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Original article

Effect of *ad libitum* feeding of Holstein Friesian calves on immunological parameters and molecular stress on a transcriptional level

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ABSTRACT

Our aim was to compare the health and performance of *ad libitum* (ADLIB) and restrictedly fed Holstein Friesian heifer calves. Calves were selected to ADLIB (n = 13) and control (n = 13) groups randomly. The period of ADLIB feeding lasted for 3 weeks after colostrum supplementation. The calves in the control group received the same milk replacer, which was supplied according to the restrained feeding schedule of the farm. There was no difference between the two groups in weight, weight gain or movement activity, furthermore in the values of glucose, albumin, total protein, BHB, AST, oxidant and antioxidant status incl. dROM, PAT and OSI. The *IL8* gene had higher levels (non significant, $p > 0.05$) of expression in the ADLIB group during the first 20 days of life, which indicates that ADLIB feeding might potentiate a stronger immune response to environmental stress. The *IGF1* gene showed increased expression in the ADLIB fed group at almost all time points, however the difference was already detected on the first day of the study, indicating the importance of individual differences even within the same breed. During the first 10 days *INS* expression was higher in the restricted group, followed by a shift by day 20 and after, when the ADLIB group showed a higher relative expression level. The observed values describe a trend that, although not significant ($p > 0.05$), would seem to indicate that ADLIB feeding might potentiate a stronger immune response to environmental stress.

1. Introduction

Dairy industry is facing a relatively high mortality rate among calves during the neonatal period and the young age (Jorgensen et al., 2017). Diseases of the respiratory and digestive systems are the most common causes of calf mortality. Changes in housing conditions, feeding regime and management provide a chance for improvement for these problems (Rosa et al., 2018).

Different feeding strategies of calves before weaning combine a set of factors such as the time intervals between feeds (*ad libitum*, restricted once a day, restricted every 3 h), the composition and amount of feed (milk, waste milk, excess colostrum, and milk replacers with diverse compositions and supplements) the timing and amount of colostrum feeding as well as the schedule of the initial introduction process of solid feed, and last but not least the timing of weaning (McCoard et al., 2019).

Several studies have addressed *ad libitum* (ADLIB) milk drinking, which has its advantages from the point of view of animal welfare. As a result, calves drink more milk and gain more weight faster (Appleby et al., 2001; Jasper and Weary, 2002). In addition, increasing the intensity of feeding in the postnatal period can affect the animal in both the long and short term. Relevant research has referred to this as 'nutritional programming' or 'developmental programming' or 'metabolic imprinting' (Guilloteau et al., 2009; Kaske

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et al., 2010); it has a lasting effect on the release of neuropeptides produced by the hypothalamus, which are responsible for feed intake, furthermore long-term weight gain as result of the flexibility of the regulatory system (Taylor and Poston, 2007).

It is recognised that calves benefit from natural suckling compared to artificial feeding, by attaining superior passive immune status (Surlis et al., 2018).

Other results from transcriptome analysis of the *jejunum* of differentially fed German Holstein calves revealed that the most distinct difference was much lower activation of the immune system of restrictedly fed Holsteins compared to their ADLIB fed offsprings (Hammon et al., 2018). The fact that differential feeding influences immune functions in agriculturally important domesticated animals as cattle (Crookenden et al., 2020), goat (Chang et al., 2015; Liu et al., 2019) and sheep (Chang et al., 2015; Tsiplakou et al., 2018; Zhang et al., 2018; Sun et al., 2019) is reflected in many publications.

The aim of the present work was to perform a comparison study on immunological parameters and molecular stress on transcriptional level between the health and performance of ADLIB and restrictedly fed Holstein Friesian heifer calves in Hungary.

2. Materials and methods

2.1. Animals and feeding

All animal treatments and samplings were in accordance with the ethical permission of the Government Office in Pest County, Budapest, Hungary (permit no.: PE/EA/1076–5/2020).

The study was performed at a large-scale Hungarian Holstein Friesian dairy farm in summer 2019, keeping around 1000 cows and their offspring.

According to the technology applied, the calves were separated from their mothers immediately after birth and placed in individual hutches (Agrobox-1, Agroplast Kft., Gyál, Hungary), where they stayed until weaning (60 days). Newborn heifer calves of good viability were randomly assigned to the experimental (n = 13, ADLIB) and control (n = 13, CON) groups. The animals selected for the study received 1 × 4 L colostrum from bottle drinkers according to the farm technology. The period of ADLIB feeding lasted for 3 weeks after colostrum supplementation.

