa, V.L.; Bernardi, J.R.; Werlang, I.C.; Goldani, M.Z.; Group, N. Could a remarkable decrease in leptin and insulin levels from colostrum to mature milk contribute to early growth catch-up of SGA infants? BMC Pregnancy Childbirth 2017, 17, 410.
46. Cannon, A.M.; Gridneva, Z.; Hepworth, A.R.; Lai, C.T.; Tie, W.J.; Khan, S.; Hartmann, P.E.; Geddes, D.T. The relationship of human milk leptin and macronutrients with gastric emptying in term breastfed infants. Pediatr. Res. 2017, 82, 72–78.
47. Gridneva, Z.; Kugananthan, S.; Rea, A.; Lai, C.T.; Ward, L.C.; Murray, K.; Hartmann, P.E.; Geddes, D.T. Human Milk Adiponectin and Leptin and Infant Body Composition over the First 12 Months of Lactation. Nutrients 2018, 10, 1125.
48. Chan, D.; Goruk, S.; Becker, A.B.; Subbarao, P.; Mandhane, P.J.; Turvey, S.E.; Lefebvre, D.; Sears, M.R.; Field, C.J.; Azad, M.B. Adiponectin, leptin and insulin in breast milk: Associations with maternal characteristics and infant body composition in the first year of life. Int. J. Obes. 2005 2018, 42, 36–43.
49. Yu, X.; Rong, S.S.; Sun, X.; Ding, G.; Wan, W.; Zou, L.; Wu, S.; Li, M.; Wang, D. Associations of breast milk adiponectin, leptin, insulin and ghrelin with maternal characteristics and early infant growth: A longitudinal study. Br. J. Nutr. 2018, 120, 1380–1387.
50. Sadr Dadres, G.; Whitaker, K.M.; Haapala, J.L.; Foster, L.; Smith, K.D.; Teague, A.M.; Jacobs, D.R., Jr.; Kharbanda, E.O.; McGovern, P.M.; Schoenfuss, T.C.; et al. Relationship of Maternal Weight Status Before, During, and After Pregnancy with Breast Milk Hormone Concentrations. Obesity 2019, 27, 621–628.
51. Zamanillo, R.; Sánchez, J.; Serra, F.; Palou, A. Breast Milk Supply of MicroRNA Associated with Leptin and Adiponectin Is Affected by Maternal Overweight/Obesity and Influences Infancy BMI. Nutrients 2019, 11, 2589.
52. Logan, C.A.; Siziba, L.P.; Koenig, W.; Carr, P.; Brenner, H.; Rothenbacher, D.; Genuneit, J. Leptin in Human Milk and Child Body Mass Index: Results of the Ulm Birth Cohort Studies. Nutrients 2019, 11, 1883.
53. Larrosa Haro, A.; Vásquez-Garibay, E.M.; Guzmán-Mercado, E.; Muñoz Esparza, N.C.; García-Arellano, S.; Muñoz-Valle, J.F.; Romero-Velarde, E. Concentration of ghrelin and leptin in serum and human milk in nursing mothers according to the type of feeding. Nutr. Hosp. 2019, 36, 799–804.
54. Logan, C.A.; Koenig, W.; Rothenbacher, D.; Genuneit, J. Determinants of leptin in human breast milk: Results of the Ulm SPATZ Health Study. Int. J. Obes. 2005 2019, 43, 1174–1180.
55. Kocaadam, B.; Koksal, E.; Ozcan, K.E.; Turkyilmaz, C. Do the adiponectin and leptin levels in preterm and term breast milk samples relate to infants' short-term growth? J. Dev. Orig. Health Dis. 2019, 10, 253–258.
56. Schneider-Worthington, C.R.; Bahorski, J.S.; Fields, D.A.; Gower, B.A.; Fernandez, J.R.; Chandler-Laney, P.C. Associations among Maternal Adiposity, Insulin, and Adipokines in Circulation and Human Milk. J. Hum. Lact. 2020, 1.
