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## BASIC ANATOMICAL-PHYSIOLOGICAL DIFFERENCES BETWEEN DONKEYS AND HORSES

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**Abstract:** The most well-known representatives of true ungulates (*Euungulata*) in our region belong to fairly heterogeneous families within the order of ungulates. Within this order, there is only one genus (*Equus*), which includes two species: the donkey (*Equus asinus*) and the horse (*Equus caballus*). At first glance, the morphological appearance of these two species is almost identical. However, many individuals (including people in the field) consider them to be merely two very closely related animals. In phylogenetic terms, they do share the same lineage, but it should be emphasized that during the evolutionary process a significant divergence has occurred between them. Therefore, it can be said that, despite their phenotypic similarity, the donkey and the horse represent distinct species.

The aim of this paper is precisely to highlight certain anatomical, physiological, and biochemical differences that exist between the donkey and the horse.

**Keywords:** anatomical, biochemical, differences, donkey, horse, physiological

## INTRODUCTION

Within the group of true ungulates (*Euungulata*), the most well-known representatives in our region belong to the rather heterogeneous family of the order Perissodactyla. Today, only one genus exists within this order, the genus *Equus*. The best-known representatives are the donkey (*Equus asinus*) and the horse (*Equus caballus*). The morphological appearance of these two species, both domestic and wild, shows many similarities. Many experts, as well as those less familiar with the field, consider them to be very closely related animals. In a distant phylogenetic sense, this is true; however, during a long evolutionary process, significant divergence occurred, so today they are phenotypically similar but nevertheless distinct animals.

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The domestic donkey originates from the African wild donkey (*Equus asinus africanus*), from the territory of northeastern Africa. Historically, three types of wild donkeys existed on the African continent: the Nubian, the Somali, and the donkey from the Atlas mountain massif. It has been conclusively established that the Atlas wild donkey has become extinct (Urošević et al., 2022). Whether the Nubian wild donkey still exists has not been reliably determined; it most likely became extinct, as it was last observed in the wild during the 1930s.

The domestication process of the wild donkey, and the emergence of the domestic donkey, were long and are still not fully understood. It is believed that this process began between 8,000 and 11,000 years ago (Trailović et al., 2021). The prevailing opinion is that the sole ancestor of the domestic donkey was the Nubian wild donkey (Kimura et al., 2011). However, when the phenotypic characteristics of the domestic donkey are compared with those of the wild donkey, certain inconsistencies and ambiguities arise, particularly regarding the presence of transverse leg stripes. The Nubian wild donkey lacks such stripes, whereas they are present in the Somali wild donkey. In addition to this difference, the Nubian donkey has a “cross” on its back, while the Somali wild donkey does not.

Unlike the domestic donkey, the domestic horse originates from ancestors from Central Asia (Adžić, 2015), most likely in regions corresponding to present-day southern Russia and parts of ancient Persia. The domestication of the horse was a longer process, generally considered to have been completed slightly more than 6,000 years ago.

An analysis of domestication areas clearly indicates that donkeys experienced a considerably harsher transition from wild to domestic forms. Among domestic donkeys, it is not uncommon to see individuals with transverse stripes on the legs and a “cross” on the back. There are also those that lack the “cross” but have stripes. This considerably complicates acceptance of a monophyletic origin of the domestic donkey. Ivanković et al. (2023) suggest that the Nubian (*Equus africanus africanus*) and Somali (*Equus africanus somaliensis*) wild donkeys interbred in the past. Adžić (2015) states that all domestic donkeys originate from both the Somali and Nubian wild donkeys.

Extremely harsh, arid climatic conditions within the natural range of wild donkeys led, over a long evolutionary process, to the modification and shaping of organic systems that enable survival in such severe natural conditions. Unlike donkeys, the ancestors of horses did not live under such harsh climatic conditions and therefore did not undergo significant changes and adaptations like donkeys did.

Unlike most other domestic animals, which have undergone certain selective breeding interventions, the donkey is the only domestic animal for which no organized selection has been carried out for centuries. They were and continue to be primarily working animals. In recent years, due to the increasing demand for donkey milk, selective measures have begun to be undertaken with the aim of increasing milk yield in female donkeys.

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## MATERIALS AND METHODS

In order to present the basic anatomical and physiological differences between the horse and the donkey, several methods were combined. Data related to horses were obtained from available literature. In the case of donkeys and mules, data on their morphological characteristics were collected through field observations conducted under natural conditions, as well as from available literature sources.

