Serum Level of Ghrelin in Umbilical Cord in Small and Appropriate for Gestational Age Newborn Infants and its Relationship to Anthropometric Measures

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ABSTRACT

Objective: To compare the cord blood ghrelin level in (SGA) infants with the level in appropriate for gestational age (AGA) infants, and determine its relationship to anthropometric measurements at delivery. **Materials and Methods:** Fifty newborn infants (30 SGA newborns and 20 AGA infants) were included in the study and were subjected to complete clinical examinations, anthropometric measurement, and ghrelin assays. **Results:** The cord blood ghrelin level in SGA infants was significantly higher than that in AGA infants. Cord ghrelin level correlated negatively with gestational age, weight, length, and body mass index in SGA group. **Conclusion:** Cord ghrelin concentration increased in SGA infants due to state of prolonged undernutrition the source of ghrelin unknown may be from the mother placenta or fetal tissues.

Key words:
Anthropometric measure, appropriate for gestational age, ghrelin, small for gestational age

INTRODUCTION

Ghrelin is a natural ligand for growth hormone (GH) secretagogue receptors and has potent GH-releasing activity in a dose-dependent manner.[1] Ghrelin has an important role in the short-term regulation of appetite and the long-term regulation of energy balance and glucose homeostasis.[2] These data suggest that ghrelin may be an important link between nutrition and growth. Ghrelin levels have been found to be elevated in patients with anorexia nervosa compared with those in healthy controls, and it is suggested that plasma ghrelin levels reflect acute and chronic energy balance in humans.[3] The presence of significant ghrelin concentrations in human cord blood has been shown, but there is no study evaluating cord blood ghrelin levels in intrauterine growth-restricted infants.[4]

MATERIALS AND METHODS

Fifty newborn infants born at Suzan University Hospital during the period of January 2009–November 2009 were enrolled in the study. The infants were divided into two groups:

Group A: Small for gestational age (SGA) infants consisted of 30 infants (16 females and 14 males); their gestational age ranged from 36 to 39 weeks and their weight ranged from 1 to 2.2 kg.

Group B: Appropriate for gestational age (AGA) infants included 20 infants (9 males and 11 females); their gestational age ranged from 38 to 41 weeks and their weight ranged from 3 to 3.6 kg.

Infants of both the groups underwent complete history taking. Complete medical examination including anthropometric measurements (weight, length, head circumference, chest circumference, mid-arm circumference, and body mass index (BMI)) was performed 6 h after birth.

Ghrelin assay

Ghrelin levels were measured by using a commercial enzyme-linked immunosorbent assay kit (Ghrelin Human EIA Kit, EK-031-30; Phoenix Pharmaceuticals, Inc., Belmont, CA, USA).

RESULTS

Table 1 shows that there were highly significant differences in anthropometric measurements between SGA and AGA groups, which were decreased in SGA. Table 2 shows that

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there was highly significant increase in ghrelin levels in SGA compared to AGA group. Table 3 shows that there was statistical negative correlation between all the studied anthropometric measurements and ghrelin level in SGA group. Table 4 shows that there was statistical negative correlation between all the studied anthropometric measurements and ghrelin level in AGA group. Figure 1 shows statistically significant inverse correlation between ghrelin level and birth weight of both SGA and AGA neonates (*P* value 0.0001, *r*=−0.675). Figure 2 shows that there was statistically significant inverse correlation between ghrelin level and BMI of SGA and AGA neonates (*P* value 0.0001, *r*=−0.493).

Table 1: Statistical comparative study of anthropometric measures between SGA and AGA

	SGA (*n*=30) Mean±SD	AGA (*n*=20) Mean±SD	*t*	*P*
Gestational age (weeks)	31.33±1.80	39.15±1.14	17.1	0.0001
Weight (kg)	1.69±0.46	3.28±0.21	15.7	0.0001
Length (cm)	39.96±3.07	50.2±0.89	14.4	0.0001
Head circumference (cm)	28.33±1.47	35.2±0.92	18.5	0.0001
Chest circumference (cm)	25.7±1.86	33.73±1.27	17.7	0.0001
Mid-arm circumference (cm)	5.6±0.86	10.92±0.76	22.4	0.0001
Body mass index (kg/m^2)	10.19±1.62	13.00±0.61	7.3	0.0001

Table 2: Statistical comparative study of ghrelin levels between SGA and AGA groups

