



## Evaluation of L-carnitine in the treatment of experimentally induced hypomagnesemia in sheep

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### ABSTRACT

The aim of this study was to evaluate the role of L-carnitine in the treatment of experimentally induced hypomagnesemia in sheep. This study was carried out on 10 ossimi rams aged 10-12 months old with an average live weight of  $35 \pm 1.1$  kg that were used for experimental induction of hypomagnesemia. Rams with induced hypomagnesaemia were divided into two groups according to the line of treatment. The first group (n=5) was treated by the traditional treatment alone while the second group (n=5) was treated by the traditional treatment in addition to L-carnitine (20 mg/kg I/V). The symptoms of hypomagnesemia appeared gradually until complete appearance of symptoms at day 28 post induction. There was significant decrease ( $P < 0.05$ ) in serum magnesium (Mg), calcium (Ca), glucose and parathyroid hormone (PTH) in experimentally induced hypomagnesemic rams. However, there were significant increase ( $P < 0.05$ ) in serum sodium (Na), potassium (K), urea, creatinine, cortisol, creatine phosphokinase (CPK) and troponin I (cTnI) in experimentally induced hypomagnesemic rams. Treatment of hypomagnesemia with traditional treatment and L-carnitine resulted in significant elevation ( $P < 0.05$ ) of serum Mg, Ca, glucose and PTH in hypomagnesemic rams than traditional treatment only. However, there were significant reduction ( $P < 0.05$ ) in serum K, urea, CPK and cTnI than traditional treatment only at 24 hour after treatment. Based on the results of this study we concluded that the addition of L-carnitine to the traditional treatment of hypomagnesaemia in sheep is effective and produced earlier and more pronounced recovery.

**Key words:** Experimental, hypomagnesemia, L-carnitine, sheep, treatment

## 1. INTRODUCTION

Magnesium (Mg), the fourth most common cation in the body which is a cofactor in more than 300 cellular enzymatic systems and has a key role in cellular metabolism (Baig et al., 2012). Hypomagnesemic tetany is a highly fatal disease affecting all ruminants of

all ages and of both sexes, certain conditions, such as fasting or reduced feed intake, may result in tetany or paresis (Hoff et al., 1993). Morbidity is usually low, but can exceed 25 % under some conditions. Low serum Mg concentration is characteristic of the disease,

and frequently serum Ca concentration is concurrently decreased. (Robert et al., 1988.)

The etiology of hypomagnesemia is complex due to numerous interacting factors influencing Mg content in the diet, as well as its availability and absorption (Robson et al., 1997). The relationship of K, Ca, and Mg in forage is an important factor in the development of hypomagnesemia. Heavy K fertilization can cause hypomagnesemia even when Ca and Mg levels are within the normal range (Grunes et al., 1984; Schonewille et al., 2000). Potassium ingestion by ruminants may be an enhancement of the urinary excretion of Mg, the major effect on Mg metabolism is a substantial reduction of absorption of Mg from the reticulorumen (Tomas and Potter, 1976; Schonewille et al., 2000)

The classical acute (tetanic) form of hypomagnesaemia is due to the critical role that magnesium plays in neuromuscular transmission. Clinical signs initially include depression and dullness, and later progress to stiffness, excitability, tremors, chewing, and hypersalivation, blinking of the third eyelid, twitching of the pinnae (ear flapping), collapse, tetanic muscle spasms, coma and death. (Foster et al., 2007). Ghanem (2013) recorded elevation of K, aspartate aminotransferase (AST), alkaline phosphatase (ALP), CPK and lactate dehydrogenase (LDH) and urea in hypomagnesemic calves. However, significant reduction in serum Ca, glucose and PTH was observed.

The traditional treatment of hypomagnesemia in ruminants includes administration of Mg and Ca salts, separately or as a combined solution (Foster et al., 2007; Elliott, 2009; Ghanem, 2013).