Over a ten-year period, different donkey populations were observed in all Balkan countries, while mules were observed in North Macedonia. During this research, a recognized method was applied (Pavlović et al., 1973), namely the photographic documentation of individual animals or specific body parts.

For the study and identification of visual differences in the appearance of the esophagus, a secondary product of slaughter, a confiscate obtained as a result of commercial slaughter, was used.

## DIFFERENCES

Differences between the donkey and the horse can be classified as anatomical, physiological, and biochemical. The most fundamental distinction concerns the number of chromosomes: the donkey possesses 62 chromosomes, whereas the horse has 64.

Herman (2009) points out that the greatest number of differences is observed in the region of the head and neck. These include differences in the lacrimal apparatus, cervical musculature, nasal cavity, pharynx, salivary glands, paranasal sinuses, dentition, as well as venous and arterial structures.

Most of these anatomical differences are not externally visible in the live animal and can only be reliably identified through anatomical dissection. In contrast, a number of morphological differences can be recognized through visual observation and comparative assessment of overall body conformation.

Physiological and biochemical differences are not externally visible, and their detection requires appropriate laboratory analyses.

In a comprehensive analysis and comparative presentation of donkeys and horses, Wissdorf et al. (2020) classified them into 15 main categories

### a) Anatomical differences

At first glance, in donkeys with dark-colored coats, a marked difference can be observed in the facial markings on the muzzle, which are absent in horses. The posterior part of the nostrils, sometimes even the entire distal half of the muzzle, as well as the corresponding part of the lower jaw, are light-colored (white). In addition, a more or less pronounced light-colored ring is present around the eyes.

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**Figure 1** Clearly visible white markings (donkey in Anatolia - original photograph, Urošević).



**Figure 2** Dorsal cross and zebroid leg stripes in a donkey in Anatolia (original photograph, Urošević).

It should be emphasized that black-coated donkeys do not exhibit these white markings. Furthermore, it is widely known that some donkeys display a “cross,” that is, two intersecting lines at the level of the withers. One pigmented line, in various shades of chestnut, runs along the spinal column, while the other extends from one shoulder, across the withers, to the opposite shoulder. In addition to this dorsal “cross,” the presence of transverse dark stripes on the limbs is also of interest. It was previously believed that donkeys with a dorsal cross did not exhibit such “zebroid” leg stripes, whereas those without a cross did. However, this assumption has not been confirmed in practice, as shown in the following photograph.

It should be noted that such combinations are also observed in donkeys in our region. Interestingly, these transverse limb stripes are also present in hybrids, namely mules. When a donkey displaying such transverse leg stripes mates with a mare, the resulting offspring is a sterile hybrid, the mule. The limbs of mules show these same transverse stripes, which are absent in horses, indicating that this trait is inherited from the donkey sire.

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**Figure 3** Mule in North Macedonia showing clearly visible transverse stripes on the forelimbs and less pronounced stripes on the hind limbs (original photograph, Urošević).

A highly significant difference is also observed in dentition, particularly with respect to the timing of eruption of both deciduous and permanent teeth. Differences in the eruption times of deciduous teeth, including incisors and premolars, in donkeys and horses are presented in the following table.

**Table 1** Eruption times of deciduous teeth (Wissdorf et al., 2020)

ANIMAL SPECIES	DONKEY	HORSE
<b>Tooth</b>	<b>Eruption time</b>	<b>Eruption time</b>
<b>I<sub>1</sub></b>	It is present at birth or appears within the first two weeks after birth.	At 5-8 days after foaling
<b>I<sub>2</sub></b>	At 40 days, with a range of 9 to 60 days	At 5-8 weeks
<b>I<sub>3</sub></b>	At 9 months, with a range of 6 to 14 months	Approximately at 5-9 months

**Table 2** Eruption times of deciduous premolars (Wissdorf et al., 2020)

ANIMAL SPECIES/TOOTH	DONKEY	HORSE
<b>Eruption time</b>		
<b>P<sub>1</sub></b>	Does not erupt	Does not erupt
<b>P<sub>2</sub>-P<sub>4</sub></b>	Present at shedding or appear within the first few days after shedding	Present at shedding or appear within the first few days after shedding

Deciduous canines are not present in the deciduous dentition. Regarding the replacement of deciduous teeth with permanent teeth, it can be noted that in donkeys this process occurs approximately three months later than in horses.