	SGA (*n*=30) Mean±SD	AGA (*n*=20) Mean±SD	*t*	*P*
Ghrelin level (pg/ml)	8.18±1.00	4.37±0.50	19.05	0.0001

Table 3: Correlation between anthropometric measures and ghrelin level in SGA group

Anthropometric measures	r	*P*
Gestational age (weeks)	−0.55	0.002
Weight (kg)	−0.63	0.0001
Length (cm)	−0.61	0.07
Head circumference (cm)	−0.34	0.0001
Chest circumference (cm)	−0.34	0.06
Mid-arm circumference (cm)	−0.14	0.4
Body mass index (kg/m2)	−0.56	0.001

Table 4: Correlation between anthropometric measures and ghrelin level in AGA group

Anthropometrics measures	r	*P*
Gestational age (weeks)	−0.48	0.05
Weight (kg)	−0.59	0.6
Length (cm)	−0.37	0.7
Head circumference (cm)	−0.26	0.6
Chest circumference (cm)	−0.17	0.4
Mid-arm circumference (cm)	−0.12	0.2
Body mass index (kg/m2)	−0.47	0.7

Grades of r: 0.00–0.24 (weak or no association), 0.25–0.49 (fair association), 0.50–0.74 (moderate association), 0.75 and more (strong association)

DISCUSSION

Ghrelin has an important role in the short-term regulation of appetite and in the long-term regulation of energy balance and glucose homeostasis.[5] In this study, a group of 50 neonates were selected from Suzan Mubarak University Hospital; they were classified into two groups: Group A (SGA infants) included infants whose birth weight was below the 10th percentile according to the intrauterine growth charts.

This study shows there were highly significant differences in anthropometric measurements between SGA and AGA

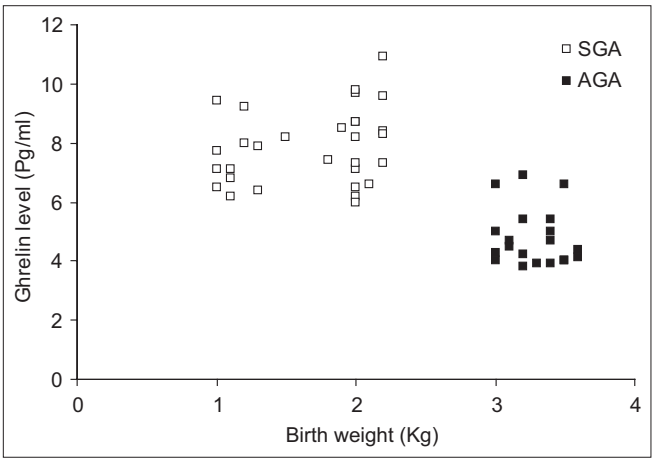

Figure 1: Correlation between ghrelin levels and weight in SGA and AGA newborns. Shows statistically significant inverse correlation between ghrelin level and birth weight of both SGA and AGA neonates (*P* value 0.0001, *r*=−0. 675)

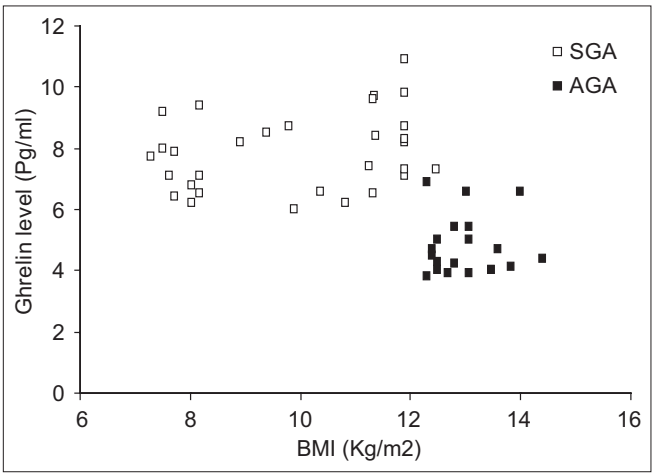

Figure 2: Correlation between ghrelin level and body mass index of SGA and AGA newborns, showing statistically significant inverse correlation between ghrelin level and body mass index of both SGA and AGA neonates (*P* value 0.0001, *r*=−0.493)