L-carnitine is the form of amino acid Lysine and Methionin which plays an important role in transforming of free fatty acids into energy. It forms free fatty acid esters and causes oxidation of free fatty acids in mitochondria. L-carnitine has a number of functions, such as transforming fatty acids into energy, preventing ketosis, carrying ATP from mitochondria to cytosole, (Haemeyer et al., 1997; Harmeyer 2001)

L-carnitine supplementation has beneficial effects on animal performance by enhancing resistance to metabolic diseases, preventing some diseases, strengthening immune system, and playing an important role in metabolic and physiological processes (Fathi and Farahzadi 2014). L-carnitine supplementation increased serum Ca concentrations in patients with renal diseases (Mercadal et al., 2018). Moreover, administration of L-carnitine in resulted in elevation of plasma glucose concentration and reduction of blood urea concentration (Chapa et al., 2001, Mercadal et al., 2018). Parenteral administration of L-carnitine was used a protective measure against pregnancy toxemia via increasing serum glucose concentration in goats (Kaçar et al., 2010).

Thus the aim of this study is to evaluate the role of L- carnitine as a supportive treatment in experimentally induced hypomagnesemia in sheep.

## **2. Materials and Methods**

### **a. Induction of hypomagnesemia**

Ten apparently healthy ossimi rams aged 10-12 months old with an average live weight of 35±1.1 kg were used for experimental induction of hypomagnesemia. Fecal examination, liver function, and kidney function tests were carried out for detection of any internal parasite, liver or kidney

affections. Hypomagnesemia was induced by daily administration of potassium chloride (1.39 gm/kg body weight) and citric acid (1.19gm/kg body weight) orally by stomach tube till appearance of the characteristic signs of hypomagnesemia according to Hazarika and Pandey (1993); Hefnawy (2000) and Constable et al. (2017). Composition and analysis of the experimental and control ration is shown in table (1).

#### b. Treatment trials

Hypomagnesemic rams were divided into two groups according to the line of treatment. The first group (n=5) was treated by the traditional treatment alone included injection 50 ml of magnesium sulphate 20% I/V, 50 ml of magnesium sulphate 20% S/C, 25 gm of magnesium chloride orally and vitamin AD3E in addition to calcium and dextrose 5% I/V (Hefnawy 2000). For the second group (n=5) the traditional treatment was applied in addition to L-carnitine (L-carnitine<sup>®</sup> 1 gm, MEPACO) 20 mg/kg I/V (Kaçar et al., 2010).

#### c. Sampling and biochemical analysis of sera

Blood samples were collected from rams before induction and after appearance of clinical signs of hypomagnesemia. Also, blood samples were collected at 6, 12 and 24 hours after treatment.

Blood samples were collected from jugular vein. The samples were allowed to clot in slanting position at room temperature for about 2 hours then the samples were centrifuged at 3000 rpm for 10 minutes, the clear sera were aspirated carefully by automatic pipette and transferred into clear dry labeled Eppendorf tubes and stored at -20°C till examination. Only clear non-hemolyzed sera were used for the biochemical examination. Magnesium was determined spectrophotometrically by using special kits

according to Fischbach and Dunning (2009). Calcium was determined according to Gindler and King (1972). Na and K were determined spectrophotometrically by using special kits according to Henry et al. (1974). Urea, creatinine and glucose were determined spectrophotometrically by using special kits according to the method described by Young (1990). Serum cortisol concentration was determined using an ELISA kit (Eucardio Laboratory, Inc., Encinitas, and CA., U.S.A.). PTH was determined by Radioimmunoassay (RIA) according to the method described by Mayar et al. (1979). CPK was determined spectrophotometrically by using special kits according to the method described by Rec. GSCC (1977). cTnI concentration was measured according to Collinson et al. (2001)

#### 2.4. Statistical analysis

The obtained results from the experiments were expressed as mean  $\pm$  SEM and were analyzed using (SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp). Differences were declared significant when ( $P < 0.05$ ).

