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Original article

Determination of Preoperative and Postoperative Serum Leptin, Ghrelin, Insulin, and Irisin Hormone Levels in Left Abomasum Displacement

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Abstract. *Background and aim:* Left Displacement Abomasum (LDA) is a metabolic disorder associated with negative energy balance, especially in dairy cattle, and might cause economic losses. This study, it was aimed to evaluate the serum levels of insulin, leptin, ghrelin, and irisin hormones responsible for energy metabolism before and after the operation in Holstein cattle with LDA. *Methods:* For this purpose, cattle were divided into three groups (Group 1: Healthy, Group 2: Pre-operative, Group 3: Post-operative) with 8 animals in each group, and blood samples were collected. In serum samples, glucose, non-esterified fatty acid (NEFA), beta-hydroxybutyrate (BHBA), total protein, triglyceride, total cholesterol, and calcium levels were measured with an autoanalyzer. In addition, commercial kits measured serum insulin, leptin, ghrelin, and irisin hormone levels with the EIA method. *Results:* Preoperative serum glucose, NEFA, and BHBA levels were higher in cattle with LDA, and total protein and triglyceride levels were lower than in healthy animals ($p<0.05$). In cattle with LDA after the operation, these values were similar to those of healthy animals. In hormone analysis, ghrelin, insulin, and irisin were found to be higher in animals with LDA, while leptin levels were found to be decreased ($p<0.05$). After the operation, the insulin levels of the cattle with LDA decreased below the pre-operative values; It was observed that leptin and irisin levels were increased ($p<0.05$). Conclusions: In cattle with LDA, increased ghrelin levels may be due to anorexic conditions; Increased insulin levels may be due to stress and negative energy balance. Decreased serum insulin levels in cattle after the operation suggested that it may be related to the insulin resistance state caused by the left displacement abomasum. Increased serum leptin can be considered an acute phase response to leptin, and an increase in serum irisin can be a marker of pain and stress.

Key words: hormonal regulation, left displacement abomasum, metabolism, negative energy balance

Introduction

The abomasum displacement is a metabolic disorder that impairs animal comfort and affects the economy in many dairy cattle races, especially the Holstein cattle (1). In economic analyses, the cost per AD diagnosis is over 700 dollars (2).

The change of the position of the abomasum that is located caudal to the cattle reticulum, on the ventral wall of the abdominal cavity, and mostly on the right side of the median line due to many reasons is called the abomasum displacement (3). Left displacement abomasum (LDA) is the displacement of the abomasum between the left abdominal wall and rumen. Abomasal hypomotility is the most important prerequisite for the abomasum displacement and is the sign of abomasal atony in dairy cattle with LDA (1). While most of the left displacements are seen postpartum, it is thought that most of the right displacements are not related to birth (1, 4).

Ghrelin discovered in 1999 is made up of 28 amino acids and is also known as a hunger hormone because of its appetizing effect. Ghrelin plays an essential role in feeding behavior in animals and the regulation of appetite in humans. Its secretion from the stomach depends on sudden and chronic fluctuation in energy balance. Additionally, it has some effects on the gastrointestinal system (5). In a recent study with Holstein Friesian cattle affected by AD, it was found that serum motilin, ghrelin, and gastrin concentrations increased and leptin concentration decreased (6). It is thought that abomasal displacement together with impaired abomasum motility may lead to gastric emptying by causing the feedback mechanism of these hormones.

Leptin acts as a ghrelin antagonist, and its serum concentration decreases in cattle with negative energy balance than without it (7). Leptin is secreted from adipocytes and regulates food intake, body weight, and energy metabolism (8). It is reported that there is a relationship between leptin genotypes and AD (9).

In genetic LDA studies, it was reported that signal pathways related to glucose homeostasis are strongly associated with AD. Energy balance impaired in AD formation is closely associated with glucose metabolism of primary importance for energy gain (9).

A hormone called irisin discovered recently is secreted from both muscle and fat tissues like leptin and it provides energy expenditure by transforming white to brown fat tissue, and by the way, regulates glucose homeostasis. Overexpression of FNDC5, the precursor of Irisin increases the use of oxygen, and the production of carbon dioxide and heat. Increasing UCP1 expression decreases ATP production from the electron transport system and increases heat production by acting as a separator. Increased UCP1 expression and therefore increased heat production is a lucrative event that provides energy expenditure in terms of glucose/lipid metabolism in individuals with insulin resistance and obese individuals (10). Zhang et al (11) aimed to show that this hormone causes weight loss ve provides glucose homeostasis, by giving mice some recombinant irisin hormone. At the end of the study, it has been reported that the irisin hormone is regulated with UCP-1 expression. Thus, it is proven that body energy metabolism is positively affected. That's why the irisin hormone is thought to be related to negative energy balance one of the most important reasons for abomasum displacement. No study has been conducted with this hormone in the abomasum displaced and healthy cattle, so we must add data about irisin levels in healthy and the abomasum displaced cattle with this study.

Based on these data, it may be assumed that impairment in energy balance and inhibition in abomasal mobility is the key for most patients. The abomasum displacement is a metabolic disorder that is more common within 1-3 months postpartum known as the transitional period caused by energy metabolism, abomasal hypomotility, and hormonal changes but the underlying metabolism is still unclear. Therefore, this study aimed to evaluate irisin, leptin, ghrelin, and insulin hormones responsible for energy metabolism before and after the operations in abomasum displaced cattle and to investigate the relationship between the abomasum displacement and these hormones.

