The Turkish Journal of Pediatrics 2022; 64: 239-245
https://doi.org/10.24953/turkjped.2021.1075

Original Article

The effect of breast milk nesfatin-1 and ghrelin levels on growth in infants with SGA

Berna Eroğlu Filibeli[1], Melike Karabulut Bayraktar[2], Saliha Aksun[3], Gönül Çatlı[4], Jülide Gülizar Yıldırım[5], Bumin Nuri Dündar[4]

[1]Divivion of Pediatric Endocrinology, [2]Department of Pediatrics, İzmir Medical Science University, Tepecik Training and Research Hospital, İzmir; Departments of [3]Biochemistry and [4]Pediatric Endocrinology, İzmir Katip Çelebi University Faculty of Medicine, İzmir; [5]Department of Public Health Nursing, İzmir Katip Çelebi University Faculty of Health Sciences, İzmir, Turkey.

ABSTRACT

Background. Current studies claim that peptides such as leptin, adiponectin, ghrelin, and nesfatin-1 found in breast milk may be responsible for the growth of infants. Therefore, we aimed to determine the association between breast milk total ghrelin and nesfatin-1 levels and anthropometric measurements of infants who were small for gestational age (SGA).

Methods. 20 SGA and 20 appropriate for gestational age (AGA) infants were enrolled in the study. Anthropometric measurements of infants were carried out at birth, 1st, and 4th months. In addition, total ghrelin and nesfatin-1 levels in the breast milk were concomitantly measured.

Results. Total ghrelin at the 4th month in breast milk waslower-level in the SGA group (p=0.015). In both groups, nesfatin-1 levels at the 4th month were lower than the values at the 1st month. Additionally, nesfatin-1 levels of SGA infants at the 4th month were higher (p=0.035).

Conclusions. Breast milk total ghrelin and nesfatin-1 levels differed in both groups, and it is probably referred to the growth discrepancy of these infants during the first months of life. Furthermore, we consider that higher breast milk nesfatin-1 levels at the 4th month may be a preventive against obesity in SGA infants who have potential risk for obesity in childhood and adulthood.

Key words: ghrelin, nesfatin-1, small for gestation age (SGA), appropriate for gestational age (AGA), breast milk.

The presence of many peptides such as leptin, ghrelin, adiponectin, obestatin, resistin, and nesfatin-1 has been shown in breast milk.[1] Ghrelin, leptin, and adiponectin molecules present in breast milk are effective in growing infants have also been reported.[2] Leptin hormone released from adipocytes plays a pivotal role in energy expenditure via the hypothalamus. In a previous study, leptin levels in small for gestational age (SGA) infants were found to be lower compared to appropriate for gestational age (AGA) and large for gestational age infants, and it has been suggested that this might contribute to faster growth of SGA infants.[3] As far as we know, it is the first research in the current literature regarding the relationship between breast milk ghrelin and nesfatin-1 levels and SGA infants' growth. Ghrelin is mainly synthesized from the stomach and is a growth hormone releaser that affects the hypothalamus-pituitary axis.[4] It exerts a stimulatory effect on food intake, and ghrelin cells have been found in the gastrointestinal tract.[5,6] It is related to the neuro-regulation of appetite, energy balance, and nutrient uptake.[7,8] Experimental studies have shown that ghrelin was found in the intestinal system, and it is associated with weight gain and calorie intake.[5,9] Ghrelin is also synthesized and released from breast tissue.[10] During the first four months of life, serum ghrelin levels of breastfed infants were higher

✉ Bumin Nuri Dündar
bumindundar@gmail.com

Received 30th April 2021, revised 18th July 2021, accepted 18th August 2021.

than formula-fed infants.[11] Cord blood ghrelin levels of SGA infants were significantly higher than AGA infants, and a negative correlation existed between anthropometric measurements and ghrelin levels in both groups.[12] A study has shown that serum ghrelin levels directly correlated with infants' age, weight, and height after the feeding period.[13]

Nesfatin-1 is also a peptide hormone with anorexigenic influences on the regulation of nutritional homeostasis.[14] In SGA infants, serum nesfatin-1 levels were higher than AGA infants, and a negative correlation had between serum nesfatin-1 levels and oral caloric intake.[15] Furthermore, nesfatin-1 has been detected in the breast milk of healthy and gestational diabetes mellitus women.[16] The role of nesfatin-1 levels in infant metabolism is not well-known.