**Table 3** Replacement of deciduous incisors with permanent incisors (Wissdorf et al., 2020)

ANIMAL SPECIES/TOOTH	DONKEY	HORSE
<b>Eruption time</b>		
I <sub>1</sub>	From 2 years and 9 months to 3 years and 9 months	From 2 and a half to 3 years old
I <sub>2</sub>	From 3 years and 9 months to 4 years and 3 months	From 3 and a half to 4 years old
I <sub>3</sub>	From 4 years and 9 months to 5 and a half years	From 4 and a half to 5 years old

The appearance of a “star” on the occlusal surface of the lower incisor is shown in the following table.

**Table 4** Appearance of the star-shaped occlusal surface on lower incisors (Wissdorf et al., 2020)

ANIMAL SPECIES/TOOTH	DONKEY	HORSE
<b>Time of appearance</b>		
I <sub>1</sub>	At 3 and a half to 4 years old	From 6 years of age, often later as well
I <sub>2</sub>	At 4 to 4 and a half years old	From 8 years of age, often later as well
I <sub>3</sub>	At 5 and a half to 7 years old	From 10 years of age, often later as well

Interestingly, the “canines” in donkeys erupt between 4 years and 3 months and 5 years of age, while in horses, they appear somewhat earlier, between 4 and 5 years. In donkeys, the replacement of premolars occurs later than in horses.

**Table 5** Eruption of premolars (Wissdorf et al., 2020)

ANIMAL SPECIES/TOOTH	DONKEY	HORSE
<b>Eruption time</b>		
P <sub>1</sub>	At 3-4 months, in 90% of cases in the upper jaw and up to 50% in the lower jaw	10-15% svih konja mjenjaju sa 5-9 meseci života. U gornjoj vilici mužjaci duplo brže nego kobile
P <sub>2</sub>	From 2 years and 9 months to 3 years old	At around 2 and a half years old
P <sub>3</sub>	From 2 years and 9 months to 3 years old	At around 2 and a half to 3 years old

P <sub>4</sub>	From 3 years and 9 months to 4 years old	At around 3 and a half years old
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As is the case with premolars, the same applies to molars. In donkeys, they erupt later than in horses.

**Table 6** Eruption of molars (Wissdorf et al., 2020)

ANIMAL SPECIES/TOOTH	DONKEY	HORSE
<b>Eruption time</b>		
<b>M<sub>1</sub></b>	At 12 months	At 6-9 months old
<b>M<sub>2</sub></b>	At 2 years and 3 months old	At around 2 years old
<b>M<sub>3</sub></b>	At 3 years and 9 months old	At around 4 years old

Thus, when determining the age of donkeys based on the type and timing of eruption of individual teeth, the rules applied to horses cannot be used. These differences are relatively easy to observe. There are also numerous differences in the tongue and pharynx, which will not be addressed here. Significant differences exist in the digestive tract of donkeys and horses, primarily in the length and capacity of its various parts. Sveček et al. (1984) reported that the length of the small intestine in horses ranges from 25 m to 39 m, of which 75% corresponds to the small intestine and 25% to the large intestine. Dmitriev et al. (1981) reported that the stomach capacity of a horse is 15-20 liters.

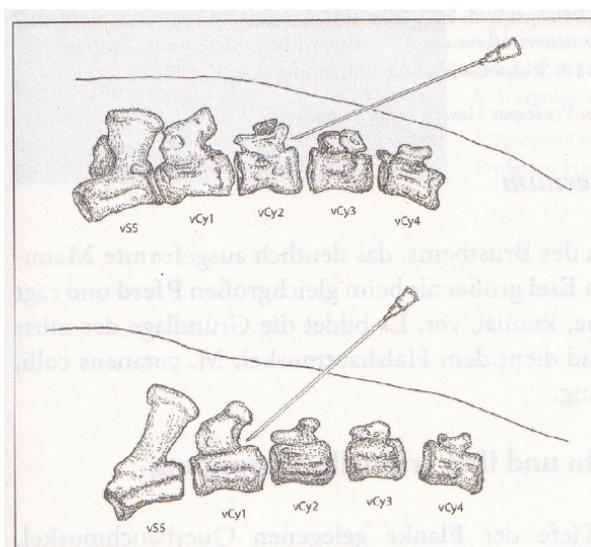
Regarding donkeys, Smith and Wood (2008) note that the length of the intestines in donkeys is approximately 24 meters, and the total capacity of the digestive tract is around 160 liters. Of this, the stomach accounts for about 9% of the total, the small intestine about 30%, the cecum about 16%, the colon about 38%, and the rectum about 7%.