The ADLIB calves received milk replacer (Rosalac Red, Schils BV, Sittard, The Netherlands) ADLIB from a calf feeding bucket with hygienic valve and teat (Albert Kerbl GmbH, Buchbach, Germany) with a capacity of eight litres. The drinker was refilled twice a day (morning and afternoon). Calf starter and drinking water were offered ADLIB from day 3 after birth. The calves were then fed according to the farm technology until weaning; the experimental and control groups no longer differed during this period. The calves in the control group received the same milk replacer, which was, however, supplied according to the restrained feeding schedule of the farm (2 × 3 L daily for the first two weeks, then 2 × 4 L daily until weaning). There was no difference between the two groups in keeping and in other circumstances (calf starter feeding, drinking water supply, weaning date); the standard technology on the farm was the guiding principle.

2.2. Health and behavioural measurements

All animals were weighed at birth, at the end of the 3-week experimental period, and at weaning. From the data we derived the following parameters: derived parameters: total weight gain (TWG) between days 0 and 21; average daily gain (ADG) between days 0 and 21; TWG between day 21 and weaning; ADG between day 21 and weaning; TWG between birth and weaning; ADG between birth and weaning.

The amount of milk consumed was measured daily in the ADLIB group. Possible clinical symptoms and treatments were recorded with the frequency required by the veterinary protocols on the farm.

For behavioural measurements HOBO Pendant G data loggers (Onset Computer Corporation, Bourne, MA, USA) were attached to the left forelegs of the calves using an elastic bandage. This instrument measures acceleration on three axes (x, y, z), allowing to calculate how much time the animals spend lying and standing. The sampling period was set to 1 min (Bonk et al., 2013); the instrument was able to store the collected data for 20 days. The data were then downloaded and the instrument was re-attached to the same leg of the animal, resulting in an average of 40 days of data for each animal (derived data: total lying time between birth to day 40; lying time between birth and day 21, lying time between days 22 and 40).

2.3. Samplings and biochemistry

Blood samples were taken into vacuum tubes containing NaF and EDTA for blood glucose or Li-heparin for other biochemical measurements (Vacuette, Greiner Bio-One International AG., Kremsmünster, Austria), and RNA preservation tubes (Tempus Blood RNA Tubes, Applied Biosystems Inc., Foster City, USA) from *v. jugularis*. The samples were taken four times during the study, between day 2 and 3, 10 and 14, 20 and 24 and at the time of weaning (days between 58 and 70), in each case between 8 and 10 am.

All samples were immediately cooled to 4 °C, and transported to the laboratory within 3 h after sampling for analysis. From the fresh heparinized whole blood samples we measured oxidant and antioxidant status (derivates of reactive oxygen metabolites, dROM and plasma antioxidant capacity test, PAT) with a FRAS4 analytical device (HandD s.r.L., Parma, Italy; Cornelli et al., 2001). The oxidative stress index (OSI = dROM/PAT × 100; Abuelo et al., 2015) was also calculated.

The remaining blood samples were centrifuged (4000 rpm for 10 min), then glucose, albumin, total protein, and urea concentrations and AST activity were measured in the plasma with a A-25 clinical biochemistry automat (Biosystems S.A., Barcelona, Spain).

2.4. Gene expression examinations

The RNA preservation tubes were stored at −20 °C until measuring interleukin-8 (IL8), insulin like growth factor 1 (IGF1) and insulin (INS) gene expression.

RNA isolaton was performed according to the manufacturers' instructions using the Tempus Spin RNA Isolation Kit (Applied Biosystems Inc., Foster City, USA) treated with DNase (Quiagen, Germany). Total RNA was quantified by a Nanodrop 1000 spectrophotometer (Nanodrop, USA, Wilmington, DE). RNA integrity was determined in an Agilent 2100 Bioanalyzer (Agilent, USA, Santa Clara, CA) with an RNA integrity number (RIN) > 5 considered sufficient for real-time reverse transcription (RT)-PCR analysis.

