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Assessing essentiality of nickel in growing Hariana heifers by determining its effect on performance, nitrogen and mineral metabolism, urease activity, and endocrine biomarkers

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ABSTRACT

The objective of this study was to determine the effect of nickel (Ni) on growth performance, nutrient utilization, urease activity, and endocrine variables in growing cattle. Growing Hariana heifers (18) were randomly assigned into three groups (n=6), i.e. groups either without Ni supplementation (Ni0.0; control) or supplemented with 1.5 mg of Ni/kg DM (Ni1.5), and 3.0 mg of Ni/kg DM (Ni3.0). The experiment lasted for 90 days. Heifers supplemented with Ni showed higher nutrient intake and average daily gain (ADG) than control group. The nutrient digestibility was not affected by treatment, while the Ni supplemented animals showed higher intake, excretion, and nitrogen balance. The urease activity was comparable and higher in the $Ni_{1.5}$ and $Ni_{3.0}$ groups than in the control group. There was no effect of treatment on the metabolism of calcium (Ca), phosphorus (P), zinc (Zn), copper (Cu), and chromium (Cr). However, iron (Fe) retention showed a negative association with Ni levels. Plasma cortisol concentration was lower while the insulin like growth factor-1 (IGF-1) and tetraiodothyronine (T4) were higher in the Ni3.0 group compared to the Ni0.0 group, with Ni1.5 being intermediate. The plasma concentrations of triiodothyronine (T3) and thyroid stimulating hormone (TSH) were not affected by dietary treatment. Plasma Ni concentration showed a dose dependent increase whereas, plasma levels of other minerals were not affected by treatment. In conclusion, dietary Ni supplementation in growing Hariana heifers improves performance and nutrient utilization by modulating urease activity and endocrine growth biomarkers.

Keywords: Endocrine biomarker, Heifer, Metabolism, Nickel, Nutrients utilization, Performance

The essentialities of macro-or-micro minerals are well established in living beings and both play a vital role in augmenting production and reproduction in farm animals. Evidence has suggested that a number of other trace elements, not previously recognized as essential, are required at least by certain animal species (Nielsen 2000). These elements are recognized as newer trace elements, because deprived animals were unhealthy and showed physiological responses to their supplementation (Afridi *et al.* 2001). Among the newer trace elements, nickel (Ni) is one of them. Recently, evidence has been presented suggesting that ruminants have an absolute requirement for Ni (McGrath *et al.* 2018). Ni plays a significant role in the regulation of protein metabolism by the activation of enzymes and hormones. A major site of action of Ni in ruminants appears to be the Ni containing enzyme urease, which is thought to play a key role in nitrogen metabolism by allowing the rumen microbes to utilize a waste product of the animal (non-protein nitrogen) as a nitrogen source for growth and production (Mazzei *et al.* 2020). Ni can show interaction with other minerals and it has been suggested that various effects of Ni are due to their interaction with Fe, Cu, Zn, Ca, etc. in the body (Kasprzak *et al.* 2003). Ni deficiency impaired Fe utilization, depresses Zn absorption and increased Ca excretion (Anke *et al.* 1995a). Ni has been reported to be a bio-ligand cofactor facilitating the intestinal absorption of the Fe in the animals (Shambhvi *et al.* 2020). At low concentrations, Ni specifically inhibited prolactin release, but at higher concentrations, it stimulated the release of growth hormone, thyrotropin, and adrenocorticotropic hormones from bovine pituitary (Yang and Ma 2021). Ni induced hypo-insulinemic response was attributed to modulating secretion of IGF-1 by stimulating α-2 adrenergic receptors in pancreatic islets (Alverez *et al.* 1993).

Knowledge regarding the role of Ni in ruminant nutrition is currently limited. However, the evidence of the essentiality of this element in laboratory animals is not a new issue. Considering these facts, this study has been designed to study the effects of Ni supplementation

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on growth performance, nutrient utilization, mineral metabolism, urease activity, and endocrine variables in growing cattle.

MATERIALS AND METHODS

Experimental design: Animal care procedures were approved (Approval No. 115/IAEC/17) and conducted under the established standards of the Institutional Animal Ethics Committee (IAEC), constituted as per the Article Number 13 of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) rules laid down by the Government of India.