### 3. Results

#### a. Clinical findings

The symptoms of hypomagnesemia appear gradually until complete appearance of symptoms at day 28 post induction. These symptoms included loss of appetite, grinding on teeth, restlessness, spasmodic defecation and urination, arched back, tetany, and staggering gait, champing of the jaw with foamy salivation, opisthotonus, nystagmus and episodes of convulsions. The rectal temperature, pulse rate and respiration rate were increased. These symptoms were disappeared after both trials of treatment. However, in case of L-carnitine group, recovery was earlier and more pronounced at 24 hrs after treatment.

b. Biochemical findings

As shown in Table 2 and Figure 1, there were significant decrease ( $P < 0.05$ ) in serum Mg, Ca, glucose and PTH in hypomagnesemic rams. However, there were significant increase ( $P < 0.05$ ) in serum Na, K, urea, creatinine, cortisol, CPK and cTnI in experimentally induced hypomagnesemic rams after 28 days of induction.

By comparing the two lines of treatment,

the results revealed that treatment of hypomagnesemia with traditional treatment and L-carnitine resulted in significant elevation ( $P < 0.05$ ) of serum Mg, Ca, glucose and PTH than traditional treatment alone after 24 hours of treatment. Additionally, there were significant decrease ( $P < 0.05$ ) in serum K, urea, CPK and cTnI 24 hours after treatment with L-carnitine.

Table 1 Composition and analysis of the experimental ration

Ingredients	%	Analysis of ingredients	%
Grounded yellow corn	47.6	TDN	69.95
Soya bean meal	14.7	CP	14
Wheat bran	18	CF	9.1
Polished rice	5	Ca	0.95
Soya bean hulls	10.9	P	0.40
Grounded lime stone	2.3	Na	0.42
Sodium chloride	0.5	CL	0.58
Ammonium chloride	0.5		
Premix vitamin and mineral mixture	0.3		
Sodium bicarbonate	0.2		