For cDNA synthesis, 400 ng of total RNA was used and transcribed to cDNA using the qPCRBIO cDNA Synthesis Kit (PCR Biosystems, UK) following the manufacturer's instructions. cDNA equivalent to 5 ng of starting total RNA was used as template for each real-time PCR reaction. Primer pairs for genes of interest and a housekeeping gene are listed in Table 1. A primer concentration of 600 nM was used in the reactions. Primer design was carried out with Primer3 software for genes of interest, namely, IGF1, IL8 and INS and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as housekeeping gene.

Table 1
Sequences of PCR primers used for qPCR analysis.

Gene of Interest (GOI)	Primer Sequence Forward ('5-'3)	Primer Sequence Reverse ('5-'3)
IGF1	TCGCATCTCTTCTATCTGGCCCTGT	GCAGTACATCTCCAGCCTCCTCAGA
IL8	AGAACTTCGATGCCAATGCAT	GGGTTTAGGCAGACCTCGTTT
INS	TCCTCAAGGAGCTGGAGGAGT	GCTGCTGTCACATTCCCCA
Housekeeping gene		
GAPDH	ACCACTTTGGCATCGTGGAG	GGGCCATCCACAGTCTTCTG

Abbreviations: IL8, interleukin-8 gene; IGF1, insulin like growth factor 1 gene; INS, insulin gene; GAPDH, glyceraldehyde-3-phosphate dehydrogenase gene.

Real-time PCR was carried out on a Roche Light Cycler96 with SYBR Green Master Mix (Applied Biosystems Inc., Foster City, USA) with 3 min denaturation, followed by 50 cycles of 95 °C for 15 s, 62 °C for 20 s and 72 °C for 15 s. High resolution melting analysis was performed for each run. Each sample were used as triplicate in (RT)-PCR.

2.5. Statistical analysis

Parameter means were compared between groups (CON and ADLIB) at the different sampling intervals. In the case of parameters measured only at one time point, the Welch two sample *t*-test was used to compare means between CON and ADLIB groups. In the case of repeated measurements the same animal, linear mixed models were fit, with subject as random effects. Model fit was evaluated by diagnostic plots.

Formula: Parameter ~ Group + Sampling interval + Group: Sampling interval (interaction term).

Graphs show the estimated marginal means and standard errors across treatments and sampling intervals. Asterisks indicate significant differences between groups (***$p < 0.001$, **$p < 0.01$, *$p < 0.05$).

Tables show the estimated marginal means and standard errors in both groups and the estimate of the difference between treatment means. Statistical analyses were performed in R statistical environment (R Core Team, 2021).

The mRNA abundance of target genes, normalised to that of the housekeeping gene, was calculated using the method of $2^{-\Delta\Delta CT}$. For the statistical analysis Kolmogorov-Smirnov: 0.200; 0.002 - not normal distribution-Mann-Whitney probe was used to compare difference between times of sampling and groups of treatment. Differences between means were considered significant at $p < 0.05$.

3. Results

3.1. Weight gain, health status and behaviour

There was no difference between the two studied groups in weight or weight gain of the calves during the experiment (Table 2).

In each of the ADLIB and CON groups, 5 calves had diarrhea during the study period, which was treated according to the usual protocol on the farm.

With HOBO devices, we were able to examine the time spent lying and standing. Animals in both groups spent an average of 19 h per day in resting position (Table 2). When the data are analyzed by separating the first three weeks of life (the period of ADLIB feeding) and the next three weeks (the second HOBO data collection), the results are different numerically, but the difference is not significant ($p > 0.05$). It can be clearly seen that the time spent lying in the second measurement period is less than in the first, which may be related to the growth of the animals: they were simply more active.

Table 2
Weight data and behaviour indicators during the study (Mean ± SEM).

Parameters	CON	ADLIB	p value
Birth weight (kg)	43.8 ± 1.1	42.9 ± 1.7	0.682
Weight at day 21 (kg)	49.2 ± 1.7	48.5 ± 2.2	0.794
Weight at weaning (kg)	91.2 ± 2.4	90.7 ± 2.1	0.856
TWG between birth and day 21(kg)	5.5 ± 1.3	5.6 ± 1.0	0.947
ADG between birth and 21 (kg)	0.26 ± 0.06	0.27 ± 0.05	0.957
TWG between day 21 and weaning (kg)	42.0 ± 1.6	42.2 ± 1.6	0.951
ADG between day 21 and weaning (kg)	1.08 ± 0.04	1.08 ± 0.04	0.966
TWG between birt and weaning (kg)	47.5 ± 2.3	47.8 ± 1.9	0.934
ADG between birth and weaning (kg)	0.79 ± 0.04	0.80 ± 0.03	0.922
Lying time between birth and day 40 (hour/day)	18.9 ± 0.2	19 ± 0.3	0.689
Lying time beween birth and day 21 (hour/day)	19.3 ± 0.1	20.0 ± 0.4	0.121
Lying time between days 21 and 40 (hour/day)	18.4 ± 0.3	17.8 ± 0.2	0.081