Studying the digestive tract of domestic donkeys, Urošević et al. (2025) found, in a sample of 9 male individuals, that the maximum length of the jejunum was 8.37 m, while the ileum reached a maximum length of 8.68 m. They observed considerable variability in the length of the small intestines. The average length was 9.52 m, with a minimum of 7.12 m and a maximum of 13.05 m. Thus, the difference in the length of the small intestines of donkeys was 5.93 m, which can be physiologically justified. As a monogastric animal, donkeys are capable of digesting a significantly higher level of cellulose in the diet compared to horses. For the digestion of cellulose fibers, the small intestine is not important; this function is carried out by the large intestine and cecum. The authors found that the length of the cecum ranged from 65.0 to 88.0 cm.

The large intestine has a relatively large diameter. In this study, the mean width of the ventral colon was 12.67 cm, while the dorsal colon had an average diameter of 15.75 cm. The total length of the ventral and dorsal colon ranged from 1.76 m to 2.30 m.

One anatomically significant feature for veterinary practice is the number of vertebrae. Donkeys have 17-19 thoracic vertebrae. It was observed that when there are 17 thoracic vertebrae, there are normally 5 lumbar vertebrae, and even when there are 19 thoracic vertebrae, the number of lumbar vertebrae remains 5.

The number of caudal (tail) vertebrae also differs. In horses, the number of caudal vertebrae ranges from 15-21, while in donkeys it is 15-17 (Wissdorf et al., 2020). Regarding epidural anesthesia, in donkeys the anesthetic is administered between the 2nd and 3rd caudal vertebra at an angle of 30°. In horses, the epidural anesthetic is administered between the 1st and 2nd caudal vertebra at an angle of 45°.



**Figure 4** Administration of anesthetic for achieving epidural anesthesia: donkey (upper view) and horse (lower view) (Wissdorf et al., 2020)

There is another very interesting difference between donkeys and horses. In approximately 30% of donkeys, the inner volume of the upper part of the esophagus is blackly pigmented (Smith & Wood, 2008). Analyzing the esophagi of 17 male and 3 female individuals, it was found that only 4 individuals did not have pigmentation at the beginning of the esophageal mucosa, and in one individual, which has not been reported in the available literature, the entire esophageal mucosa was blackly pigmented.



**Figure 5.** Typical pigmentation of the esophageal mucosa in a donkey (Original photo, Urošević)



**Figure 6** Completely pigmented esophageal mucosa (Original photo, Ćupić Miladinović)

In the available literature, there are no reports of the complete pigmentation of the esophageal mucosa, making this, to the best of our knowledge, the first publication of such a finding.

In a study on the histological and histochemical composition of the donkey esophagus, Abood et al. (2023) describe the microscopic structure of the donkey esophagus and note a peculiarity in the form of variable pigmentation in different parts of the esophagus. However, no analyses of this pigment were performed. Whether it is melanin or another substance remains an open question. This raises further questions: why does melanin, or another pigment, accumulate in the esophageal mucosa of donkeys? Could this be due to a previously undefined migration and aggregation of melanocytes in the esophageal mucosa? Alternatively, it may result from unresolved irritation of the esophageal mucosa, leading to the accumulation of melanocytes.

Additionally, there is a significant difference in hoof structure. In donkeys, the hoof is longer than in horses and has a cylindrical shape. The horn of the donkey's hoof is harder and denser compared to that of the horse (Hafner, 2013).

### b) Physiological and biochemical differences

Characteristic differences occur in the triad, body temperature, pulse, and respiratory rate.

**Table 7** Comparative values of the triad in adult donkeys, horses, and juveniles (Wissdorf et al., 2020)

ANIMAL SPECIES	TEMPERATURE (°C)	HEART RATE/MIN.	RESPIRATION/MIN.
<b>Donkey</b>	37.1 (36.2-37.8)	44 (30-68)	20 (12-44)
<b>Donkey foal</b>	37.6 (36.2-38.9)	60 (40-80)	28 (16-48)
<b>Horse</b>	37.7 (37.5-38.0)	38 (28-48)	13 (8-18)
<b>Foal</b>	38.1 (37.8-38.5)	In the first days of life: 60-100. Later, from 3-12 months: 45-75	In the first days of life: 30 (20-40)

Based on the data from the previous table, the differences are clearly visible. Significantly greater differences occur during the exercise of these animals. Knežević, Jurković, and Trailović (2013) investigated the effects of physical exercise on the body of the domestic mountain horse and the Balkan donkey.