Table 2 Biochemical findings in healthy, experimentally induced hypomagnesemic (Diseased) rams, traditional treatment alone and traditional treatment with L- carnitine (Means  $\pm$  SEM).

	Mg	Ca	Na	K	Urea	Creatinine	Glucose	Cortisol	PTH	CPK	cTnl
	(mg/dl)	(mg/dl)	(mEq/L)	(mEq/L)	(mg/dl)	(mg/dl)	(mg/dl)	(U/L)	(U/L)	(U/L)	(U/L)
Healthy	2.5 $\pm$ 0.1a	10.1 $\pm$ 0.2a	144.7 $\pm$ 0.6c	4.6 $\pm$ 0.1c	16.7 $\pm$ 0.4c	0.7 $\pm$ 0.0c	48.0 $\pm$ 0.8b	4.2 $\pm$ 0.2b	10.3 $\pm$ 0.6a	68.8 $\pm$ 2.8c	0.04 $\pm$ 0.01d
Diseased	0.7 $\pm$ 0.1e	7.5 $\pm$ 0.3d	153.1 $\pm$ 1.2a	7.5 $\pm$ 0.3a	25.2 $\pm$ 1.1a	1.6 $\pm$ 0.1a	36.3 $\pm$ 2.2c	7.2 $\pm$ 0.5a	7.6 $\pm$ 0.6c	92.3 $\pm$ 1.6a	1.07 $\pm$ 0.06a
Traditional treatment only											
6h	1.4 $\pm$ 0.2d	8.7 $\pm$ 0.2c	151.0 $\pm$ 1.5b	6.0 $\pm$ 0.1b	21 $\pm$ 0.6b	1.2 $\pm$ 0.1b	44.0 $\pm$ 0.6b	4.8 $\pm$ 0.1c	7.8 $\pm$ 0.2b	80.3 $\pm$ 1.2b	0.65 $\pm$ 0.03b
12h	1.5 $\pm$ 0.2d	9.0 $\pm$ 0.1b	148.7 $\pm$ 1.2c	5.4 $\pm$ 0.3b	18.7 $\pm$ 0.9b	0.8 $\pm$ 0.0c	46.0 $\pm$ 0.6b	4.2 $\pm$ 0.1b	8.3 $\pm$ 0.2b	73.3 $\pm$ 0.9b	0.44 $\pm$ 0.07b
24h	1.8 $\pm$ 0.1c	9.2 $\pm$ 0.0b	145.0 $\pm$ 0.6c	5.1 $\pm$ 0.2b	18.3 $\pm$ 0.3b	0.7 $\pm$ 0.0c	47.7 $\pm$ 0.9b	3.7 $\pm$ 0.1b	8.8 $\pm$ 0.2b	72 $\pm$ 2.5b	0.11 $\pm$ 0.02c
Traditional treatment and L- carnitine											
6h	1.8 $\pm$ 0.1c	8.9 $\pm$ 0.5c	150.7 $\pm$ 0.3b	6.2 $\pm$ 0.4b	21.3 $\pm$ 0.9b	1.1 $\pm$ 0.1c	45.7 $\pm$ 0.3b	4.3 $\pm$ 0.2b	7.6 $\pm$ 0.3c	81.7 $\pm$ 2.7b	0.6 $\pm$ 0.06b
12h	2.1 $\pm$ 0.1b	10.1 $\pm$ 0.2a	147.0 $\pm$ 0.6c	5.4 $\pm$ 0.5b	17.0 $\pm$ 0.6c	0.9 $\pm$ 0.1c	48 $\pm$ 0.6b	3.4 $\pm$ 0.2c	9.0 $\pm$ 0.6b	74.7 $\pm$ 2b	0.21 $\pm$ 0.05c
24h	2.4 $\pm$ 0.2a	10.6 $\pm$ 0.2a	143.7 $\pm$ 0.3c	4.5 $\pm$ 0.2c	16.0 $\pm$ 0.6c	0.7 $\pm$ 0.1c	53 $\pm$ 0.6a	3.0 $\pm$ 0.0c	9.9 $\pm$ 0.6a	63.7 $\pm$ 1.9c	0.05 $\pm$ 0.01d