This study aimed to investigate the relationship between breast milk total ghrelin (TGh) and nesfatin-1 levels and anthropometric measurements of SGA infants in the first four months of life.

Material and Methods

Twenty SGA and 20 AGA infants were included in the study. SGA and AGA were defined as a birth weight below the 10th percentile and birth weight between the 10th and 90th percentile for gestational age and gender, respectively.[17] Anthropometric measurements of all infants, including weight, supine length, head circumference, chest circumference, mid-arm circumference, triceps skinfold thickness, were performed by the same researcher at birth, 1st, and 4th months. Weight was measured using an electronic scale (±5 g, EBSC 20, NECK), and the supine length was measured by a standard baby measuring board (± 0.1 cm). Body mass index (BMI; kg/m^2) was calculated by dividing the weight by the square of height. Head circumference was measured using a narrow non-stretch tape, passing it around the head, placing it on the most anterior protuberance of the forehead and the most posterior protuberance of the head's back with the nearest 0.1 cm. Chest circumference and mid-arm circumference measurements were recorded to the nearest 0.1 cm, using a non-elastic, flexible measuring tape. Chest circumference was measured at the level of the nipple during expiration. Mid-arm circumference was measured at the mid-point between the tip of the acromion process and the right upper arm's olecranon process. Triceps skinfold thickness was measured from the left side of the body to the nearest 0.1 mm, at the midpoint between the acromion and olecranon protrusions on the arm's posterior centerline using a skinfold caliper.

Infants with congenital malformations, chromosomal abnormalities, intrauterine infections, or fed with formula or mix were excluded from the study. In addition, mothers with preeclampsia, gestational diabetes mellitus, medications, or multiple pregnancies and those who did not sign the informed consent were excluded. The mothers of the infants were non-obese healthy postpartum women, and were on no medication. Five milliliters of breast milk were taken at the 1st and 4th months. Samples were collected in glass tubes and stored at -80°C until TGh and nesfatin-1 levels were assayed.

The local ethics committee of Tepecik Training and Research Hospital for Interventional Clinical Studies approved the study (Date:09.02.2017, Number:21). Informed verbal and written consent was obtained from the parents. The study was conducted by the principles of the Declaration of Helsinki.

Assays

Breast milk TGh and nesfatin-1 were determined by enzyme-linked immunosorbent assay (ELISA). Nesfatin-1 levels were measured with Nesfatin-1 Phoenix kits ((1-82)/NUCB-2, Phoenix Pharmaceuticals, Inc., USA), and TGh levels were measured with Ghrelin Phoenix kits (Phoenix Pharmaceuticals, Inc., USA). Seven samples of standard materials with known concentrations for nesfatin-1 and ghrelin

molecules were studied with patient samples. The color intensity of all pieces in the plates was read as absorbance with the semi-automatic ELISA plate reader (Biotek, EL800, USA). Standard calibration curves were obtained by absorbance given by the standards. TGh and nesfatin-1 concentrations were calculated from the absorbance values in breast milk samples using standard calibration curves.

Statistical analysis

Statistical analysis was performed using SPSS, version 25 (SPSS, Chicago, IL, USA). Measured values were expressed as mean ± SD (minimum-maximum). The Kolmogorov-Smirnov test evaluated the normal distribution of the data. The Chi-square test was used to compare the nominal variables between the groups. Mann Whitney-U and Wilcoxon signed-rank tests were used for non-normally distributed variables. Compatibility for normal distribution of the numeric measurement by independent groups was analyzed using the independent sample t-test. Pearson correlation test was applied to calculate the correlation between breast milk TGh and nesfatin-1 levels and infants' anthropometric measurements. A $p< 0.05$ value was considered statistically significant.

Results

The SGA group's anthropometric measurements were lower than the AGA group at the birth and 1st month ($p<0.05$). In the 4th month, except for weight and chest circumference, the differences disappeared between the two groups ($p>0.05$) (Table I).