Abbreviations: ADLIB, group of calves fed *ad libitum* milk replacer during the first 3 weeks of life, then restricted until weaning; CON, control group in restricted feeding until weaning; TWG, total weight gain; ADG, average daily gain.

3.2. Metabolic and redox parameters

During the experimental period, the following parameters were examined in calves: glucose, albumin, total protein, BHB, AST, oxidant and antioxidant status incl. dROM, PAT and OSI (Table 3). No significant ($p > 0.05$) difference was found in the values measured. All metabolic indices correspond to the physiological values of the calves. A decrease in plasma glucose concentration and an increase in plasma BHB concentration at the 4th sampling were observed.

At the first three time points the OSI values of the experimental group were numerically, but not significantly ($p > 0.05$) higher than those of the control group, and at the 4th sampling time point it was lower.

3.3. Gene expression

IL8 gene activity was higher in ADLIB fed calves during the first 20 days of life. The difference between the ADLIB and restrictedly fed group was the greatest on the 10th day of life, although the difference was not significant ($p > 0.05$) (Fig. 1). Based on the relative expression measured on day 50, IL8 gene activity was already higher in the control group, but the difference was still not statistically supported ($p > 0.05$).

The relative expression of the IGF1 gene was higher in the ADLIB fed group, but not on the 20th day of life. Relative expression was much higher in the ADLIB fed group on day 0 of the study; however, this striking difference did not represent a statistically significant ($p > 0.05$) difference between the two groups. As can be seen in Fig. 1, the ADLIB group also had an extremely high standard deviation value at day 0 of life in IGF1. This is due to the outlier value of one individual. However, since (RT)-PCR was

Table 3
Metabolic parameters during the study, estimated marginal means and SEM.

Parameter	Week								SEM	p value		
	1		2		3		8					
	CON	ADLIB	CON	ADLIB	CON	ADLIB	CON	ADLIB		Group	Age	Group*Age
dROM	105	119	112	120	108	118	121	119	7.9	0.294	0.723	0.728
PAT	2669	2705	2454	2424	2250	2278	2889	2754	74.5	0.565	<0.0001	0.640
OSI	4.0	4.5	4.7	5.0	4.9	5.2	4.2	4.4	0.3	0.214	0.0289	0.959
Total prot	65.2	66.5	60.7	61.1	59.6	64.6	66.5	65.1	2.4	0.663	0.0032	0.230
Albumin	39.8	40.2	41.7	41.4	41.9	44.3	46.3	45.8	1.0	0.420	<0.0001	0.460
BHB	0.06	0.08	0.06	0.03	0.05	0.05	0.27	0.27	0.03	0.948	<0.0001	0.893
Glucose	6.6	6.3	6.7	5.7	5.5	5.7	5.0	4.8	0.3	0.185	<0.0001	0.189
AST	31.7	33.7	40.8	41.5	40.1	39.1	60.2	54.9	3.4	0.826	<0.0001	0.731
Urea	6.6	5.5	2.2	1.8	2.1	2.5	4.1	3.0	0.6	0.180	<0.0001	0.526

Abbreviations: ADLIB, group of calves fed *ad libitum* milk replacer during the first 3 weeks of life, then restricted until weaning; CON, control group in restricted feeding until weaning; BHB, beta-hydroxybutyrate; AS, aspartate-aminotransferase; dROM, derivates of reactive oxygen metabolites; PAT, plasma antioxidant test; OSI, oxidative stress index (OSI = dROM/PAT × 100).