Values with different letters within the same column are significantly different at  $P < 0.05$

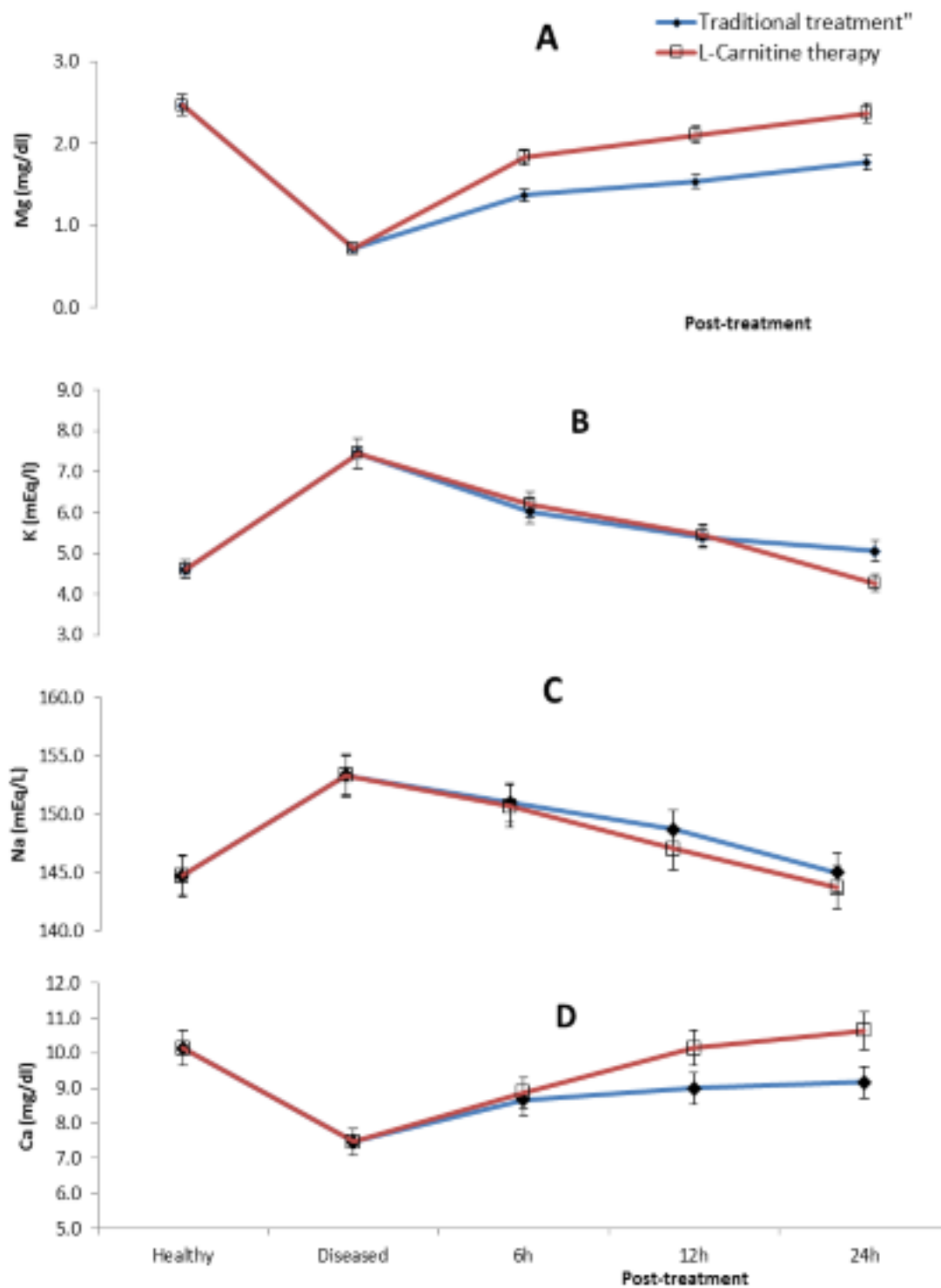


Figure 1a: Mg, k, Na and Ca serum levels in healthy, experimentally induced hypomagnesemic (Diseased) rams, traditional treatment alone and traditional treatment with L- carnitine.