The increases in anthropometric measurements throughout four months were examined in all infants. There was no difference in the delta anthropometric measurements during the first month between SGA and AGA groups ($p>0.05$). However, in the fourth month, the increases in BMI, head circumference, chest circumference, mid-arm circumference, and triceps skinfold thickness were significantly higher in the SGA group ($p=0.003$, $p=0.006$, $p<0.001$, $p=0.007$, $p<0.001$).

Table I. SGA and AGA infants' anthropometric measurements at birth, 1st month and 4th month.

		Weight (g)	Body Mass index (kg/m²)	Head Circumference (cm)	Chest Circumference (cm)	Mid-arm Circumference (cm)	Triceps Skinfold Thickness (mm)
At birth	SGA (n=20)	345.25±177.65	10.6±0.17	33±0.29	28.9±0.33	5.1±0.16	5.1±0.16
	AGA (n=20)	3361.25±315.08	13.1±0.21	34.85±0.93	32.63±1.32	6.49±0.74	6.4±0.73
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
1st month	SGA (n=20)	3558±477.80	13.14±1.59	35.70±1.23	33.88±2.22	8.3±0.36	8.3±1.64
	AGA (n=20)	4607.50±471.04	14.67±1.18	37.3±1.09	37.07±1.47	9.5±0.28	9.55±1.28
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
4th month	SGA (n=20)	6255.50±679.80	16.34±2.12	40.43±0.96	40.35±1.66	11.61±1.87	11.6±1.23
	AGA (n=20)	7057±521.04	16.95±1.51	41±1.03	41.45±1.41	11.55±1.58	11.5±1.58
	p	**<0.001**	>0.05	>0.05	**<0.001**	>0.05	>0.05

SGA: Small for gestational age, AGA: Appropriate for gestational age. Values were expressed as mean ± standard deviation.

Table II. The concentrations of breast milk total ghrelin in SGA and AGA infants.

Total Ghrelin (pg/mL)	SGA (n=20)	AGA (n=20)	*p*
1st month	624.05±53.7	536.90±27.2	>0.05[a]
4th month	521.80±45.7	596.45±26.9	**0.015[a]**
p	>0.05[b]	>0.05[b]	

SGA: Small for gestational age, AGA: Appropriate for gestational age
[a]Mann Whitney-U test, [b]Wilcoxon signed-rank test

Table III. The concentrations of breast milk nesfatin-1 in SGA and AGA infants.

Nesfatin-1 (pg/mL)	SGA (n=20)	AGA (n=20)	*p*
1st month	447.4±86.5	375±35.4	>0.05[a]
4th month	305.2±30.3	267±122.2	**0.034[a]**
p	**0.006[b]**	**<0.001[b]**	

SGA: Small for gestational age, AGA: Appropriate for gestational age
[a]Mann Whitney-U test, [b]Wilcoxon signed-rank test

Table IV. Correlation between anthropometric measurements and breast milk nesfatin-1 level in the SGA group (n=20).

Anthropometric measurements	Nesfatin-1 at 1st month		Nesfatin-1 at 4th month	
	r	*p*	r	*p*
Weight(g)	-0.436	>0.05	-0.330	>0.05
Body Mass index (kg/m²)	-0.043	>0.05	0.115	>0.05
Head Circumference (cm)	-0.568	**0.009**	-0.265	>0.05
Chest Circumference (cm)	-0.428	>0.05	0.003	>0.05
Mid-arm Circumference (cm)	-0.425	>0.05	-0.144	>0.05
Triceps Skinfold Thickness (mm)	-0.210	>0.05	-0.263	>0.05

Table V. Correlation between anthropometric measurements and breast milk total ghrelin level in the SGA group (n=20).

Anthropometric measurements	Total ghrelin at 1st month		Total ghrelin at 4th month	
	r	*p*	r	*p*
Weight(g)	-0.189	>0.05	0.146	>0.05
Body Mass index (kg/m²)	-0.186	>0.05	0.222	>0.05
Head Circumference (cm)	-0.159	>0.05	-0.014	>0.05
Chest Circumference (cm)	-0.415	>0.05	0.069	>0.05
Mid-arm Circumference (cm)	0.291	>0.05	-0.04	>0.05
Triceps Skinfold Thickness (mm)	-0.305	>0.05	-0.223	>0.05

Breast milk TGh and nesfatin-1 levels were compared between SGA and AGA groups. There was no significant difference between the 1st and 4th-month breast milk TGh levels in both groups (p>0.05). While there was no difference between SGA and AGA groups in terms of the TGh levels at the 1st month, breast milk TGh levels at the 4th month were significantly higher in the AGA group (p=0.015) (Table II).

