

Effect of Low Birthweight on Serum Thyroid Hormones, Glucose, Urea and Blood pH in Newborn Lambs

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Abstract: In this study, serum thyroid hormone, glucose and urea levels as well as blood pH values were compared between six control (birthweight ≥ 2.5 kg) and seven experimental Merino lambs (birthweight < 2.5 kg, hypotrophic) at 2, 4, 8 and 24 h postpartum. Serum levels of total thyroxin (T_4), free thyroxin (FT_4), total triiodothyronine (T_3 ; with exception of 24 h postpartum), free triiodothyronine (FT_3 ; with the exception of 4, 8 and 24 h postpartum) and glucose were lower in hypotrophic lambs compared to the controls. However, the serum urea levels of hypotrophic animals were higher than those of the controls. On the other hand, serum T_3 , FT_3 and FT_4 levels determined at 4 and 8 h were higher than those at 2 and 24 h postpartum in both groups. A similar case was also observed in the serum T_4 levels of hypotrophic lambs. In addition, the serum glucose levels of hypotrophic lambs were higher and the blood pH values of both groups were lower at 2 h postpartum. In conclusion, It was observed that low birthweight affected neonatal thyroid function, serum glucose and urea levels in lambs.

Key Words: Thyroid hormone, glucose, urea, blood pH, lamb

Yeni Doğan Kuzularda Düşük Doğum Ağırlığının Serum Tiroit Hormonları, Glikoz, Üre ve Kan pH'sı Üzerindeki Etkisi

Özet: Bu çalışmada, altı kontrol (doğum ağırlığı ≥ 2.5 kg) ve yedi düşük doğum ağırlığına sahip (doğum ağırlığı < 2.5 kg, hipotrofik) merinos kuzuda, doğumdan sonraki 2., 4., 8. ve 24. saatlerde serum tiroit hormonları, glikoz ve üre düzeyleri ile kan pH'sı değerleri karşılaştırıldı. Deneme periyodu boyunca, hipotrofik hayvanların serum total tiroksin (T_4), serbest tiroksin (FT_4), total triiyodotironin (T_3 ; 24.saatteki değeri hariç), serbest triiyodotironin (FT_3 ; 4., 8. ve 24. saatlerdeki değeri hariç) ve glikoz düzeyleri kontrol kuzuları ile karşılaştırıldığında daha düşük miktarlardaydı. Hipotrofik kuzuların serum üre düzeyleri ise kontrol hayvanların aynı değerinden daha yüksekti. Diğer yandan, her iki grupta doğumdan sonraki 4. ve 8. saatlerde belirlenen serum T_3 , FT_3 ve FT_4 düzeyleri, 2. ve 24. saatlerdeki aynı değerler ile karşılaştırıldığında artmış bulundu. Hipotrofik kuzuların serum T_4 düzeyinde de benzer bir görünüm vardı. İlave olarak, diğer örnekleme zamanlarına göre doğumdan sonraki 2. saatte, hipotrofik kuzuların serum glikoz düzeyleri daha yüksek, her iki grubun kan pH'sı değerleri daha düşüktü. Sonuç olarak, düşük doğum ağırlığının kuzularda neonatal tiroit fonksiyonunu, serum glikoz ve üre düzeylerini etkilediği gözlemlendi.

Anahtar Sözcükler: Tiroit hormonları, glikoz, üre, kan pH'sı, kuzu

Introduction

It has been noted that there is a sudden rise in serum thyroid hormone concentrations immediately after birth in livestock (1). The high level of thyroid hormones found in calves is not surprising, since thyrotropin is suddenly released upon exposure to a cold environment and this increases total thyroxin (T_4) level and that the peripheral deiodination of T_4 to total triiodothyronine (T_3) is extremely high in the early postnatal period (2). Neonatal changes in plasma total iodothyronine levels have been also studied in lambs. The major feature observed is the large increase in plasma T_3 levels during the first hours of

life occurring with (3) or without (4,5) a rise in plasma T_4 levels.

It was found that the plasma levels of T_4 and T_3 were influenced by different extrinsic and intrinsic factors and one of the most important factors were plasma binding proteins that carry thyroid hormones to target cells (6). These thyroid hormone binding proteins associate with T_4 and/or T_3 , with varying affinities and capacities in different species (7). Davison et al. (8) have emphasised that an important factor that affects binding characteristics is hydrogen ion concentration in the blood. Rudas et al. (9) have reported that high hydrogen ion

concentrations increased the binding of thyroid hormones.