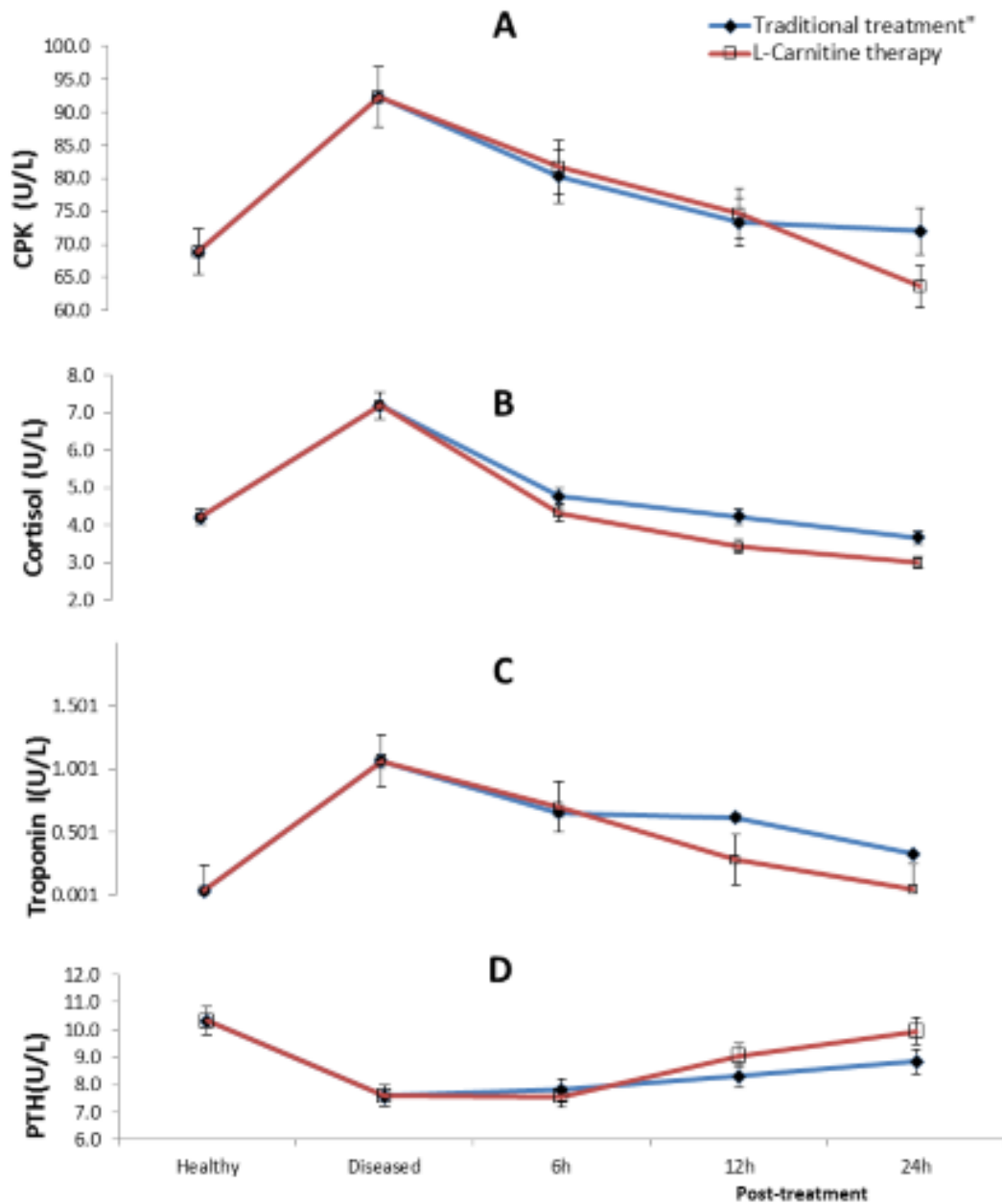


Figure 1b: CPK,cortisol, troponin I and PTH serum levels in healthy, experimentally induced hypomagnesemic (Diseased) rams, traditional treatment alone and traditional treatment with L- carnitine.