Breast milk nesfatin-1 levels at the 1st month were significantly higher than the 4th-month

levels in both groups (p=0.006, p<0.001). Breast milk nesfatin-1 levels at the 4th month were lower in the AGA group (p=0.034). Nevertheless, there were no differences in nesfatin-1 levels at 1st-month breast milk between groups (p>0.05) (Table III).

The relationship between anthropometric measurements of infants and breast milk TGh and nesfatin-1 levels was evaluated by Pearson correlation analysis. In the AGA group, there was no correlation between the anthropometric measurements of infants and breast milk TGh and nesfatin-1 levels (at 1st and 4th months) (p>0.05). While there was no correlation between anthropometric measurements of SGA infants and breast milk TGh levels, only head circumferences of SGA infants were negatively correlated with breast milk nesfatin-1 levels at the 1st month (r= -0.568, p= 0.009) (Table IV and Table V).

Discussion

SGA infants grow faster and show a different growth pattern than AGA infants in the postnatal period.[18,19] Similarly, in our study, SGA infants overgrew and showed catch-up growth in many anthropometric measurements at the 4th month.

Studies related to ghrelin's effect on infants' growth have conflicting results. In SGA infants, serum ghrelin levels were significantly higher than AGA infants.[20] In another study performed on term and preterm infants, plasma ghrelin was inversely correlated with birth weight and body length in the term infants.[21] On the other hand, increases in ghrelin levels in colostrum, transition, and mature milk suggest that ghrelin levels in breast milk might also be parallel to infant growth.[16] Cesur et al.[22] showed that 4th month-breast milk active ghrelin levels positively correlated with term infants' weight gain. In our study, 4th month-breast milk TGh levels were lower in the SGA groups. Because the anthropometric parameters of the SGA infants at four months caught up, this decrease might be explained with a protective step from rapid growth by reducing appetite and calorie intake. However, no correlation between infants' anthropometric measurements and breast milk TGh levels in both groups was determined. Additionally, breast milk TGh levels in the 4th month were lower than in the 1st month, although not statistically significant. This decrease might be related to an increase in active ghrelin levels, like previously reported.[22] However, active ghrelin levels could not be evaluated in our study. Active ghrelin in breast milk may have a more pronounced effect than TGh on the catch-up period.

Serum nesfatin-1 level was not different among preterm and term infants, but it was higher in SGA infants than in AGA infants.[15] Also, in the same study, it was reported that serum nesfatin-1 levels were high at birth but decreased in the first seven days and increased after seven days over again.[15] In the current study, we found that breast milk nesfatin-1 level significantly reduced during the first four months of life, both in AGA and SGA infants. However, the breast milk nesfatin-1 level at the 4th month was higher in the SGA group than in the AGA group. One of the important health benefits of breast milk is its protective effect against obesity.[23] As we know, early rapid weight gain in SGA infants is associated with increased obesity risk in later life.[24] We suggest that higher breast milk nesfatin-1 levels in SGA infants at four months might help prevent early rapid weight gain in SGA infants that grow fast but have an increased risk of obesity in later life.[25] Only head circumference measurements at 1st month were negatively correlated with breast milk nesfatin-1 levels at 1st month. However, this correlation did not exist in the 4th month, and it might be explained by the small number of cases. These results supported that nesfatin-1 may also play an essential role in the catch-up period.

The effects of breast milk peptides on the growth of infants may occur directly or indirectly. Peptides are broken down in the intestinal

system. It has been shown that some peptides in breast milk resist proteolytic degradation in the gastrointestinal tract during the infantile period due to low gastric proteolytic activity and high permeability of intestine mucosa.[23,26] A long isoform of the leptin receptor was found in the human small intestines' enterocytes.[27] Experimental results have revealed that the expression of ghrelin mRNA in lambs' stomach increased rapidly in the early period and slowed down in the later period, and there was a significant linear correlation between this change and stomach weight in lambs.[9] The effects of ghrelin on the intestinal tract have not been resolved clearly; however, the results suggest that it is closely related to appetite, weight gain, and energy metabolism. However, there is no evidence that breast milk nesfatin-1 can pass into the systemic circulation or preserve biological function or has a receptor in the intestinal system.

