Research paper

Impact of gastrointestinal parasitism on dry matter intake and live weight gain of lambs: A meta-analysis to estimate the metabolic cost of gastrointestinal nematodes

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A B S T R A C T

This study aimed to estimate the effect of gastrointestinal nematodes (GIN) on the productive performance assessed by the live-weight change (LWC) of lambs, and the metabolic cost associated with parasitism by means of a meta-analysis. Data used in the meta-analyses were obtained from twenty papers selected using the following criteria: (a) lambs with (I) and without (NI) GIN; (b) lambs fed ad libitum; (c) LWC data; (d) feed consumption data; and (e) chemical composition of diets. The effect of diet composition (crude protein [CP] and metabolizable energy [ME]) on dry matter intake (DMI), and the effect of composition and nutrient intake (DMI and CP intake [CPI]) and ME intake (MEI) on LWC was evaluated using respective regression analyses. The metabolic cost of worm burden was determined as the difference in CP and ME requirements between NI and I lambs for each adult parasite. The CP and ME cost were evaluated for lambs at two different levels: maintenance level 0 g LWC and 100 g LWC. The worm burden had an impact on the DMI and LWC of lambs ($P < 0.05$). The association of CP x infection level was the best predictor of DMI. The association between MEI and infection level were the best predictors of LWC. The metabolic cost of GIN increased to 0.30 mg CP/kg $LW^{0.75}$ and 0.0056 kJ ME/kg $LW^{0.75}$ for each adult parasite. The metabolic cost was not modified by diet quality (maintenance level 0 g LW/day or 100 g LW/day). In conclusion, GIN has a negative effect on DMI and LWC. The metabolic cost of GIN infection can be covered by supplying the additional requirements for protein and energy in the diet of infected lambs.

1. Introduction

Several studies have evaluated the interaction between nutrition and gastrointestinal nematodes (GIN) (Abbott et al., 1988; Bown et al., 1986; Bricarello et al., 2005; Knox and Steel, 1999; Retama-Flores et al., 2012; Sykes and Coop, 1977, 1976; Wallace et al., 1996). It is generally accepted that there is a greater need for nutrients in lambs infected with GIN, which results in lower productive performance (Cei et al., 2018; Kahn et al., 2000; Kyriazakis et al., 1994). Many review papers have reported the relationship between nutrition and parasites, including experiments showing that feed supplementation of infected animals allows them to be resilient against GIN. Thus, supplementation allows production levels similar to those of non-infected animals to be achieved (Hoste et al., 2016; Torres-Acosta et al., 2012). Cei et al. (2018) suggested a correlation between parasite numbers and health parameters, where the greater the number of parasites the greater the loss of productive and health parameters. Therefore, the presence of GIN represents an additional nutrient requirement (protein and energy) for infected lambs. However, the nutrient requirement necessary to cover the costs of different GIN infections in growing lambs has rarely been estimated or reported. Metabolic cost is defined as the amount of energy and protein required by an animal to overcome an adverse/negative effect (i.e. parasitism) and to achieve a similar performance (i.e. weight gain, milk production, gestation) to that of an animal free of any negative factor (Retama-Flores et al., 2012). Only two studies have evaluated the metabolic cost of GIN infection in lambs, the first under

pen conditions (Liu et al., 2005) and the second under field conditions (Retama-Flores et al., 2012). However, an estimation of the metabolic cost can be improved by using data from studies with different conditions: parasitological (worm burden and species of parasites) and nutritional (quantity of energy and protein). These data can be incorporated into a meta-analysis to determine the metabolic cost of infection with GIN. Given that grazing ruminants are a common host of GIN infections, an estimation of the metabolic cost of GIN is key when deciding the opportunity cost of using extra feed to cover the metabolic costs of GIN, or to eliminate the GIN population with conventional or non-conventional anthelmintics (Torres-Acosta et al., 2012). This decision should also consider aspects such as cost of feed, animal welfare, development of anthelmintic resistance, and other consequences on animal management. Therefore, the aim of this study was to estimate the metabolic cost of GIN (in terms of energy and protein) on the productive performance (live weight change [LWC]) of lambs by meta-analysis.

2. Materials and methods

2.1. Database

Data were acquired from published literature regarding parasitized lambs fed diets without secondary metabolites. The keywords used for the research were "sheep", "intake", and "GIN".