On the other hand, the thyroid gland maintains the level of metabolism in the tissues that is optimal for their normal function. Thus, thyroid hormones influence certain blood metabolites, such as glucose and urea (10). These hormones also affect growth and maturation in mammals (11), and depressed plasma thyroid hormone levels have been reported in low birthweight infants during the first days of life (12). In addition, positive relationships have been observed between birthweight and plasma T_3 and/or T_4 levels in newborn rats (13) and lambs (4,5).

Theriez et al. (14) and Houssin and Brelurut (15) showed that the mortality rate dramatically rose in newborn lambs when the birthweight was lower than 2.5 kg. In addition, suckling could affect plasma thyroid hormone levels in mammals (16,17). However the origin, duration and clinical significance of thyroid hormone deficiency related to low birthweight are not well understood.

In order to gather information on the above topics we studied the changes in serum thyroid hormone levels in control and low birthweight (hypotrophic) lambs during the first 24 h of life. In addition, serum glucose, urea and blood pH levels were monitored to determine neonatal changes.

Materials and Methods

The experiment was conducted with 13 newborn Merino ram lambs born spontaneously between 148 and 152 days of gestation. The animals were obtained from the Animal Research Institute in Konya, Turkey. Guiding principles in the care and use of animals were observed. Two groups were formed: the control ($n = 6$; birthweight ≥ 2.5 kg; mean birth weight 2.77 ± 0.20 kg; length of gestation, 150.17 ± 0.60 days) and experimental lambs [hypotrophic; $n = 7$; birthweight < 2.5 kg; mean birth weight 1.97 ± 0.13 kg ($P < 0.05$ with controls); length of gestation, 149.57 ± 0.57 days ($P > 0.05$ with controls)]. All animals were removed from their ewes and received limited amounts of a bovine colostrum pool (2.5 g / 100 g birthweight, 4, 8, 12, 16, 20 and 24 h postpartum).

Blood samples were taken from the jugular vein 2, 4, 8 and 24 h after birth and collected anaerobically in plastic syringes. Blood was transferred to a test tube with no anticoagulant to obtain serum. The serum samples were immediately frozen at -20 °C until analysis. In addition, blood samples were collected from the jugular vein, avoiding contact with air for blood pH measurement.

Blood pH was determined by using a digital pH meter (Orion Research Model, SA210) within 5 min after sampling. Serum T_4 , T_3 , FT_4 and FT_3 concentrations were determined by using the radioimmunoassay method as previously described by Anderson et al. (18). Glucose and urea levels were measured on a clinical chemistry analyser (Gilford Impact 400E, Gilford Systems, OH).

Data for the parameters in the study were grouped and expressed as mean \pm pooled standard errors of means. All data in the same groups of lambs were subjected to analysis of variance, if appropriate ($P < 0.05$); post hoc analysis was carried out using the Duncan's test for multiple comparisons, whereas Student's t-test was used to assess differences between the two groups of lambs. Statements of statistical significance are based on $P < 0.05$ (19).

Results

As shown in Table 1, the serum T_3 , FT_3 and FT_4 levels of the lambs rose significantly at 4 and 8 h postpartum compared to their concentrations at 2 h postpartum. Thereafter, these values significantly decreased after 24 h in both groups ($P < 0.05$). In addition, the serum T_4 level of the hypotrophic lambs showed a similar trend ($P < 0.05$), but increased serum T_4 levels at 4 h were not statistically significant compared to the same parameter at 2 h ($P > 0.05$), and it did not change significantly in the controls during the study ($P > 0.05$). The values of the T_3/FT_4 ratio were unaffected in both groups ($P > 0.05$).

The serum glucose levels of hypotrophic lambs decreased significantly after 2 h of life when compared to those at 4, 8 and 24 h ($P < 0.05$), although the same value remained constant during the experimental period in the controls ($P > 0.05$). Serum urea levels were not significantly different during the first 24 h of life in both groups ($P > 0.05$). In addition, blood pH levels were found to increase at 4, 8 and 24 h when compared to

Table 1. The levels of serum total thyroxin (T_4), total triiodothyronine (T_3), free thyroxin (FT_4), free triiodothyronine (FT_3) and T_3/FT_4 ratio in newborn control (n = 6) and hypotrophic (n = 7) lambs.