Growing female Hariana cattle (18) were randomly assigned into three dietary treatments based on initial body weight (125±3.0 kg) and initial age basis (10±2.0 months). Animals either received a basal diet devoid of supplemental Ni ($Ni_{0.0}$; control) or were supplemented with 1.5 mg ($Ni_{1.5}$), and 3.0 mg ($Ni_{3.0}$) of Ni/kg DM as $NiSO_4.6H_2O$ (Loba Chemical Pvt. Ltd., Mumbai, India) for a period of 90 days. The nutrient requirements of experimental animals were met by feeding a total mixed ration (TMR) consisting of concentrate: green berseem fodder: wheat straw in the proportion of 45:35:20 (NRC 2001). To ensure that each animal consumed the required amount of Ni, the calculated amount of Ni premix was fed by mixing it with 100 g of concentrate mixture.

Observations recorded, sampling, and laboratory analysis: A metabolism trial with 4 days adaptation period followed by a 7 days collection period was conducted at the end of the study. Net feed consumption during the trial period was recorded daily by weighing feedstuffs offered and orts left. Total urine voiding over a 24 h period was collected using a URO-FLEX (urine collection bag, capacity 2 L, Ramsons) equipped with a uro-cath 2-way foley balloon catheter (Size 16FG, Ramsons). However, faeces excreted during 24 h was collected manually. About 1% of the thoroughly mixed faeces voided during 24 h was taken for the chemical analysis. 10 g of another faecal sample was taken and stored in glass containers having 10 ml of 25% H_2SO_4 solution. For the nitrogen and mineral estimation, 6% of the total urine voided in 24 h was sub sampled.

The representative samples of feedstuffs offered, orts left, and faeces voided were analyzed for proximate composition (AOAC 2005). However, fibre fractions were determined according to the procedures given by Van Soest *et al.* (1991). The mineral content in the samples of feedstuffs, orts left, faeces, urine, and plasma were analyzed by using an Atomic Absorption Spectrophotometer (AAS; Perkin Elmer AAnalyst 300, USA). The ingredients and chemical composition of the basal diet fed during the experimental period are given in Supplementary Table 1.

Peripheral blood samples were collected at day 0, 30, 60 and 90 post-Ni supplementation. Blood samples were centrifuged at 1200 × g for 30 min at 4ºC and separated plasma was stored at −20 °C until further analysis. Plasma concentration of cortisol, IGF-1, T_3, T_4, and TSH were determined by the use of bovine specific ELISA test kits (Cayman's Chemical Company, Ann Arbour, Michigan, USA). Ruminal urease activity, measured as unit pH change, was estimated by urease index (AOCS 2011).

Statistical analysis: The generated data was analyzed by repeated measures using the PROC MIXED procedure of SPSS (V21.0; SPSS Inc., Chicago, IL, USA). The effects of treatment, period, and their interaction on the concentration of endocrine variables, urease activity, and plasma mineral levels were analyzed by using the following model:

$$Y_{ijk} = \mu + T_i + D_j + (T \times D)_{ij} + e_{ijk}$$

Table 1. Effect of Ni supplementation on performance and nutrients digestibility

Attribute	Treatment			SEM	*p* value$^{\beta}$		
	$Ni_{0.0}$	$Ni_{1.5}$	$Ni_{3.0}$		T	D	T×D
Performance							
DMI (kg/d)	5.47^{a}	6.23^{b}	7.39^{c}	0.58	0.025	0.011	0.045
ADG (g/d)	475.71^{a}	500.00^{a}	667.14^{b}	43.03	0.013	<0.001	0.039
Nutrients digestibility (g/kg DM)							
DM	714.6	737.7	748.4	14.83	0.288		
OM	723.2	748.5	758.0	16.31	0.324		
CP	755.6^{a}	786.4^{b}	806.0^{c}	14.75	0.043		
EE	812.8	823.9	825.4	10.49	0.114		
aNDFom	592.2	609.2	611.7	24.01	0.091		
aADFom	555.6	589.7	593.8	24.85	0.172		
N metabolism							
N intake$^{\epsilon}$ (g/d)	122.53^{a}	139.56^{b}	165.55^{c}	3.19	<0.001		
Fecal N excretion (g/d)	29.95^{a}	29.81^{a}	32.12^{b}	1.25	0.018		
Urinary N excretion (g/d)	24.67^{a}	26.58^{ab}	30.29^{b}	1.38	0.003		
Total N excretion (g/d)	54.62^{a}	56.39^{ab}	62.41^{b}	2.19	<0.001		
N balance (g/d)	67.91^{a}	83.16^{b}	103.13^{c}	2.38	0.001		
N retention (% of N intake)	55.43^{a}	59.59^{b}	62.30^{c}	2.05	0.028		