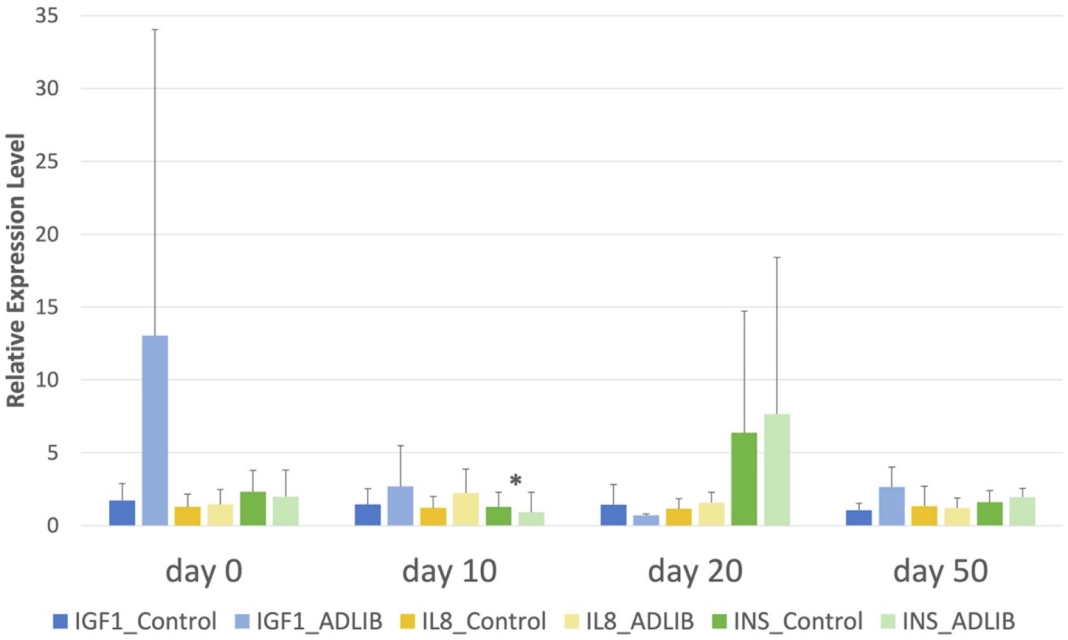

Fig. 1. Relative gene expression in Holstein Friesian calves.

performed in triplicate and this individual no longer caused such bias on later days of life, it was not excluded from the analyses.

On day 10 the relative expression level of INS was significantly lower ($p = 0.003$) in the ADLIB group compared to the restrictedly fed, control group. It is worth pointing out that relative expression increased by day 20 in both groups (Fig. 1). However, no statistically significant ($p > 0.05$) differences in the relative expression of the INS gene were detected between the groups, except on day 10.

4. Discussion

During ADLIB milk feeding, calves tend to drink more milk (Appleby et al., 2001) and gain more weight during the drinking period (Nocek and Braund, 1986); however, this is not always observed (Korst et al., 2017; Hu et al., 2019). The two groups did not differ in their bodyweight and weight gain during our study. It was clear at the end of our study that the milk replacer data were not recorded properly in the ADLIB group by the farm staff, therefore we have no information about the milk replacer consumption.

In similar experiments, the number of days of diarrhea was the same, but calves had to be treated for fewer days to resolve the symptoms (Nocek and Braund, 1986; Todd et al., 2017). In our case, the farm protocol required treating sick calves for a given number of days, and we could not deviate from this schedule for any of our experimental animals. Furthermore, several experiments demonstrate that after weaning, calves fed ADLIB lose their advantage (Todd et al., 2017).

Animals in both groups spent an average of 19 h per day in resting position, which is in line with what can be expected from young calves (Hänninen et al., 2005). The animals were more active in the second measurement period without significant ($p > 0.05$) difference between the two groups.

No significant ($p > 0.05$) difference was found between the two groups in the metabolic values measured. All metabolic indices corresponded to the physiological values typical of calves. It was interesting to observe a decrease in plasma glucose concentration and an increase in plasma BHB concentration and AST activity at the 4th sampling. This is most likely related to rumen development and rumen fermentation that are already intense by the time of weaning.

OSI values in the first three samples in the experimental group were not significantly ($p > 0.05$) higher than those in the control

group and then lower at the time of the 4th sampling. This is due to the fact that in the case of the first three samples the dROM values from which the OSI index is derived were higher in the experimental group than in the control, although the difference was not significant ($p > 0.05$). These values characteristic of oxidative stress have not been studied in calves. The dROM values otherwise correspond to those previously measured in dairy cows (Hejel et al., 2021) and fall within the normal range based on human limits. PAT values were similar in the two groups. Here again, the values are similar to those previously measured in dairy cows and to human normal values (Hejel et al., 2021).