**Table 8** Results of triad examination in horses and donkeys before, during specific exercise phases, and after exercise (Knežević, Jurković, and Trailović, 2013)

ANIMAL SPECIES	EXERCISE TEST	TEMPERATURE	HEART RATE (min.)	RESPIRATION (min.)
<b>Horses (X±SD)</b>	<i>Before the test</i>	37.62 ± 0.15	43.67 ± 7.97	13.17 ± 5.60
	<i>1st check</i>	38.27 ± 0.21	75.33 ± 30.19	20.83 ± 10.59
	<i>2nd check</i>	38.95 ± 0.36	80.67 ± 39.55	25.67 ± 10.25
	<i>3rd check</i>	38.72 ± 0.53	65.33 ± 10.01	29.17 ± 9.33
	<i>4th check</i>	38.45 ± 0.57	67.50 ± 26.32	23.67 ± 11.50
<b>Donkeys (X±SD)</b>	<i>Before the test</i>	36.70 ± 0.57	49.00 ± 4.24	28.00 ± 0.00
	<i>1st check</i>	37.65 ± 0.35	58.00 ± 2.83	32.00 ± 0.00
	<i>2nd check</i>	37.85 ± 0.21	52.00 ± 5.66	34.00 ± 2.83
	<i>3rd check</i>	37.3 ± 0.21	42.00 ± 2.83	30.00 ± 2.83
	<i>4th check</i>	37.60 ± 0.28	50.00 ± 2.83	32.00 ± 0.00

The authors also conducted an examination of hematological parameters before, during specific exercise phases, and after exercise.

**Table 9** Results of testing hematological factors in horses before, at various stages of exercise, and after exercise test (Knežević, Jurković, and Trailović, 2013)

ANIMAL SPECIES / PARAMETERS	HORSES (X±SD)			
	Before the test	1st check	2nd check	4th check
<b>Leukocytes (x 10<sup>9</sup>/L)</b>	9.22 ± 0.79	10.43 ± 1.67	10.86 ± 1.03	12.21 ± 2.49
<b>Lymphocytes (x 10<sup>9</sup>/L)</b>	2.00 ± 0.27	2.89 ± 1.03	2.48 ± 0.57	2.97 ± 1.03
<b>MID (%)</b>	0.48 ± 0.33	0.49 ± 0.33	0.42 ± 0.27	0.67 ± 0.19
<b>Gran. (x 10<sup>9</sup>/L)</b>	6.72 ± 0.65	7.08 ± 0.94	7.88 ± 1.07	8.58 ± 1.84
<b>Eryth. (x 10<sup>12</sup>/L)</b>	6.23 ± 1.03	7.11 ± 0.82	7.39 ± 1.02	7.69 ± 0.97
<b>Hgb. (g/L)</b>	98.83 ± 12.30	113.33 ± 5.61	117.33 ± 10.69	121.67 ± 9.03

<b>HCT (l/L)</b>	32.64 ± 3.05	34.46 ± 1.42	37.51 ± 2.25	38.12 ± 2.31
<b>MCV (fl)</b>	53.17 ± 3.92	51.83 ± 3.87	51.50 ± 4.18	49.83 ± 3.76
<b>MCH (pg)</b>	16.00 ± 0.75	16.05 ± 1.19	15.95 ± 0.84	15.90 ± 1.04
<b>MCHC (g/L)</b>	303.17 ± 11.79	310.83 ± 9.91	311.83 ± 12.67	318.85 ± 8.88
<b>Platelets (x 10<sup>9</sup>/L)</b>	199.83 ± 43.27	211.33 ± 24.52	215.50 ± 34.71	194.17 ± 52.80
<b>MPV (fL)</b>	7.78 ± 0.22	7.93 ± 0.19	8.12 ± 0.31	8.13 ± 0.35

**Table 10** Results of testing hematological factors in donkeys before, at various stages of exercise, and after exercise test (Knežević, Jurković, and Trailović, 2013)