$^{a\text{-}c}$Mean values within a row with unlike superscript letters are significantly different for each dietary treatment ($p \leq 0.05$).

where, Y_{ijk}, dependent variable; μ is the overall mean of the population; T_i, mean effect of the treatment; D_j, mean effect of day of sampling (*j*=0, 30, 60, and 90 days of dietary treatment); $(T\times D)_{ij}$, effect of the interaction between the effect of Ni supplementation and the day of sampling; and e_{ijk}, unexplained residual element assumed to be independent and normally distributed. Animals tested within a group were considered as a random effect, while group, period (sampling days), and their interaction were considered as the fixed effects. Data regarding nutrient intake, apparent nutrient digestibility, and nitrogen and mineral balance were analyzed using the one-way ANOVA procedure.

RESULTS AND DISCUSSION

Growth performance and apparent nutrient digestibility: Heifers offered diets supplemented with Ni had a greater ($p<0.05$) DMI and ADG compared to those fed on basal diets devoid of supplemental Ni (Table 1). The intake of CP, DCP, and TDN was also higher ($p<0.05$) in heifers receiving diets supplemented with Ni. Intake of nutrients and ADG were greater in experimental heifers fed on a diet supplemented with 3.0 mg of Ni/kg DM.

Similar to the present findings, higher ADG and feed efficiency in calves receiving Ni supplementation when compared to calves receiving the basal diet devoid of supplemental Ni was reported by Singh *et al.* (2019). Anke *et al.* (1977) noted that goats fed a diet supplemented with 10 ppm Ni gained faster than goats receiving a diet containing 1 ppm Ni. The addition of 5 ppm Ni has been shown to increase growth rate and feed efficiency in lambs and steers fed on high-energy, low-protein diets (Spears *et al.* 1979, Spears 1984). Oscar *et al.* (1987) also observed higher ADG and improved feed conversions in Angus steers fed on 5 ppm Ni supplemented diets compared to non-Ni supplemented steers. The higher feed intake and growth rate in Ni supplemented heifers appeared to be correlated with activity levels of ruminal urease, an enzyme that has been shown to require Ni.

Although the digestibility of different nutrients, specifically protein, was better in Ni supplemented heifers but mean values showed a non-significant ($p<0.05$) difference. The digestibility of CP in 3.0 mg of Ni/kg DM group was 6.67% higher compared to the non-supplemented group. Higher DM and fibre digestibility in goats receiving diets supplemented with 1.0 ppm Ni was reported by Yousuf (2005). However, Spears *et al.* (1978a) observed no influence of Ni supplementation on nutrient utilization in lamb. Bersenyi (2003) observed depressed digestibility of protein by 3-4% and that of crude fibre by 20-25% in rabbits exposed to higher Ni levels (500 mg Ni/kg diet). Spears *et al.* (1979) stated that ruminants benefited more from Ni supplementation while on low protein diets as the ruminal urease enzyme converts endogenous urea to