57. Dal Bello, F.; Mecarelli, E.; Gastaldi, D.; Savino, F.; Medana, C. Nano-HPLC-HRMS Analysis to Evaluate Leptin Level in Milk Samples: A Pilot Study. Appl. Sci. 2020, 10, 6135.
58. Galante, L.; Lagström, H.; Vickers, M.H.; Reynolds, C.M.; Rautava, S.; Milan, A.M.; Cameron-Smith, D.; Pundir, S. Sexually Dimorphic Associations between Maternal Factors and Human Milk Hormonal Concentrations. Nutrients 2020, 12, 152.
59. Joung, K.E.; Martin, C.R.; Cherkerzian, S.; Kellogg, M.; Belfort, M.B. Human milk hormone intake in the first month of life and physical growth outcomes in preterm infants. J. Clin. Endocrinol. Metab. 2021, 106, 1793–1803.
60. Lihn, A.S.; Pedersen, S.B.; Richelsen, B. Adiponectin: Action, regulation and association to insulin sensitivity. Obes. Rev. 2005, 6, 13–21.
61. Çatlı, G.; Olgaç Dündar, N.; Dündar, B.N. Adipokines in breast milk: An update. J. Clin. Res. Pediatr. Endocrinol. 2014, 6, 192–201.
62. Nigro, E.; Scudiero, O.; Monaco, M.L.; Palmieri, A.; Mazzarella, G.; Costagliola, C.; Bianco, A.; Daniele, A. New insight into adiponectin role in obesity and obesity-related diseases. BioMed Res. Int. 2014, 2014, 658913.
63. Fields, D.A.; Schneider, C.R.; Pavela, G. A narrative review of the associations between six bioactive components in breast milk and infant adiposity. Obesity 2016, 24, 1213–1221.
64. Newburg, D.S.; Woo, J.G.; Morrow, A.L. Characteristics and potential functions of human milk adiponectin. J. Pediatr. 2010, 156, S41–S46.
65. Martin, L.J.; Woo, J.G.; Geraghty, S.R.; Altaye, M.; Davidson, B.S.; Banach, W.; Dolan, L.M.; Ruiz-Palacios, G.M.; Morrow, A.L. Adiponectin is present in human milk and is associated with maternal factors. Am. J. Clin. Nutr. 2006, 83, 1106–1111.
66. Woo, J.G.; Guerrero, M.L.; Altaye, M.; Ruiz-Palacios, G.M.; Martin, L.J.; Dubert-Ferrandon, A.; Newburg, D.S.; Morrow, A.L. Human milk adiponectin is associated with infant growth in two independent cohorts. Breastfeed. Med. Off. J. Acad. Breastfeed. Med. 2009, 4, 101–109.
67. van der Lely, A.J.; Tschop, M.; Heiman, M.L.; Ghigo, E. Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. Endocr. Rev. 2004, 25, 426–457.
68. Kojima, M.; Kangawa, K. Ghrelin: Structure and function. Physiol. Rev. 2005, 85, 495–522.
69. Dündar, N.O.; Dündar, B.; Cesur, G.; Yilmaz, N.; Sütçu, R.; Ozgüner, F. Ghrelin and adiponectin levels in colostrum, cord blood and maternal serum. Pediatr. Int. Off. J. Jpn. Pediatr. Soc. 2010, 52, 622–625.
70. Aydin, S.; Aydin, S.; Ozkan, Y.; Kumru, S. Ghrelin is present in human colostrum, transitional and mature milk. Peptides 2006, 27, 878–882.
71. Gronberg, M.; Tsolakis, A.V.; Magnusson, L.; Janson, E.T.; Saras, J. Distribution of obestatin and ghrelin in human tissues: Immunoreactive cells in the gastrointestinal tract, pancreas, and mammary glands. J. Histochem. Cytochem. 2008, 56, 793–801.
72. Kierson, J.A.; Dimatteo, D.M.; Locke, R.G.; Mackley, A.B.; Spear, M.L. Ghrelin and cholecystokinin in term and preterm human breast milk. Acta Paediatr. 2006,

95, 991–995.