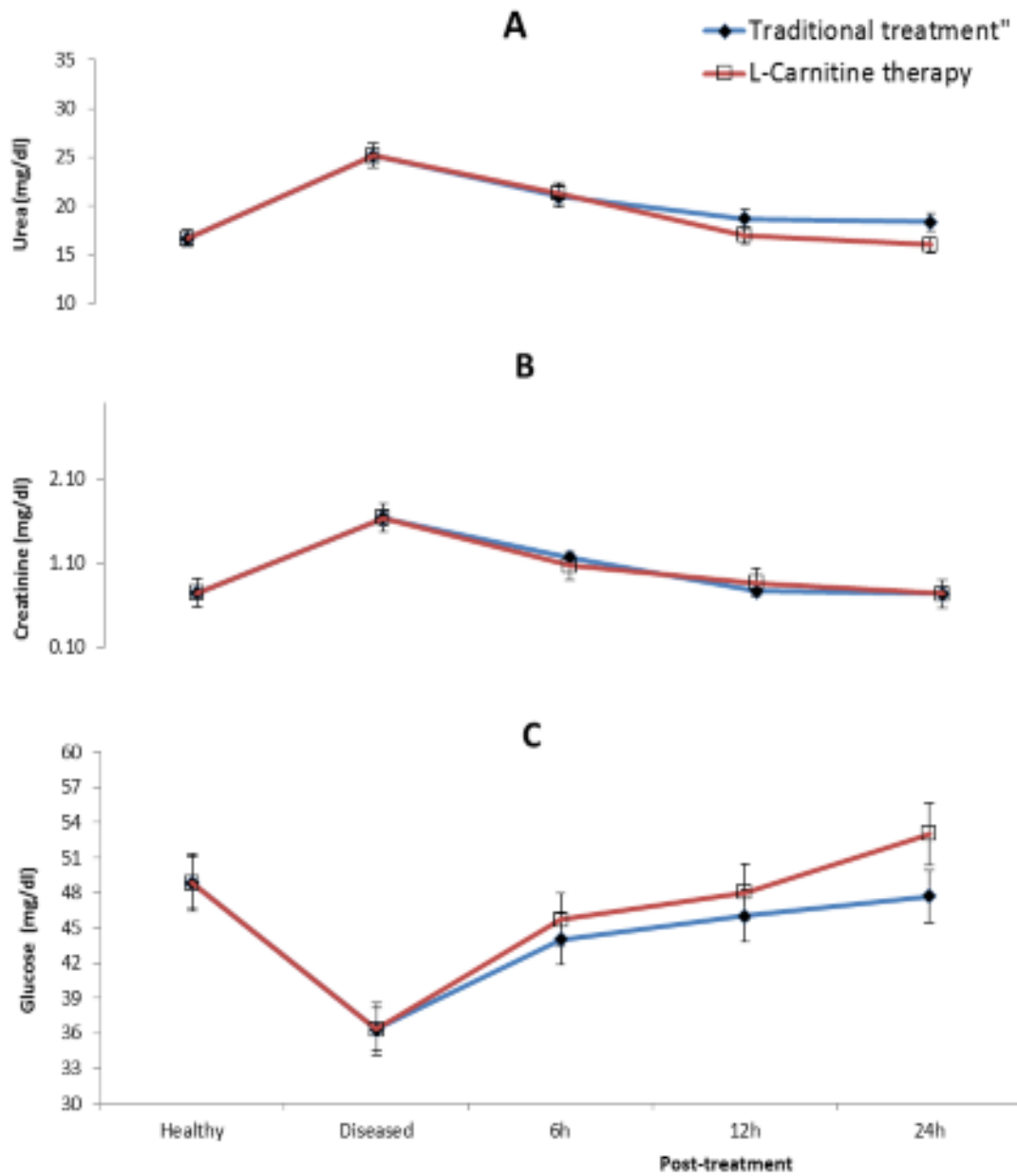


Figure 1c: Urea, creatinine and glucose serum levels in healthy, experimentally induced hypomagnesemic (Diseased) rams, traditional treatment alone and traditional treatment with L-carnitine.



#### 4. Discussion

Mg has been shown to be involved in several enzyme activities in the body, a major intracellular divalent cation and also associated with many physiological and biochemical functions (Constable et al., 2017). The diagnosis of clinical hypomagnesemic tetany is general made by a combination of history, clinical signs and response to treatment. Clinical signs rapidly progress to death (McCoy, 2004).

Clinical hypomagnesemia was induced experimentally in sheep in the current study after oral administration of K chloride and citric acid for 28 days which is consistent with findings of Hazarika and Pandey (1993), Hefnawy (2000) Abd El-Maksoud et al., 2012 and Constable et al., (2017). K ingestion by ruminants may be an enhancement of the urinary excretion of Mg, the major effect on Mg metabolism is a substantial reduction of absorption of Mg from the reticulorumen (Tomas and Potter, 1976; Zelal, 2017)

Regarding the clinical symptoms of hypomagnesemia in sheep, as appearing gradually till 28 days post induction. Similar findings were recorded by Hefnawy( 2000) and constable et al. (2017). These signs appeared clearly when Mg level fall below 1 mg/dl which was coincided with Kunkel et al. (1953) and Hefnawy (2000). Tetany does not occur until the serum magnesium falls below this concentration (Constable et al., 2017).