Table 2. Effect of Ni supplementation on mineral metabolism

Mineral	Treatment			SEM	*p* value
	$Ni_{0.0}$	$Ni_{1.5}$	$Ni_{3.0}$		
Ni intake (mg/d)	6.95[a]	17.26[b]	31.56[c]	0.92	0.004
Ni voided in faeces and urine (mg/d)	6.64[a]	16.63[b]	30.41[c]	1.50	0.002
Ni balance (mg/d)	0.46[a]	0.63[b]	1.15[c]	0.01	<0.001
Ni retention (% of Ni intake)	4.36[a]	7.99[b]	12.21[c]	0.39	0.001
Ca intake (g/d)	51.97[a]	59.19[b]	70.21[c]	3.89	0.015
Ca voided in faeces and urine (g/d)	32.92[a]	38.47[b]	44.50[c]	2.08	<0.001
Ca balance (g/d)	19.05[a]	20.72[ab]	25.71[b]	1.19	0.036
Ca retention (% of Ca intake)	36.62	35.01	36.63	2.27	0.998
P intake (g/d)	22.97[a]	26.17[b]	31.04[c]	1.09	0.029
P voided in faeces and urine (g/d)	10.91[a]	12.27[b]	14.85[c]	0.82	0.001
P balance (g/d)	12.07[a]	13.89[ab]	16.19[b]	1.14	0.017
P retention (% of P intake)	52.52	53.10	52.15	3.91	1.000
Fe intake (mg/d)	1811.94[a]	2063.69[b]	2447.94[c]	48.14	0.007
Fe voided in faeces and urine (mg/d)	1266.11[a]	1463.28[b]	1787.71[c]	25.09	0.028
Fe balance (mg/d)	545.83[a]	600.40[b]	660.23[c]	18.20	0.004
Fe retention (% of Fe intake)	30.12[b]	29.09[ab]	26.97[a]	1.17	0.027
Zn intake (mg/d)	252.60[a]	287.70[b]	341.27[c]	11.29	<0.001
Zn voided in faeces and urine (mg/d)	182.26[a]	210.21[b]	249.60[c]	8.93	0.039
Zn balance (mg/d)	70.35[a]	77.49[b]	91.67[c]	2.91	0.003
Zn retention (% of Zn intake)	27.85	26.93	26.79	1.09	0.944
Cu intake (mg/d)	108.58[a]	123.67[b]	146.69[c]	9.58	0.047
Cu voided in faeces and urine (mg/d)	94.58[a]	107.92[b]	130.79[c]	5.40	0.001
Cu balance (mg/d)	14.00	13.75	15.90	2.92	0.835
Cu retention (% of Cu intake)	12.89	11.12	10.84	2.03	0.496

[a-c]Mean values within a row with unlike superscript letters were significantly different for each dietary treatment ($p\leq0.05$).

ammonia that is used for the synthesis of microbial protein.

In the present study, nitrogen balance was 34.15% higher for heifers supplemented with 3.0 mg of Ni/kg DM and 18.34% higher for those fed with 1.5 mg of Ni/kg DM compared to those fed the control diet. Urinary nitrogen to faecal nitrogen excretion was lower ($p<0.05$) in heifers fed 3.0 mg of Ni/kg DM diets compared to those fed 1.5 mg of Ni/kg DM and non-Ni supplemented diets. Ni containing ruminal urease enzyme is required for hydrolysis of dietary and endogenous urea that is recycled to the rumen (Patra and Aschenbach 2018). In this manner, Ni supplementation may influence nitrogen recycling and dietary nitrogen metabolism which is of major importance in ruminants consuming low protein diets (Goshtashpour-parsi *et al.* 1974). No information is available regarding the effects of Ni supplementation on nitrogen metabolism in animals.

Urease activity and mineral metabolism: The dietary supplementation of Ni showed significant effect ($p<0.001$) on urease activity and activity was observed comparable and higher in $Ni_{1.5}$ and $Ni_{3.0}$ groups than non-Ni supplemented group (Fig. 1). Urease activity in Ni supplemented group starts increasing at day 60 post Ni-supplementation and continued until the end of the study.

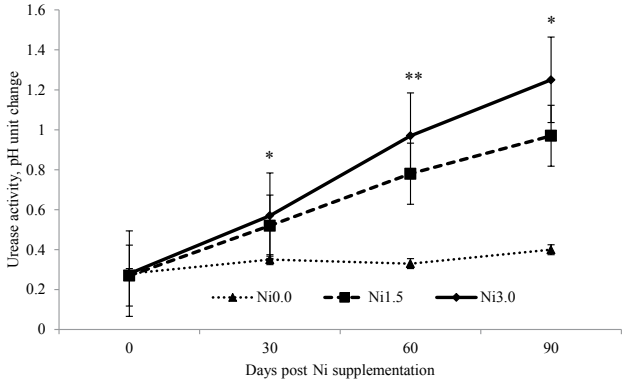

Fig. 1. Effect of Ni supplementation on ruminal urease activity; single (*$p\leq0.05$) and double (**$p<0.001$) asterisks represents statistical significance compared with control.