We tested IL8, INS and IGF1 gene expression in the two groups studied. During the first 20 days of life IL8 expression was higher in the ADLIB fed group. IL8 is an important regulator of immune function, its higher levels of expression indicate a more alert state of the immune system system (Baggiolini and Clark-Lewis, 1992). As other conditions were equalized and the overall health status of the animals was similar between the groups, higher levels of IL8 indicate that ADLIB feeding might induce stronger immune response to environmental stress in Holstein Friesian calves. The difference between the ADLIB and restrictedly fed groups was highest on day ten, however with no statistical significance ($p > 0.05$). Our results correlate with previous studies in other species such as chicken, where heat stress induced the elevation of IL8 expression postulated as a sign of better adaptation to heat stress (Saleh and Al-Zghoul, 2019), and in calves with diarrhea, where elevated IL8 expression was found to be a part of molecular adaptation to disease (Rosa et al., 2018).

INS and IGF1 are important genes of metabolic regulation (Blum, 2006). The insuline-like growth factor-1 gene showed increased expression in the ADLIB fed group at almost all time points, however the difference was already detected on the first day of the study, indicating the importance of individual differences even within the same breed.

INS gene expression was higher in the restrictedly fed group at the beginning of the experiment with a shift by day 20. Our results suggest trends that are supported by other studies, that ADLIB feeding of calves during the first weeks of life might be superior to restricted feeding with respect to better immunological status and metabolic parameters, however we only saw a tendency of the changes of the markers studied with no statistical significance. It is an important field of research to find appropriate molecular markers to detect fine changes in the immunological and metabolic status of young calves in response to heat stress and other forms of environmental stress. The effect of diverse interventions can also be screened via the detection and follow-up of expression patterns. The IL8, IGF1 and INS genes might provide useful tools in some of these settings, however these genesshould be widened with even more impactful ones on immune function and metabolic stress response or with genes whose expression is more sensitive to environmental changes.

In our study ADLIB and restricted feeding didn't have a major impact on the expression of genes under investigation (IL8, INS, IGF1). There is a need to identify and evaluate a wider range of molecular markers present in blood samples that are involved in the immune function and metabolic status of dairy cattle in herds in order to establish a robust set of markers allowing easier examination of the effects of different feeding strategies and other interventions in response to heat stress in field settings.

Even in the absence of statistical significance ($p > 0.05$), the results of our study fit into the trend suggested by other studies that calves that received milk ADLIB in the first weeks of their lives have better immune status (Hammon et al., 2018; Schaff et al., 2018) and better metabolic values (Maccari et al., 2015) than restrictedly fed calves.

It is important to find, in this area of research, biomarkers that allow faithful monitoring of the changes taking place in the immune processes and metabolic values of young calves when the way of application and the amount of food – in this case, milk – are changed. The IGF1, INS, and IL8 genes are useful tools for this purpose, but we need to look for other genes whose expression is much more sensitive to environmental changes and also maps immune defense responses. A carefully planned feeding program may have a positive effect on postnatal development.

5. Conclusion

We compared the health and performance of ADLIB and restrictedly fed Holstein Friesian heifer calves by behavioral measurements, biochemical parameters and (RT)-PCR analysis. Our findings revealed that there was no difference between the two groups in weight, weight gain, movement activity or biochemical parameters. We observed a higher relative expression levels of IL8 gene during the first 20 days of life in the ADLIB group, while on day 50 this was reversed. IGF1 gene also showed higher relative expression levels in the ADLIB-fed group at the day 0, 10 and 50. The exception was day 20 of life, when the restricted group showed higher gene activity. These differences were not statistically significant. However, INS activity was statistically significantly higher in the restricted group at the day 10 then, on days 20 and 50, the ADLIB group was characterized by higher gene activity, although the latter differences were not statistically significant. These results suggest that the immune status of calves fed *ad libitum* in the first weeks of life may be better, which may enhance a stronger immune response to environmental stress, therefore further targeted studies are recommended.

Data and model availability statement

None of the data were deposited in an official repository. The data presented in this study are available on request from the corresponding author.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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