There was significant decrease in serum Ca in hypomagnesemic rams that was coincided with Foster et al. (2007), Haigney et al. (2007) Abd El-Maksoud et al. (2012) and Rani (2015) who reported that hypomagnesemia influences Ca metabolism by reducing the secretion of PTH in response

to hypocalcaemia and reducing tissue sensitivity to PTH, particularly in bone, gut and kidney, which are all important for Ca absorption. There were significant increase in serum Na and K in hypomagnesemic rams which was coincided with Constable et al. (2017) who reported that ruminants grazing on high K pasture may result in depression of Na: K ratio in the rumen fluid which reduces the absorption of Mg in ewes. Similar to the present study, Ghanem (2013) also recorded significantly increased blood urea in hypomagnesaemic calves. Also, the significant decrease of glucose in the present study may be due to reduction of the food intake associated with hypomagnesaemia (Hazarika and Pandey 1993; Hoff et al., 1993; Attia, 1999; El-Sangary et al., 2011; Ghanem 2013 and Rani 2015). Moreover, Baig et al. (2012) attributed the decrease in serum glucose to the interrelationship between Mg and carbohydrate metabolism. The significant decrease of cortisol may be due to stress reaction involving the adrenal–glucocorticoid axis increased circulating K concentration and lowered Mg transport across the choroidal plexus, which was one of causes of this disease (Robson et al., 2004). There was significant increase in serum CPK that indicated muscular damage in hypomagnesemic rams. This result was also supported by Ghanem (2013) and Constable et al., (2017). Significant increase in serum cTnI in the current study was in agreement with Kumar and Sagar (2013) and Celik et al. (2016) which may be associated with increased myocardial damage (Chang et al., 1985). Mg plays a role in controlling calcium entry into the cells, thus affecting the cardiac smooth muscle tone (Čvorišćec et al., 2009).

The traditional treatment of hypomagnesemia in ruminants includes administration of Mg and Ca salts, separately

or as a combined solution (Foster et al., 2007; Elliott 2009; Ghanem 2013; Zelal 2017). In the present study, hypomagnesemic rams recovered completely within 24 hours after traditional treatment and L-carnitine. They resumed their appetite and biochemical profile to be around normal level. Findings of the present study are coincided with Pinsent and Cottom (1987) and Foster (2007) in small ruminants and Ghanem (2013) in calves.

Treatment of hypomagnesemic rams with traditional treatment and L-carnitine resulted in significant elevation of serum Mg, Ca and PTH in experimentally induced hypomagnesemic rams than traditional treatment only. Haarenen (2003) and Mercadal et al.(2018) recorded that L-carnitine supplementation increased serum calcium concentration. The traditional treatment with L-carnitine resulted in significant elevation of serum glucose in hypomagnesemic rams than traditional treatment only which is coincided with the results of Kaçar et al., (2010) and Chapa et al., (2001). Giduck and fontenot (1987) and Baig et al. (2012) recorded that the increase in glucose increases absorption of Mg. According to the results of the present study the positive effect of L-carnitine on serum magnesium could be attributed to L-carnitine positive effect on both calcium and glucose.

There was significant decrease in serum urea with L-carnitine injection 24 hour after treatment. Similar finding was recorded by Mercadal et al. (2018). There was significant decrease in serum K in case of L-carnitine treatment. This result was coincided with Laboni et al., (1987) who reported that L-carnitine deficiency may play a major role in Na-K pump dysfunction in uremic patients. There was significant decrease in serum

cortisol with L-carnitine injection which is agreed with Parnetti et al. (1990).

There were significant decrease in serum cTnI and CPK at 24 hours after treatment with L- carnitine. This result was in agreement with Sun et al., 2011 who recorded that serum level of myocardium injury marker (cTnI) returned to the normal levels after L-carnitine administration. L-carnitine reduces the myocardial injury mainly through improving carbohydrate metabolism and reducing the toxicity of high levels of free fatty acids (Buermer et al., 2006; Dinicolantonio et al., 2013). Additionally, Giamberardino et al. (1996) reported that L-carnitine has a protective effect against pain and muscle damage and reduce serum CPK.

## 5. Conclusion

Based on the results of this study we concluded that the injection of L- carnitine with the traditional treatment of hypomagnesaemia in sheep was effective and produced earlier and more pronounced recovery than traditional treatment only.

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