Age (hours)	Groups	T_4 ($\mu\text{g/dl}$)	T_3 (ng/dl)	FT_4 (ng/dl)	FT_3 (ng/dl)	T_3/FT_4 ratio
2 h	Control	10.68 \pm 0.43	218.47 \pm 4.05 ^b	2.11 \pm 0.14 ^b	0.55 \pm 0.05 ^b	105.26 \pm 5.63
4 h		9.86 \pm 0.57	254.49 \pm 7.18 ^a	3.08 \pm 0.17 ^a	0.72 \pm 0.05 ^a	84.14 \pm 5.61
8 h		9.41 \pm 0.39	248.76 \pm 3.28 ^a	2.98 \pm 0.27 ^a	0.70 \pm 0.05 ^a	87.07 \pm 8.00
24 h		8.93 \pm 0.63	206.24 \pm 3.43 ^b	2.20 \pm 0.16 ^b	0.46 \pm 0.04 ^b	96.18 \pm 7.25
2 h	Hypotrophic	5.24 \pm 0.34 ^{b*}	179.57 \pm 8.37 ^{b*}	1.55 \pm 0.10 ^{b*}	0.38 \pm 0.04 ^{b*}	117.76 \pm 9.84
4 h		6.86 \pm 0.62 ^{ab*}	216.80 \pm 9.22 ^{a*}	1.98 \pm 0.09 ^{a*}	0.60 \pm 0.05 ^a	110.49 \pm 7.93
8 h		7.12 \pm 0.65 ^{a*}	219.34 \pm 5.12 ^{a*}	2.00 \pm 0.12 ^{a*}	0.62 \pm 0.08 ^a	111.41 \pm 8.63
24 h		5.18 \pm 0.68 ^{b*}	190.40 \pm 8.66 ^b	1.59 \pm 0.44 ^{b*}	0.42 \pm 0.03 ^b	120.54 \pm 15.31

* Values in same ages within columns are significantly different between control and hypotrophic lambs ($P < 0.05$), according to Student's t-test.

^{a, b} Values in each groups as individuals within columns with no common superscripts are significantly different ($P < 0.05$), according to ANOVA and Duncan's multiple range tests.

Age (hours)	Groups	Glucose (mg/dl)	Urea (mg/dl)	Blood pH
2 h	Control	43.23 \pm 1.35	25.40 \pm 1.74	7.34 \pm 0.020 ^b
4 h		48.82 \pm 1.37	25.13 \pm 2.05	7.39 \pm 0.011 ^a
8 h		51.49 \pm 1.97	26.35 \pm 1.87	7.41 \pm 0.013 ^a
24 h		50.45 \pm 2.72	27.82 \pm 1.25	7.44 \pm 0.010 ^a
2 h	Hypotrophic	39.09 \pm 0.61 ^{a*}	32.14 \pm 1.24 [*]	7.28 \pm 0.025 ^b
4 h		32.54 \pm 0.91 ^{b*}	32.16 \pm 1.35 [*]	7.36 \pm 0.024 ^a
8 h		30.43 \pm 0.84 ^{b*}	33.17 \pm 0.71 [*]	7.40 \pm 0.018 ^a
24 h		30.10 \pm 0.92 ^{b*}	34.94 \pm 0.70 [*]	7.42 \pm 0.008 ^a

* Values in same ages within columns are significantly different between control and hypotrophic lambs ($P < 0.05$), according to Student's t-test.

^{a, b} Values in each groups as individuals within columns with no common superscripts are significantly different ($P < 0.05$), according to ANOVA and Duncan's multiple range tests.

Table 2. The levels of serum glucose, urea and blood pH in newborn control (n = 6) and hypotrophic (n = 7) lambs.

their levels at 2 h ($P < 0.05$) in the controls and hypotrophic animals (Table 2).

As seen in Tables 1 and 2, during the entire period studied the serum levels of T_4 and FT_4 were depressed in hypotrophic lambs ($P < 0.05$). The same was true for serum levels of T_3 and FT_3 with the exception of 24 h postpartum for T_3 and 4, 8 and 24 h postpartum for FT_3 . On the other hand, serum glucose levels were lower and serum urea concentrations were higher in hypotrophic animals than in controls ($P < 0.05$). However, there was no significant difference in blood pH and the values of the T_3/FT_4 ratio between control and hypotrophic lambs ($P > 0.05$).