The inclusion criteria were as follows:

1) Have used lambs as experimental animals;
2) Containing information of body weight and age;
3) Containing data of larval dose, parasitic load (eggs per gram of faeces or number of adult parasites), and infection type (mixed or mono specific);
4) Containing (or allow the estimation of) information on feed consumption, LWC, and diet composition;
5) *Ad libitum* feed supply.

The information search was performed with the meta-search engine of CONRICYT-Mexico, which includes the Web of Science, Scopus, and EBSCO. Additional information was searched using the databases of ScienceDirect, Cambridge Journal, and Springer Link. The initial search yielded 7000 papers, which were discarded if they were literature reviews, contained data on the consumption of plants with secondary metabolites, used animals different from lambs, did not have feed consumption data, or the feed was not supplied *ad libitum*.

A total of 22 experiments in 20 papers with data paired on parasitism were obtained and divided into two categories: infected lambs (65 data and 583 sheep) and non-infected lambs (44 data and 360

sheep).

Data of Metabolic Live Weight (kg LW$^{0.75}$), Crude Protein (% CP), Metabolizable Energy (ME, MJ/kg DM), LWC (g/kg LW$^{0.75}$), Dry Matter Intake (DMI g/kg LW$^{0.75}$), CP Intake (CPI g/kg LW$^{0.75}$), ME Intake (MEI MJ/kg LW$^{0.75}$) and worm burden were analyzed, because they were the most frequently found in the studies.

2.2. Statistical analysis

The data set for each of the following variables: (a) Diet composition (%): CP, ME; (b) Intake (g/kg LW$^{0.75}$): DMI, CPI, MEI (MJ/kg LW$^{0.75}$); and (c) LWC (g/kg LW$^{0.75}$) was used to generate a scatter plot divided into two categories for each study. There was insufficient information to include other variables.

The scatter plot allowed us to make a contingency table for the LWC variable where we evaluated the possibility of the lambs losing weight if they were infected.

The data set was analyzed to assess the effect of diet composition, worm burden, or its interaction on DMI (g DM/kg LW$^{0.75}$) and the relationship between diet composition, intake, worm burden, or its interaction on LWC (g/kg LW$^{0.75}$). Regression analysis was performed using PROC MIXED of SAS (Huuskonen et al., 2014) using the following model:

$$Y = B_0 + B_1X_{1ij} + b_0 + b_1X_{1ij} + e_{ij}$$

where B_0 and B_1X_{1ij} are the fixed effects (interception and effects of independent variables) and b_0, b_1, and e_{ij} are the effects of the random experiment (interception and slope), where i = 1,…, n studies and j = 1,…, n values. Unstructured variance–covariance matrix for the intercepts and slopes (TYPE = UN option) was used in the random statement. Root mean squared errors presented in tables were adjusted for random study effects as described by St-Pierre (2001). Akaike information criterion (AIC) was used to select the best models (Schuba et al., 2017).

The metabolic cost for GIN worm burden in terms of ME and CP was estimated as the difference in MEI and CPI between non-infected lambs and infected lambs. For this purpose, the requirements of ME and CP were estimated using the best fit models for maintenance (0 g LWC) and 100 g LWC for a 25 kg LW lamb (11.18 kg LW$^{0.75}$).

3. Results

The distribution of the data for the CP and ME variables is shown in Fig. 1. The concentration of CP varied between 5% to 21.4% for NI, and from 5% to 26.9% for I (Fig. 1a). The variation in ME concentration for both categories (I and NI) was 7.2 to 11.7 MJ/kg DM (Fig. 1b). Fig. 2 shows the distribution of data for the CPI and MEI variables by category
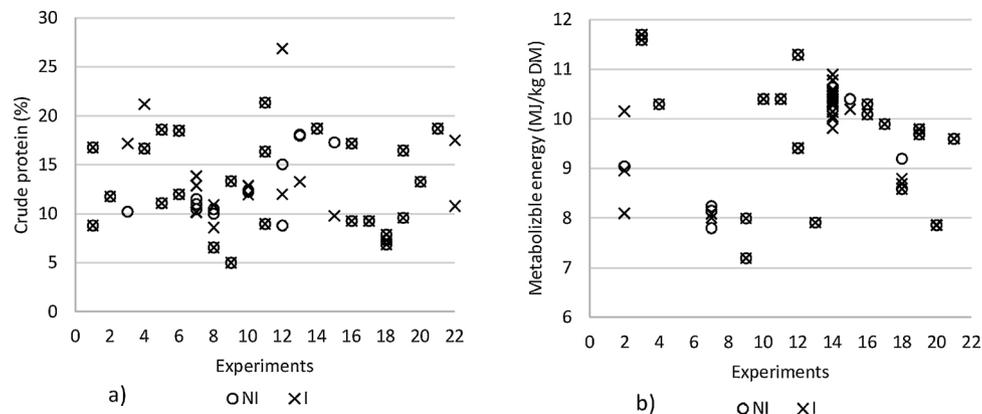