groups. Also, Table 2 shows that the level of ghrelin was highly statistically significantly increased in SGA group when compared to that in AGA group ($P<0.0001$). Our results are in agreement with the reports of Onal *et al.*[6] and Kitamura *et al.*[7] They reported that the cord blood ghrelin in SGA infants was significantly higher than that of AGA infants ($P=0·0001$). Also, Farquhar *et al.*[8] showed that ghrelin concentrations were 40% higher in SGA neonates compared to those in AGA neonates ($P<0.001$). Moreover, Cortelazzi *et al.*[9] studied the ghrelin levels during intrauterine life and reported that ghrelin levels in intrauterine growth restriction (IUGR) fetuses were significantly higher than those found in AGA fetuses ($P<0.005$). In this study, there was significant negative correlation between ghrelin levels in cord blood and both gestational age and weight of neonates, which confirm our results that ghrelin increases in SGA neonates. This was in agreement with the finding of Chanoine *et al.*[10] We found that the cord ghrelin levels in infants born by vaginal delivery were not different from those of infants born by Cesarean section and concluded that delivery mode did not affect the cord ghrelin levels. Our results are in agreement with the results of James *et al.*,[11] Soriano *et al.*,[12] and Chan *et al.*[13] The increased levels of circulating ghrelin after weight loss is consistent with a role of ghrelin in the long-term regulation of body weight in humans. In addition, Nakazato *et al.*[14] found that continuous administration of ghrelin increases the body weight, and besides increasing food intake, exogenous ghrelin decreases the metabolic rate and the catabolism of fat, thereby affecting all the aspects of the system of energy regulation in such a way as to increase the body weight. Shiiya *et al.*[15] and Haqq *et al.*[16] have also reported that plasma ghrelin concentrations negatively correlated with BMI in humans. Similarly, in our study, we found that cord ghrelin concentrations correlated with birth weight and BMI, which is consistent with the results of the previous studies. Birth weight is suggested to be a marker of adiposity in newborns. Additionally, body weight measurement is the easiest and the most reliable method among the anthropometric measurements to indicate the nutritional status of newborns, and birth weight is the most used marker indicating fetal neonatal growth. Several mechanisms may be responsible for the high ghrelin levels observed in IUGR fetuses. First, this pattern of secretion may be an additional component of the altered somatotrophic axis observed in growth-restricted fetuses. Indeed, the plasma GH levels in cord blood were higher in IUGR fetuses than in normal fetuses and negatively correlated with birth weight, probably as a result of the reduced Insulin-like growth factor 1 (IGF-1) levels present in this pathological condition.[17,18] Therefore, it is likely that low IGF-I associated with IUGR may induce ghrelin overproduction, although the feedback mechanisms regulating ghrelin secretion are still poorly understood. Alternatively, the increased levels of ghrelin observed in IUGR fetuses may be related to the role of this peptide in energy balance. Also, Horvath *et al.*[19] found that ghrelin appears to be negatively correlated with BMI, body fat mass, and leptin levels .These data indicate that IUGR is associated with several hormonal changes that, although not strictly correlated, include the increase in ghrelin levels as well as the previously reported changes in GH and leptin. The source of ghrelin on cord plasma is unknown. It may originate from the maternal compartment, or may be secreted by the placenta into the fetal circulation, or may come directly from fetal tissues. In rats, Gualillo *et al.*[20] found that ghrelin mRNA in the stomach, regarded as the main source of ghrelin, is not affected by pregnancy. A placental source of ghrelin cannot be ruled out. However, in humans, although ghrelin mRNA is detectable in both first trimester and term placenta by reverse-transcription polymerase chain reaction, the peptide is detected only in the first trimester placenta, but not at term by immunocytochemistry. Ghrelin levels are produced by the fetus is indicated by the lack of difference between arterial and venous concentration as well as by the evidence that ghrelin is almost absent in the placenta during the third trimester.[21] Bellone *et al.*[22] showed that ghrelin secretion increases from delivery to 4th day of life and progressive increase in the circulating total ghrelin levels in the days after birth has been demonstrated. Feeding does not exert its well-known inhibitory effect on the circulating total ghrelin levels. It had already been demonstrated that food intake inhibits morning ghrelin secretion in adults, but not in prepubertal children. This ghrelin refractoriness to food intake from birth to childhood would therefore suggest that this hormone plays a role as an anabolic drive in the phase of growth and development.