Discussion

It has been reported that four factors, at least, may contribute to immediate postnatal hyperiodothyroninemia such as abrupt depletion of the preformed foetal hormonal iodine stores, preferential T_3 secretion, increases in T_4 to T_3 monodeiodination in the peripheral tissues and a release of thyroid hormone content from peripheral reservoirs to plasma. In addition, the course of postnatal hyperiodothyroninemia was dependent on the maturation level reached at birth, food intake, and cooling relative to extrauterine environment. For these reasons, increased serum thyroid hormone levels of newborn lambs, calves and piglets have been emphasised

(1). In agreement with these data, serum thyroid hormone levels were generally found to be higher in our lambs, especially in the controls, according to the normal values noted for adult sheep (18).

In the study, the lambs were removed from the ewes and bottle-fed with small amounts of the same colostrum in both groups to obtain the same conditions for the lambs, because food intake and suckling affect serum thyroid hormone levels (16,17). Lower milk ingestion was observed in hypotrophic animals (20). Thus, neonatal changes in the serum thyroid hormones of controls recorded in the present experiment were similar to those observed in food-restricted lambs in some previous works (20,21), showing that during the first 4 to 8 h of life, plasma T_3 , FT_3 and FT_4 rose, whereas plasma T_4 did not change, and then plasma T_4 , T_3 , FT_4 and FT_3 decreased from 8 to 16 h postpartum. On the other hand, it was found that at birth, plasma glucose levels were low and remained constant until 36 h postpartum (20), as observed in this study. However, in another experiment, the plasma glucose concentrations of restricted lambs were found to decrease between 8 and 16 h postpartum and remain very low until 36 h postpartum (21). Furthermore, the same investigators (20,21) reported that plasma urea levels were high at birth and increased sharply during the first 36 h of life; however, increases of serum urea concentrations in the present experiment were not significant.

In hypotrophic lambs, serum T_4 , T_3 , FT_4 and FT_3 levels increased at 4 and 8 h of life, with exception of 4 h for T_4 , and then they decreased at 24 h postpartum. In addition, the serum levels of T_4 and FT_4 were markedly depressed in hypotrophic lambs during the first 24 h of life when compared to those in the controls, and the same was true for serum levels of T_3 (except 24 h postpartum) and FT_3 (except 4, 8 and 24 h postpartum). Similar observations have been reported for newborn low birthweight infants (12,22). In contrast to the results reported in human newborns (23), the T_3/FT_4 ratio values were not altered by hypotrophy, and this may indicate that the condition did not affect peripheral T_4 to T_3 conversion. Similar observations and suggestions in lambs were also reported by Wrutniak and Cabello (20).

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During the experimental period, serum glucose levels were lower in hypotrophic lambs than in the controls, and the same parameter was lower 4, 8 and 24 h postpartum compared to its value at 2 h postpartum in hypotrophic animals. This could be partly explained by depressed food digestibility (24) and probably by higher energy needs linked to a greater sensitivity to neonatal cooling as observed by Alexander (25). The serum urea levels of hypotrophic lambs were found to increase compared to the controls and they did not change during the study. The rise in serum urea levels might be due to the increased utilisation of aminoacids for neoglucogenesis in view of the importance of hypoglycaemia and such a regulation occurs from foetal life (26). In brief, the hypoglycaemia and hyperuraemia observed at birth in those animals argue in favour of the occurrence of foetal undernutrition, probably induced by placental insufficiency due to a large litter size gestation.

Although there were no significant differences between control and hypotrophic animals in blood pH, these values of the lambs in both groups were low at 2 h of life, they rose progressively until 24 h postpartum, and there was a significant difference in blood pH at 2 h when compared to the same values at 4, 8 and 24 h postpartum in the present experiment. Our report agrees with others showing that blood pH was very low immediately after birth, probably due to the birth stress and due to a metabolic compensation of the acid-base balance, and its value returns to normal physiological levels in lambs (27) and calves (9). Similarly, it has been found that blood pH values were low at birth, rose progressively until 16 h and did not change thereafter in newborn lambs (28). In addition, Keçeci (29) has also declared that blood pH increased gradually at 1, 24 and 72 h postpartum in newborn lambs, whereas the serum T_4 level decreased over time.

In conclusion, the data show that neonatal differences during the first 24 h of life occurred in serum T_4 , T_3 , FT_4 , FT_3 , glucose, urea and blood pH in newborn lambs which had a restricted diet with normal birthweight and low birthweight. It is emphasised that there were significant differences in T_4 , T_3 , FT_4 , FT_3 , glucose and urea levels between the two groups.

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