73. Fu, Z.; Gilbert, E.R.; Liu, D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. Curr. Diabetes Rev. 2013, 9, 25–53.
74. Whitmore, T.J.; Trengove, N.J.; Graham, D.F.; Hartmann, P.E. Analysis of insulin in human breast milk in mothers with type 1 and type 2 diabetes mellitus. Int. J. Endocrinol. 2012, 2012, 296368.
75. Hassiotou, F.; Lai, C.; Filgueira, L.; Stuebe, A.; Hartmann, P.; Geddes, D. Mammary cells synthesize insulin during lactation (622.3). FASEB J. 2014, 28, 622–623.
76. Steppan, C.M.; Bailey, S.T.; Bhat, S.; Brown, E.J.; Banerjee, R.R.; Wright, C.M.; Patel, H.R.; Ahima, R.S.; Lazar, M.A. The hormone resistin links obesity to diabetes. Nature 2001, 409, 307–312.
77. Park, H.K.; Ahima, R.S. Resistin in rodents and humans. Diabetes Metab. J. 2013, 37, 404–414.
78. Yura, S.; Sagawa, N.; Itoh, H.; Kakui, K.; Nuamah, M.A.; Korita, D.; Takemura, M.; Fujii, S. Resistin is expressed in the human placenta. J. Clin. Endocrinol. Metab. 2003, 88, 1394–1397.
79. Ilcol, Y.O.; Hizli, Z.B.; Eroz, E. Resistin is present in human breast milk and it correlates with maternal hormonal status and serum level of C-reactive protein. Clin. Chem. Lab. Med. 2008, 46, 118–124.
80. Pemberton, C.; Wimalasena, P.; Yandle, T.; Soule, S.; Richards, M. C-terminal pro-ghrelin peptides are present in the human circulation. Biochem. Biophys. Res. Commun. 2003, 310, 567–573.
81. Zhang, J.V.; Ren, P.G.; Avsian-Kretchmer, O.; Luo, C.W.; Rauch, R.; Klein, C.; Hsueh, A.J. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. Science 2005, 310, 996–999.
82. Lacquaniti, A.; Donato, V.; Chirico, V.; Buemi, A.; Buemi, M. Obestatin: An interesting but controversial gut hormone. Ann. Nutr. Metab. 2011, 59, 193–199.
83. Mesmin, C.; Fenaille, F.; Becher, F.; Tabet, J.C.; Ezan, E. Identification and characterization of apelin peptides in bovine colostrum and milk by liquid chromatography-mass spectrometry. J. Proteome Res. 2011, 10, 5222–5231.
84. Tatemoto, K.; Hosoya, M.; Habata, Y.; Fujii, R.; Kakegawa, T.; Zou, M.X.; Kawamata, Y.; Fukusumi, S.; Hinuma, S.; Kitada, C.; et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochem. Biophys. Res. Commun. 1998, 251, 471–476.
85. Kleinz, M.J.; Davenport, A.P. Emerging roles of apelin in biology and medicine. Pharmacol. Ther. 2005, 107, 198–211.
86. Habata, Y.; Fujii, R.; Hosoya, M.; Fukusumi, S.; Kawamata, Y.; Hinuma, S.; Kitada, C.; Nishizawa, N.; Murosaki, S.; Kurokawa, T.; et al. Apelin, the natural ligand of the orphan receptor APJ, is abundantly secreted in the colostrum. Biochim. Biophys. Acta 1999, 1452, 25–35.
87. Wang, Z.; Greeley, G.H., Jr.; Qiu, S. Immunohistochemical localization of apelin in human normal breast and breast carcinoma. J. Mol. Histol. 2008, 39, 121–124.
88. Castan-Laurell, I.; Dray, C.; Attane, C.; Duparc, T.; Knauf, C.; Valet, P. Apelin, diabetes, and obesity. Endocrine 2011, 40, 1–9.

Keywords

leptin;adiponectin;ghrelin;insulin;obestatin;resistin;apelin;human milk;metabolic hormones