Urease has been shown to be a Ni metalloenzyme and found to contain 6-8 atoms of Ni in a mole of enzyme (Fishbein *et al.* 1976). Ruminal urease hydrolyses dietary NPN and recycled urea into NH_3-nitrogen that can be utilized by most of the rumen bacteria for microbial protein synthesis (Hailemariam *et al.* 2021). In this study, Ni supplementation improved the activity of a ruminal urease enzyme. Starnes *et al.* (1982) and Milne *et al.* (1990) also observed higher rumen bacterial urease activity in 5 mg Ni/kg DM and 5 mg Ni/day, respectively, in sheep fed on high-energy and low protein diets. Murrah buffalo calves supplemented with 10 ppm Ni showed higher urease activity than the 5 ppm and non-Ni supplemented groups (Thamizhan 2020).

Treatment dependent higher DMI resulted in a significantly higher ($p<0.05$) intake of Ca, P, Ni, Fe, Zn, Cu, and Cr (Table 2). As the dietary intake of minerals increased, their excretion in faeces and urine also increased ($p<0.05$). However, no differences among treatments for the balance of Cu were observed. Ni supplementation had no effect on Ca, P, Zn, Cu, and Cr retention, whereas Ni retention had a positive and Fe retention had a negative association with supplemental Ni levels.

Ni has been reported to alter the metabolism of a number of other elements in the body but the interrelationships are complex and poorly understood (Kasprzak *et al.* 2003). Most ingested Ni remains unabsorbed in the gastrointestinal tract and is excreted in the faeces (Nielsen *et al.* 1987). Bersenyi (2003) also observed no interaction between supplemental Ni with Zn, Mn, Fe, and Cu. However, Anke *et al.* (2002) noted disturbed Ca, Zn, Fe, etc. metabolism in Ni depleted subjects. Sunderman (2007) conducted a study to observe the Ni distribution in the body and observed that Ni absorption is directly related to supplemental Ni level and absorbed Ni is excreted mainly through urine. Schnegg and Kirchgessner (1976a) reported that Fe absorption was

Table 3. Effect of Ni supplementation on plasma endocrine variables and mineral levels

Attribute	Treatment			SEM	*p* value$^{\beta}$		
	$Ni_{0.0}$	$Ni_{1.5}$	$Ni_{3.0}$		T	D	T×D
Plasma hormonal levels							
Cortisol level (ng/ml)	4.63^{b}	4.39^{ab}	3.94^{a}	0.04	0.004	0.296	0.994
IGF-1 level (ng/ml)	192.03^{a}	217.35^{b}	256.08^{c}	8.67	0.001	0.017	0.928
T_3 level (ng/ml)	3.93	3.87	4.02	0.46	0.382	0.485	0.940
T_4 level (ng/ml)	83.88^{a}	87.87^{ab}	97.71^{b}	3.67	0.001	0.032	0.692
T_4: T_3 ratio	21.34	22.71	24.31	4.79	0.483	0.773	0.976
TSH level (mIU/l)	6.43	6.64	6.78	0.52	0.291	0.459	0.776
Plasma mineral levels							
Ni (µg/l)	56.00^{a}	77.92^{b}	98.50^{c}	6.00	0.002	0.030	0.049
Ca (mg/l)	107.8	107.4	108.5	5.21	0.183	0.339	0.907
P (mg/l)	52.71	53.93	54.36	3.7	0.492	0.519	0.734
Fe (mg/l)	3.36	2.61	2.05	0.06	0.086	0.283	0.994
Zn (mg/l)	1.38	1.32	1.32	0.10	0.291	0.442	0.995
Cu (mg/l)	0.82	0.79	0.77	0.02	0.519	0.692	1.000

$^{a-c}$Mean values within a row with unlike superscript letters are significantly different for each dietary treatment ($p\leq0.05$).

inhibited during Ni deficiency. Ni supplementation at the levels of 5, 10, 20 or 50 ppm in the diet increased the Fe content of marginally Fe adequate rats (Nielsen *et a.* 1984). Ni deficiency in goat lower Ca and Zn concentrations in blood, bones and milk suggest effects of Ni deficiency on Ca and Zn metabolism (Anke *et al.* 2002).