Fig. 1. Data on dietary concentrations of (a) crude protein (%CP) and (b) metabolizable energy (ME MJ/kg DM), of infected (I) and non-infected (NI) lambs in each experiment included in the meta-analysis.
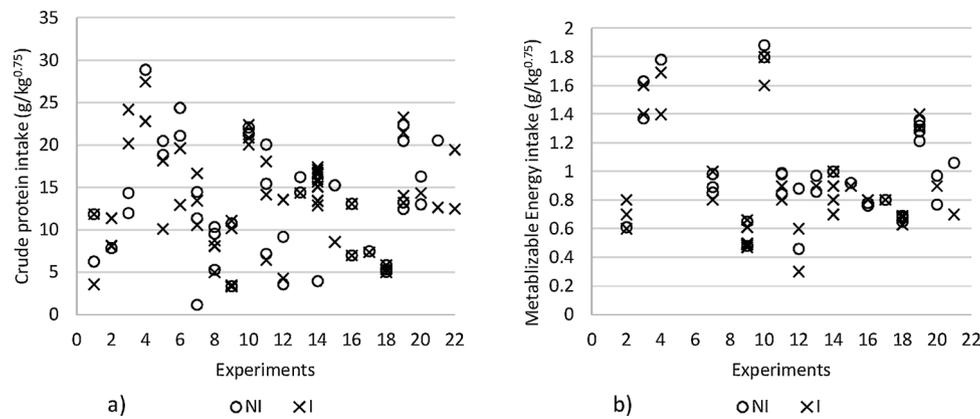
Fig. 2. Data of (a) crude protein intake (CPI) and (b) metabolizable energy intake (MEI) of infected (I) and non-infected (NI) lambs in each experiment included in the meta-analysis.
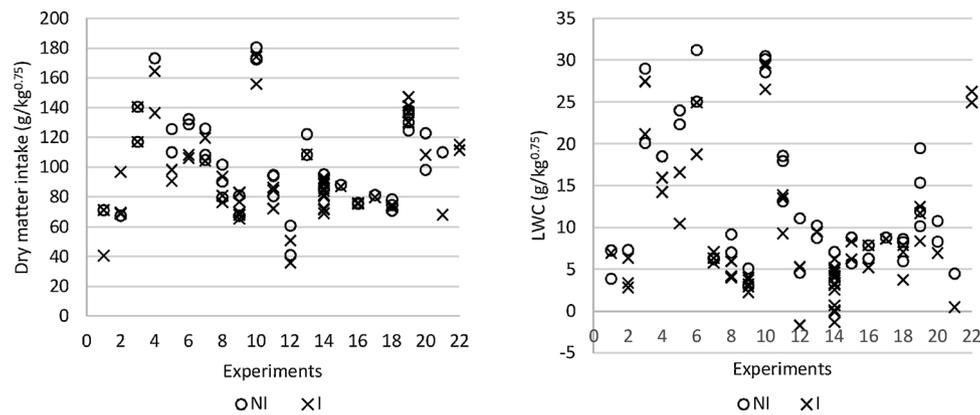

Fig. 3. Data of dry matter intake (DMI) and live weight change (LWC) of infected (I) and non-infected (NI) lambs in each experiment included in the meta-analysis.

(I and NI) for each study. The range of the CPI for NI was from 1.2 to 28.9 g/kg $LW^{0.75}$ and from 3.3 to 27.5 g/kg $LW^{0.75}$ for I (Fig. 2a). The variation in the MEI was from 0.46 to 1.88 MJ/kg $LW^{0.75}$ for NI and from 0.30 to 1.80 MJ/kg $LW^{0.75}$ for I (Fig. 2b). The variations in the DMI and LWC are shown in Fig. 3. The DMI of NI varied from 40.8 to 180.7 g/kg $LW^{0.75}$ and from 35.9 to 174.4 g/kg $LW^{0.75}$ for I (Fig. 3a). The LWC was in a range from 3.1 to 31.3 g/kg $LW^{0.75}$ for NI and from −1.7 to 29.6 for I (Fig. 3b). The metabolic weight of lambs in the studies ranged from 6.9 to 16.8 kg $LW^{0.75}$ for both categories (I and NI).