There were some limitations to our study. The follow-up period was limited to four months which was relatively short for evaluating catch-up growth. We could not measure breast milk active ghrelin levels or serum levels of TGh and nesfatin-1. Another limitation was the small number of cases in the AGA and SGA groups. We also aimed to record the duration and frequency of feeding infants with breast milk included in the study, but data could not be collected due to incomplete records.

In conclusion, breast milk ghrelin and nesfatin-1 may play an important role in SGA infants' growth, and their effects on infant metabolism remain an undiscovered and controversial issue. Therefore, we believe that nesfatin-1 and ghrelin levels in both serum and breast milk should be investigated with a larger study population to reach a final judgment. Also, long-term follow-up studies are needed to better understand the effects of breast milk ghrelin and nesfatin-1 on growth, especially in SGA infants.

Ethical approval

The ethics committee of Tepecik Training and Research Hospital for Interventional Clinical Studies approved the study (Date: 09.02.2017, Number: 21).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BND, GÇ; data collection: MK, BEF; data analysis and interpretation: MK, BEF, SA, JGY; drafting of manuscript: BEF, MK; critical review of manuscript: BND, GÇ. All authors approve and take responsibility for the final version of the manuscript.

Source of funding

This study was supported by a grant from the Growing Child Association.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Karatas Z, Durmus Aydogdu S, Dinleyici EC, Colak O, Dogruel N. Breastmilk ghrelin, leptin, and fat levels changing foremilk to hindmilk: is that important for self-control of feeding?. Eur J Pediatr 2011; 170: 1273-1280. https://doi.org/10.1007/s00431-011-1438-1
2. Çatlı G, Olgaç Dündar N, Dündar BN. Adipokines in breast milk: an update. J Clin Res Pediatr Endocrinol 2014; 6: 192-201. https://doi.org/10.4274/jcrpe.1531
3. Dundar NO, 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 2005; 18: 181-187. https://doi.org/10.1515/JPEM.2005.18.2.181
4. Colldén G, Tschöp MH, Müller TD. Therapeutic potential of targeting the ghrelin pathway. Int J Mol Sci 2017; 18: 798. https://doi.org/10.3390/ijms18040798

5. Blanco AM, Bertucci JI, Valenciano AI, Delgado MJ, Unniappan S. Ghrelin suppresses cholecystokinin (CCK), peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) in the intestine, and attenuates the anorectic effects of CCK, PYY and GLP-1 in goldfish (Carassius auratus). Horm Behav 2017; 93: 62-71. https://doi.org/10.1016/j.yhbeh.2017.05.004

6. Lin Y, Liang Z, He L, et al. Gut ghrelin regulates hepatic glucose production and insulin signaling via a gut-brain-liver pathway. Cell Commun Signal 2019; 17: 8. https://doi.org/10.1186/s12964-019-0321-y

7. Baldelli R, Bellone S, Broglio F, Ghigo E, Bona G. Ghrelin: a new hormone with endocrine and non-endocrine activities. Pediatr Endocrinol Rev 2004; 2: 8-14.

8. Savino F, Lupica MM, Liguori SA, Fissore MF, Silvestro L. Ghrelin and feeding behaviour in preterm infants. Early Hum Dev 2012; 88: 51-55. https://doi.org/10.1016/j.earlhumdev.2011.12.028

9. Wang W, Cheng L, Guo J, Ma Y, Li F. Expression of Ghrelin in gastrointestinal tract and the effect of early weaning on Ghrelin expression in lambs. Mol Biol Rep 2014; 41: 909-914. https://doi.org/10.1007/s11033-013-2935-2

10. Kierson JA, Dimatteo DM, Locke RG, Mackley AB, Spear ML. Ghrelin and cholecystokinin in term and preterm human breast milk. Acta Paediatr 2006; 95: 991-995. https://doi.org/10.1080/08035250600669769

11. Savino F, Fissore MF, Grassino EC, Nanni GE, Oggero R, Silvestro L. Ghrelin, leptin and IGF-I levels in breast-fed and formula-fed infants in the first years of life. Acta Paediatr 2005; 94: 531-537. https://doi.org/10.1111/j.1651-2227.2005.tb01934.x