The supplementation of Ni had no effect on the plasma levels of Ca, P, Fe, Zn, Cu, and Cr. However, there was an increasing ($p<0.05$) trend for plasma Ni levels (Table 3). Serum Ni varies among the species but comparatively little within species if Ni exposure is not excessively altered. Ni content (µg/l) normally ranges between 4-5 for pigs, 3-4 for goats, 1-4 for rats, and 6.5-14 for rabbits (Milne *et al.* 1990). Similar to the findings of the present study, Whanger (1973) observed no effect of Ni supplementation on plasma and tissue levels of other minerals. Lambs receiving no supplemental Ni had lower levels of Fe in their lungs than animals that had been receiving supplemental Ni (Spears *et al.* 1979). Thamizhan (2020) found a higher plasma Fe concentration in Murrah buffalo calves supplemented with 10 ppm Ni in comparison to 5 ppm and 0 ppm groups. Spears and Hatfield (1978) also found that serum Ca and P were not affected by dietary Ni supplementation in lambs.

Endocrine variables: The plasma concentration of endocrine variables is given in Table 3. Plasma cortisol concentration decreased while IGF-1 and T_4 levels increased significantly ($p<0.05$) in a dose dependent manner as the supplemental level of Ni increased (Supplementary Figs 1-3). There were no effects of Ni supplementation on the plasma concentrations of T_3 and TSH in all groups.

Information regarding the beneficial impact of Ni on endocrine variables is lacking and most of the studies that demonstrate the effects of this element are restricted as toxic metals. Ni may play a significant role in the stimulation or inhibition of the release of growth hormone, thyrotropin, and adrenocorticotropic hormones from the bovine pituitary (Stejskal *et al.* 2006, Yang and Ma 2021). Concentrations of Ni were inversely related to plasmatic cortisol, which agrees with the *in vitro* hormone release inhibition proposed for the divalent cation by Lorenson *et al.* (1983). Significant inverse effects were observed for Ni on levels of cortisol in human subjects (Candahia *et al.* 2008).

IGF-1 is an anabolic hormone mainly synthesized in the liver and locally expressed in peripheral tissues (Sherlock and Toogood 2007) under the control of pituitary growth hormone (GH). Ni exposure was associated with impaired GH-IGF-1 axis function (Watanabe *et al.* 2018). In the present study, Ni supplementation showed a positive influence on the plasmatic concentration of IGF-1. However, dietary Ni as $NiCl_2$ in excess (300 mg/kg diet) in broilers birds reduced IGF-1 content in the small intestine (Wu *et al.* 2013). Similarly, inhibited release of GH from the bovine pituitary gland was also reported by Dormer *et al.* (1973) in Ni exposed subjects.

Thyroid hormone metabolism is affected by several metabolic and nutritional factors (Mercer and Trayhurn 1987), particularly the intake of feed (Chopra *et al.* 1975). In the present study, higher feed intake in Ni supplemented groups might be the reason behind greater thyroxin levels. Stangi and Kirchgess (1998) observed that dietary Ni depleted rats had total T_4 and T_3 levels in plasma that were reduced by about 14 and 13% compared to the controls. The Ni deficiency driven effects on thyroid hormones were mainly caused by the Ni induced impaired Fe status (Chen *et al.* 1983). Thyroxine peroxidase, which is a haeme Fe containing enzyme in the thyroid gland (Chen *et al.* 1983), could be responsible for the observed alterations in thyroid hormone level.

In conclusion, dietary Ni supplementation in growing Hariana heifers improves feed intake, growth performance, and nitrogen retention. Better performance of Ni supplemented heifers might be due to higher urease activity and plasmatic concentration of endocrine growth biomarkers. However, nickel supplementation did not exert any adverse effect on other minerals metabolism except it had a negative interaction with iron metabolism. It seems to be worth to supplement nickel in growing cattle by subsequent studies and supplementing nickel at low nitrogen diet is required.

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