The results of the contingency table indicate that infected lambs were 2.17 times more likely to lose weight with a confidence interval of 1.37–3.45 compared with non-infected lambs.

3.1. DMI and LWC

The DMI was 94.0 ± 28.58 and 104.8 ± 32.82 g/kg $LW^{0.75}$ for infected and non-infected lambs, respectively. Data showed that the interaction between worm burden and CP had an impact on the DMI of lambs (Table 1). The best model for LWC was the interaction between MEI and worm burden (Table 2). In addition, the association of CP and worm burden was a model that predicted LWC.

3.2. Metabolic cost to level of infection

The estimated metabolic cost of the GIN worm burden was 0.30 mg CP/kg $LW^{0.75}$ and 0.056 kJ ME/kg $LW^{0.75}$ for each adult parasite. The metabolic cost was similar for lambs fed at maintenance level (0 g LWC/day) and for animals with 100 g LWC/day.

4. Discussion

4.1. DMI

This study reports that the worm burden affected the DMI of infected lambs. However, the best model to explain the DMI was the interaction of CP and worm burden. Of the total number of studies analyzed, 59% (13/22 experiments) showed evidence of a negative effect of parasitism on DMI (Abbott et al., 1988; Coop et al., 1995; Downey et al., 1972; Haile et al., 2004; Kimambo et al., 1988; Kyriazakis et al., 1996, 1994; Sykes et al., 1988; Sykes and Coop, 1977, 1976; Van-Houtert et al., 1995). In monospecific infections with abomasal or intestinal nematodes, two factors explain the reduced consumption: 1) for abomasal nematodes, increased blood gastrin concentrations and the

Table 1
Relationship between DMI (g/kg $LW^{0.75}$), dietary composition variables and worm burden in lambs estimated by a mixed model regression analysis.

Variable x	Intercept	S.E.	P-value	X_1	S.E.	P-value	X_2	S.E.	P-value	Adj. RSME	AIC
CP* worm burden	92.80	7.40	< 0.01	0.65	0.27	0.03	−0.0003	0.0001	0.01	13.35	893.1
Worm burden	101.65	6.74	< 0.01	−0.0002	0.0001	< 0.01				14.12	899.2

CP, Crude Protein (%); I, infected with GIN.
Adj. RMSE = residual mean squared error adjusted for random study effects; AIC = Akaike's information criteria.

Table 2
Relationship between LWC (g/kg LW$^{0.75}$) and the variables of macronutrient consumption (g/kg LW$^{0.75}$) and worm burden estimated by a mixed model regression analysis.

Variable x	Intercept	S.E.	P-value	X$_1$	S.E.	P-value	X$_2$	S.E.	P-value	Adj. RSME	AIC
MEI* worm burden	−7.13	3.22	0.04	17.76	3.68	< 0.01	−0.0001	0.00002	< 0.01	1.20	378.4
MEI	−4.56	3.94	0.26	13.97	4.58	< 0.01				1.03	415.8
DMI	−6.45	2.89	0.04	0.17	0.04	< 0.01				1.19	597.7
CPI* worm burden	6.66	1.22	< 0.01	0.33	0.12	0.01	−0.0001	0.00002	< 0.01	1.70	605.6
CPI	4.35	0.97	< 0.01	0.43	0.11	< 0.01				1.47	614.6

MEI, Metabolizable Energy Intake; CPI, Crude Protein Intake; DMI, Dry matter intake.
Adj. RMSE = residual mean squared error adjusted for random study effects; AIC = Akaike's information criteria.

release of gastrin and pepsinogen in the abomasum are factors that cause decreased food intake (Fox, 1997); 2) for intestinal nematodes, Coop and Sykes (2001) suggested that the reduced intake of sheep infected with GIN (*Trichostrongylus colubriformis*) reflected a response to an imbalance in the protein amount that reaches the liver and peripheral tissues, due to priority in the use of amino acids captured to repair the gastrointestinal tissue and for the development of immunity. Fox et al. (1997) reported that in mixed infections (abomasal and intestinal), animal might compensate for the effects of GIN infection while the main sites of digestion and absorption are unaffected.