12. Abdel Hakeem AH, Saed SZ, El Rehany MA, Yassin EE. Serum level of ghrelin in umbilical cord in small and appropriate for gestational age newborn infants and its relationship to anthropometric measures. J Clin Neonatol 2012; 1: 135-138. https://doi.org/10.4103/2249-4847.101694

13. Savino F, Grassino EC, Fissore MF, et al. Ghrelin, motilin, insulin concentration in healthy infants in the first months of life: relation to fasting time and anthropometry. Clin Endocrinol (Oxf) 2006; 65: 158-162. https://doi.org/10.1111/j.1365-2265.2006.02561.x

14. Dore R, Levata L, Lehnert H, Schulz C. Nesfatin-1: functions and physiology of a novel regulatory peptide. J Endocrinol 2017; 232: 45-65. https://doi.org/10.1530/JOE-16-0361

15. Cheng YY, Zhao XM, Cai BP, Ma LN, Yin JY, Song GY. Nesfatin-1 in newborns: relationship with endocrine and metabolic and anthropometric measures. J Pediatr Endocrinol Metab 2012; 25: 727-732. https://doi.org/10.1515/jpem-2012-0095

16. Aydin S. The presence of the peptides apelin, ghrelin and nesfatin-1 in the human breast milk, and the lowering of their levels in patients with gestational diabetes mellitus. Peptides 2010; 31: 2236-2240. https://doi.org/10.1016/j.peptides.2010.08.021

17. Lubchenco LO, Hansman C, Boyd E. Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. Pediatrics 1966; 37: 403-408. https://doi.org/10.1542/peds.37.3.403

18. Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. Pediatr Res 1995; 38: 733-739. https://doi.org/10.1203/00006450-199511000-00017

19. Campisi SC, Carbone SE, Zlotkin S. Catch-Up growth in full-term small for gestational age infants: a systematic review. Adv Nutr 2019; 10: 104-111. https://doi.org/10.1093/advances/nmy091

20. Farquhar J, Heiman M, Wong AC, Wach R, Chessex P, Chanoine JP. Elevated umbilical cord ghrelin concentrations in small for gestational age neonates. J Clin Endocrinol Metab 2003; 88: 4324-4327. https://doi.org/10.1210/jc.2003-030265

21. Ng PC, Lee CH, Lam CW, Chan IH, Wong E, Fok TF. Ghrelin in preterm and term newborns: relation to anthropometry, leptin and insulin. Clin Endocrinol (Oxf) 2005; 63: 217-222. https://doi.org/10.1111/j.1365-2265.2005.02328.x

22. Cesur G, Ozguner F, Yilmaz N, Dundar B. The relationship between ghrelin and adiponectin levels in breast milk and infant serum and growth of infants during early postnatal life. J Physiol Sci 2012; 62: 185-190. https://doi.org/10.1007/s12576-012-0193-z

23. Badillo-Suárez PA, Rodríguez-Cruz M, Nieves-Morales X. Impact of metabolic hormones secreted in human breast milk on nutritional programming in childhood obesity. J Mammary Gland Biol Neoplasia 2017; 22: 171-191. https://doi.org/10.1007/s10911-017-9382-y

24. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life--a systematic review. Obes Rev 2005; 6: 143-154. https://doi.org/10.1111/j.1467-789X.2005.00183.x

25. Hong YH, Chung S. Small for gestational age and obesity related comorbidities. Ann Pediatr Endocrinol Metab 2018; 23: 4-8. https://doi.org/10.6065/apem.2018.23.1.4

26. Baldi A, Ioannis P, Chiara P, Eleonora F, Roubini C, Vittorio D. Biological effects of milk proteins and their peptides with emphasis on those related to the gastrointestinal ecosystem. J Dairy Res 2005; 72: 66-72. https://doi.org/10.1017/S002202990500110X

27. Barrenetxe J, Villaro AC, Guembe L, et al. Distribution of the long leptin receptor isoform in brush border, basolateral membrane, and cytoplasm of enterocytes. Gut 2002; 50: 797-802. https://doi.org/10.1136/gut.50.6.797