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REFERENCES

1. Kojima, M, Kangawa K. Ghrelin: Structure and function. Physiol Rev 2005;85:495-522.
2. Tritos NA,Kokkotou EG. The physiology and potential clinical applications of ghrelin, a novel peptide hormone. Mayo Clin Proc 2006;81:653-60.
3. Kojima M. The discovery of ghrelin – A personal memory. Regul Pept 2008;145:2-6.
4. Kojima M, Kangawa K, Murakami N, Mondal MS, Date Y, Nakazato M, *et al*. Ghrelin in neonatal rats: Distribution in stomach and its possible role. J Endocrinol 2002;173:239-45.
5. Zou CC, Hung K, Liang K, Zhao ZY. Polymorphism of the ghrelin/obestatin gene and ghrelin leveles in Chinese children with short stature. Clin Endocrionl (Oxf) 2008;69:99-104.

6. Onal EE, Cinaz P, Atalay Y, Turkyilmaz C, Bideci A, Akturk A, *et al.* Umbilical cord ghrelin concentrations in small-and appropriate-for-gestational age newborn infants: Relationship to anthropometric markers. J Endocrinol 2004;180:267-71.
7. Kitamura S, Yokota I, Hosoda H, Kotani Y, Matsuda J, Naito E, *et al.* Ghrelin concentration in cord and neonatal blood: Relation to fetal growth and energy balance. J Clin Endocrinol Metab 2003;88:5473-7.
8. 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;88:4324-7.
9. Cortelazzi D, Cappiello V, Morpurgo PS, Ronzoni S, Nobile De Santis MS, Cetin I, *et al.* A Circulating levels of ghrelin in human fetuses. Eur J Endocrinol 2003;149:111-6.
10. Chanoine JP, Yeung LP, Wong AC, Birmingham CL. Immunoreactive Ghrelin in Human Cord Blood: Relation to anthropometry, leptin, and growth hormone. J Pediatr Gastroenterol Nutr 2002;35:282-6.
11. James RJ, Drewett RF, Cheetham TD. Low cord ghrelin levels in term infants are associated with slow weight gain over the first 3 months of life. J Clin Endocrinol Metab 2004;89:3847-50.
12. Soriano-Guillen L, Barrios V, Chowen JA, Sanchez I, Vila S, Quero J, *et al.* Ghrelin levels from fetal life through early adulthood: Relationship with endocrine and metabolic and anthropometric measures. J Pediatr 2004;144:30-5.
13. Chan JL, Bullen J, Lee JH, Yiannakouris N, Mantzoros CS. Ghrelin levels are not regulated by recombinant leptin administration and/or three days of fasting in healthy subjects. J Clin Endocrinol Metab 2004;89:335-43.
14. Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, *et al.* A role for ghrelin in the central regulation of feeding. Nature 2001;409:194-8.
15. Shiiya T, Nakazato M, Mizuta M, Date Y, Mondal MS, Tanaka M,*et al.* Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. J Clin Endocrinol Metab 2002;87:240-4.
16. Haqq AM, Farooqi IS, O'Rahilly S, Stadler DD, Rosenfeld RG, Pratt KL,*et al*. Serum ghrelin levels are inversely correlated with body mass index, age, and insulin concentrations in normal children and are markedly increased in Prader–Willi syndrome. J Clin Endocrinol Metab 2003;88:174-8.
17. Arosio M, Cortelazzi D, Persani L, Palmieri E, Casati G, Baggiani AM. Circulating levels of growth hormone, insulin-like growth factor-I and prolactin in normal, growth retarded and anencephalic human fetuses. J Endocrinol Invest 1995;18:346-53.
18. Gluckman PD, Pinal CS. Maternal-placental-fetal interactions in the endocrine regulation of fetal growth: Role of somatotrophic axes. Endocrine 2002;19:81-9.
19. Horvath TL, Diano S, Sotonyi P, Heiman M, Tschop M. Minireview: Ghrelin and the regulation of energy balance – a hypothalamic perspective. Endocrinology 2001;142:4163-9.
20. Gualillo O, Caminos J, Blanco M, Garcìa-Caballero T, Kojima M, Kangawa K, *et al*. A novel placental derived hormone. Endocrinology 2001;142:788-94.
21. Cortelazzi D, Cappiello V, Morpurgo PS, Ronzoni S, Nobile De Santis MS, Cetin I, *et al.* Circulating levels of ghrelin in human fetuses. Eur J Endocrinol 2003;149:111-6.
22. Bellone S, Baldelli R, Radetti G, Rapa A, Vivenza D, Petri A, *et al.* Ghrelin Secretion in Preterm Neonates Progressively Increases and Is Refractory to the Inhibitory Effect of Food Intake. J Clin Endocrinol Metab 2006;91:1929-33.

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