However, 41% of the experiments (9/22) did not find any effect of parasitism on the DMI. Of these experiments, four (4/9) used a monospecific *Haemonchus contortus* infection, and 3 of these showed a tendency to decrease their DMI (Wallace et al., 1999, 1996, 1995), while in the fourth experiment, no effect of parasitism on the consumption of DM was reported (Bricarello et al., 2005). All these studies had a worm burden (< 2500 adult parasite) which can be considered low. Of two experiments (2/9) that used monospecific *T. colubriformis* infection, one found a tendency for reduced intake (Bown et al., 1986) and one did not find any effect (Kahn et al., 2000). Kahn et al. (2000) employed a feeding protocol that allowed the elimination of differences in feed consumption between experimental groups while evaluating the differences in metabolizable protein supply. They found that feed consumption was not affected by infection status (infected or non-infected), or by the type of feed (moderate or high metabolizable protein).

Three experiments (3/9) used mixed infections with a moderate adult parasite burden (3000 to 20,000 adult parasites) where diets supplied a high concentration of dietary nutrients (Knox, 1997; Knox and Steel, 1999; Retama-Flores et al., 2012). The DMI in these studies tended to be reduced possibly indicating an effect of the diet quality on DMI.

4.2. LWC

The present meta-analysis showed that worm burden has an impact on the productive performance (LWC) of lambs. In 73% of the experiments (16/22) analyzed there was an effect of parasitism with GIN on LWC (Abbott et al., 1988; Bown et al., 1986; Coop et al., 1995; Downey et al., 1972; Haile et al., 2004; Kahn et al., 2000; Kimambo et al., 1988; Kyriazakis et al., 1996, 1994; Retama-Flores et al., 2012; Sykes et al., 1988; Sykes and Coop, 1977, 1976; Van-Houtert et al., 1995). The latter was probably due to a higher proportion of dietary nutrients being diverted from growth to other processes, such as the synthesis of plasma proteins, repair of the gastrointestinal tract and mucus secretion, which might have been increased due to the presence/action of GIN (Coop and Kyriazakis, 2001, 1999; Torres-Acosta et al., 2004). This indicates protein metabolism was increased as a pathophysiological response to GIN (Yu et al., 2000).

However, 27% of the experiments (6/22) reported no effect of parasitism on LWC lambs. Four experiments (4/6) used a monospecific *H. contortus* infection. All had a tendency to decrease the LWC of lambs (Bricarello et al., 2005; Wallace et al., 1999, 1996, 1995). However, it is likely that the low worm burden (< 2500) was the main cause of the lack of effect of GIN on LWC. Two papers (2/6) used mixed infections, and both had a tendency to reduce the LWC (Knox, 1997; Knox and Steel, 1999). However, the moderate worm burden and good quality diet (high energy and protein content) in these studies might have favored resilience and thus a lack of effect of GIN on LWC.

The results of the present meta-analysis suggest an interaction between parasitism and the consumption of nutrients (energy and protein). Therefore, an increase in nutrient intake allows a positive LWC despite the infection; however, this positive LWC will not be the same as that of a non-infected animal. This might be because of the reduction in nutrient utilization efficiency induced GIN, which depends on the species of nematode, the quantity of implanted larvae in the animal (worm burden), the site of infection and the nutritional quality of the diet. Our study shows that the best model to explain LWC is the association between MEI and worm burden. Most of the experiments included in the meta-analysis had a higher concentration of protein in the diet of infected animals compared with non-infected animals, while the dietary energy concentration of infected and non-infected animals was similar. These studies were designed to test the hypothesis that supplying protein to infected animals will overcome the negative effects of GIN. However, the results of the meta-analysis indicate that infected animals require more energy to maintain a LWC similar to that of non-infected animals. This is a similar finding to that reported in a literature review by Hoste et al., (2005). The MEI is more important than protein for GIN infected animals probably because during abomasal infections the endogenous protein loss can be reabsorbed at the intestinal level (Rowe et al., 1988). However, recycling of protein has an energy cost and therefore the ME requirement is increased compared with animals with lower protein recycling. A similar effect was reported in paired feeding studies where the efficiency of ME for growth was reduced in lambs infected with GIN (Sykes and Coop, 1977, 1976).