<b>ANIMAL SPECIES / PARAMETERS</b>	<b>DONKEYS (X±SD)</b>			
	<b>Before the test</b>	<b>1st check</b>	<b>2nd check</b>	<b>4th check</b>
<b>Leukocytes (x 10<sup>9</sup>/L)</b>	15.85 ± 1.50	17.91 ± 0.62	18.54 ± 1.72	18.65 ± 1.23
<b>Lymphocytes (x 10<sup>9</sup>/L)</b>	4.57 ± 0.35	6.80 ± 2.23	8.14 ± 0.73	5.16 ± 1.95
<b>MID (%)</b>	0.45 ± 0.65	0.09 ± 0.01	0.46 ± 0.64	0.11 ± 0.01
<b>Gran. (x 10<sup>9</sup>/L)</b>	10.83 ± 1.99	11.02 ± 1.75	9.94 ± 0.74	13.38 ± 2.56
<b>Eryth. (x 10<sup>12</sup>/L)</b>	6.43 ± 0.28	6.73 ± 0.25	6.99 ± 0.142	6.63 ± 0.32
<b>Hgb. (g/L)</b>	109.00 ± 3.00	114.33 ± 4.51	117.33 ± 6.81	114.33 ± 4.93
<b>HCT (l/L)</b>	35.85 ± 0.62	36.97 ± 1.84	38.12 ± 2.47	35.86 ± 2.22
<b>MCV (fl)</b>	55.67 ± 3.06	55.00 ± 2.00	54.33 ± 5.52	54.33 ± 1.13
<b>MCH (pg)</b>	16.93 ± 0.29	16.80 ± 0.63	16.77 ± 0.64	16.93 ± 0.55
<b>MCHC (g/L)</b>	302.67 ± 12.06	305.67 ± 1.53	307.67 ± 1.13	311.67 ± 2.08
<b>Platelets (x 10<sup>9</sup>/L)</b>	357.00 ± 21.63	358.00 ± 22.34	341.33 ± 39.27	256.50 ± 84.15
<b>MPV (fL)</b>	7.17 ± 0.21	7.27 ± 0.32	7.37 ± 0.23	7.33 ± 0.06

It is interesting to observe how the values of biochemical parameters changed in horses and donkeys during this same test.

**Table 11** Results of testing biochemical parameters in horses and donkeys before, at various stages of exercise, and after exercise test (Knežević, Jurković, and Trailović, 2013)

ANIMAL SPECIES / PARAMETERS	HORSES AND DONKEYS (X±SD)				
	Before the test	1st check	2nd check	4th check	
Total proteins (g/L)	Horses	58.17 ± 27.39	68.50 ± 9.77	59.83 ± 10.17	69.83 ± 10.07
	Donkeys	64.00 ± 2.83	61.50 ± 4.95	57.00 ± 12.73	58.00 ± 12.73
Albumins (g/L)	Horses	24.50 ± 2.51	24.67 ± 1.97	25.33 ± 2.42	25.67 ± 2.25
	Donkeys	24.70 ± 3.25	21.80 ± 5.94	25.40 ± 0.57	24.65 ± 2.26
Urea (mmol/L)	Horses	5.35 ± 0.95	5.18 ± 0.66	5.48 ± 0.93	6.42 ± 0.99
	Donkeys	7.45 ± 2.47	10.00 ± 0.00	10.80 ± 0.85	9.95 ± 0.49
Creatinine (µmol/L)	Horses	49.83 ± 25.60	49.33 ± 14.40	55.17 ± 16.67	61.50 ± 16.99
	Donkeys	100.00 ± 16.97	116.00 ± 8.49	101.50 ± 24.04	101.00 ± 24.04
CK (U/L)	Horses	352.50 ± 49.38	358.00 ± 60.65	378.00 ± 67.96	474.00 ± 210.96
	Donkeys	-	-	-	-
AST (U/L)	Horses	295.00 ± 44.53	301.50 ± 49.17	312.00 ± 50.69	338.83 ± 77.20
	Donkeys	181.50 ± 61.52	161.00 ± 111.72	213.00 ± 74.95	215.50 ± 119.50
LDH (U/L)	Horses	739.17 ± 94.85	740.50 ± 89.23	738.83 ± 109.83	838.83 ± 154.59
	Donkeys	888.50 ± 471.64	466.00 ± 46.67	593.00 ± 202.23	475.00 ± 144.25

### CONCLUSION

Based on the above, the following conclusions can be drawn:

- Morphologically, horses and donkeys appear to be identical animals.
- Although they are phenotypically similar, differences do exist between them.
- These differences can be classified as anatomical and physiological-biochemical.
- Regarding anatomical differences, the majority are found in the head and neck region (differences in the lacrimal apparatus, neck musculature, nasal cavity, pharynx, salivary glands, paranasal sinuses, teeth, veins, and arteries).
- As for physiological-biochemical differences, they are primarily reflected in body temperature, pulse, and respiratory rate.

**Conflict of interest statement:** The authors declare that there is no conflict of interest.

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