4.3. Metabolic cost

The metabolic cost of infection can vary due to several factors: infection (parasite species, larval dose rate, the location of infection, type of infection), animal (species, breed) and diet (feeding level) (Coop and Kyriazakis, 1999). However, no specific values have been reported for these effects. Therefore, from the meta-analysis results we estimated the metabolic cost of parasitism in lambs, considering the worm burden and feeding level. The metabolic cost obtained represented the additional CP and ME per adult parasite (burden) to obtain the same LWC as a non-infected animal. Several authors have measured the increase of protein or loss of nitrogen in the gastrointestinal tract, with variable results ranging from 1 g/d to 5 g/d nitrogen equivalent to 0.56 g CP/kg LW$^{0.75}$ to 2.80 g CP/kg LW$^{0.75}$ for an animal of 25 kg LW. However, they did not estimate the metabolic cost of parasitism (Coop and Kyriazakis, 1999; Kimambo et al., 1988; Liu et al., 2005; Poppi et al., 1986). The range seems to arise from differences in the GIN burden as some authors observed that the larval dose used for infection influences the nitrogen loss (Steel et al., 1980; Abbott et al., 1984; Poppi et al., 1986). The present meta-analysis results confirm that worm burden has a metabolic cost for infected lambs.

Few studies have evaluated the effect of GIN on energy metabolism. Usually, the main hypothesis is that infections have a protein cost rather than an energy cost (Coop and Kyriazakis, 2001; Coop and Sykes, 2001; Houdijk et al., 2001; Liu et al., 2003). Nevertheless, Retama-Flores et al., (2012) reported an energy cost per each adult parasite of $0.04 \, kJ/kg \, LW^{0.75}$ in lambs under field conditions while Liu et al. (2005) reported a metabolic cost per each adult parasite of $0.04 \, kJ/kg$ $LW^{0.75}$, which can be estimated assuming 25% establishment both at maintenance and 100 g LWC/d in lambs under pen conditions. Both estimations are close to our current estimation of $0.056 \, kJ/kg \, LW^{0.75}$. The difference between metabolic cost estimation may be explained by conditions such as the type of study (pen or field) and diet quality. However, although the present meta-analysis results yield a higher energy cost for infected lambs compared with previous reports, it includes a wider range of worm burden and diet quality (energy concentration), thus overcoming the limitations of previous estimations where protein supply was mainly assessed. Therefore, the present estimation is likely to be closer to the true metabolic cost of GIN.

In addition to protein, energy supply is essential for the synthesis of the increased mass of tissues associated with immunity, which is costly from an energy point of view. In addition, immune cell functions such as migration, cytokinesis, phagocytosis, antigen processing, antigen presentation, activation and effector functions require energy (Liu et al., 2005). In agreement, the present results indicate that infected animals must also be supplemented with energy to obtain a LWC similar to non-infected animals. A supplementation scheme should aim to balance dietary protein and energy, and therefore supplements based solely on protein-rich or energy-rich feedstuffs would not yield an optimal response. This aspect needs to be specially considered when lambs are kept under grazing/browsing conditions because legume pods (Ortiz-Domínguez et al., 2017) and tree foliage (Torres-Acosta et al., 2016) have high protein levels. Therefore, all the nutrients contained in the supplement are important for better productivity (Torres-Acosta et al., 2012).

A scenario to estimate the metabolic cost was modelled comparing animals with and without established GIN infection. The results show that the metabolic cost increased linearly for each adult parasite and the magnitude of the effect was similar at both feeding levels.

Previous reports showed that an increased nutrient supply (supplement) reduced the impact of GIN infection, *i.e.* reducing their establishment (Brunet et al., 2008; Retama-Flores et al., 2012). However, it should be noted that the estimated metabolic cost in the present work relates to the established GIN and thus it is a different aspect of the GIN-host nutrition interaction.

5. Conclusion

The present study showed that GIN has a metabolic cost of $0.30 \, mg$ $CP/kg \, LW^{0.75}$ and $0.056 \, kJ \, ME/kg \, LW^{0.75}$ for each adult parasite in lambs. Detrimental effects on the DMI and LWC were observed in lambs infected with GIN. The CP × worm burden was the best predictor of DMI and the MEI × worm burden was the best predictor of LWC. Therefore, infected lambs must be supplemented with protein and energy to reach a LWC similar to that of non-infected animals.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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