Materials and Methods

Animals

Holstein breed cattle (n=8) aged 2.5-3 years at early lactation (in the first 1-3 weeks of lactation) who applied to Burdur Mehmet Akif Ersoy University Veterinary Faculty Surgery Clinics with LDA diagnosis and referred to the operation constituted the patient group in this current project. Patient animals were followed two different times before (pre-op LDA) and immediately after the operation (post-op LDA). Additionally, clinically healthy Holstein breed early lactating (n=8) cattle from the farms of the Burdur region constituted the control group for comparison.

The Diagnosis of The Abomasum Displacement

Occultation and osculopercussion are used for clinical diagnosis of abomasum displacement. These procedures are performed at the level of 11, 12, and 13.

costa, in the intercostal space and left paralumbar fossa. The routine examination was performed by listening to "metallic click" in occultation and "ping" in osculopercussion in the region of interest (12).

Performance of The Left Abomasum Displacement Operation

In animals with LDA, the abomasum was fixed to anatomic situs by applying the left paralumbal abomasopexy technique with a toggle pin (13). In this technique, the left paralumbar fossa was first shaved. Following the regional antisepsis, a 20 cm skin incision was made on the left paralumbar fossa. The abomasum was reached after cutting the muscles and opening the peritoneum. A toggle pin was inserted into the desufflation cannula, and the abomasum was reached from the dorsal side. After the Toggle pin was sent in the abomasum, gas within it was allowed to come out of desufflation cannula. When it was decided that the abomasum descended into anatomic situs, desufflation cannula was taken out. The tips of a toggle pin thread were passed through the hole at the tip of the Gerlach needle. Gerlach needle with thread attached was placed in the palm of the right hand. The tip of the Gerlach needle was taken out from the right side of the median line by entering the left paralumbar fossa. The tips of the Toggle pin thread were pulled out of the needle tip. The abomasum was fixed to the right side of the median line by placing gauze between the tips of the thread. After the operation, IM antibiotic treatment was given for 5 days (Redipen injectable suspension 100ml/Sanovel).

Collecting Serum Samples

Blood samples were drawn from V. jugularis of sick animals before (pre-op LDA), and immediately after the operation (post-op LDA) and collected in vacuum tubes with gel. Similarly, blood samples from the control group cattle were also collected in vacuum tubes with gel. Collected blood samples were centrifuged at 500X g for 15 min after coagulation and sera were separated. Serum samples were preserved at − 20 °C until analysis.

Analysis of Serum Samples

Some biochemical analyses of serum samples [glucose, free fatty acid (FFA), β-hydroxybutyric acid (BHBA), calcium, total cholesterol (T.Chol), triacylglycerol (TG), total protein] were performed with an autoanalyzer (Randox RX Monaco / USA). Serum insulin, irisin, leptin, and ghrelin hormone analyses were performed by the EIA method using commercial kits (BT-Lab cat no: E0015B0, BT-Lab cat no: E2318B0, BT-Lab cat no:EA0007Bo, BT-Lab cat no:E262Bo).

Statistical Analysis

Collected data were evaluated with IBM SPSS 22.0 for the Windows package program. Shapiro-Wilk test was used to evaluate the normality. Levene test was used for homogeneity of variance. It was determined that data in all groups were normally distributed. In groups where variances were homogenously distributed, intergroup comparisons were made by variance analysis (one-way ANOVA test), and the TUKEY HSD test was used for multiple comparisons. In groups where variances were not homogenously distributed, intergroup comparisons were made by Welch analysis (one-way ANOVA test), and the Tamhane test was used for multiple comparisons.

Results

As a result of the study, BHBA, NEFA, and glucose levels in blood sera of the animals with LDA before and after the operation were higher compared to healthy animals; while calcium, triglycerides, and total protein levels were decreased ($P<0.05$) (Tab 1, Fig 1).

There is a statistically significant difference between columns with different superscripts ($p<0.05$).

For serum hormone parameters, ghrelin, and insulin levels in blood sera before the operation of the abomasum displaced animals were higher compared to healthy animals; while serum leptin level was lower ($P<0.05$). In the postoperative group, serum irisin and leptin were higher, and serum insülin was lower than preoperative levels ($p<0.05$) (Tab 2, Fig 2).

Table 1. Biochemical Parameters Change Before and After the Operation in Cows with LDA

Parameter	Control *(n=8)* $\bar{x}$±*sd*	Pre-op *(n=8)* $\bar{x}$±*sd*	Post-op *(n=8)* $\bar{x}$±*sd*	*p*
Calcium (mg/dL)	8,31±0,50[a]	4,24±1,73[b]	4,96±2,97[b]	<0,001
BHBA (mmol/L)	0,51±0,150[a]	1,89±,1,17[b]	1,68±1,05[b]	0,005
NEFA (mmol/L)	0,66±0,177[a]	1,66±0,69[b]	1,91±0,46[b]	<0,001
Triglycerides (mg/dL)	29,10±,8,58[a]	14,81±,5,37[b]	16,40±6,48[b]	0,001
Total protein (g/dL)	7,68±0,76[a]	6,34±0,50[b]	6,41±0,41[b]	<0,001
Glucose (mg/dL)	46,72±6,88[a]	83,18±27,22[b]	99,68±34,78[b]	0,001
Cholesterol (mg/dL)	102,22±18,30	78,61±29,42	85,26±33,64	0,241

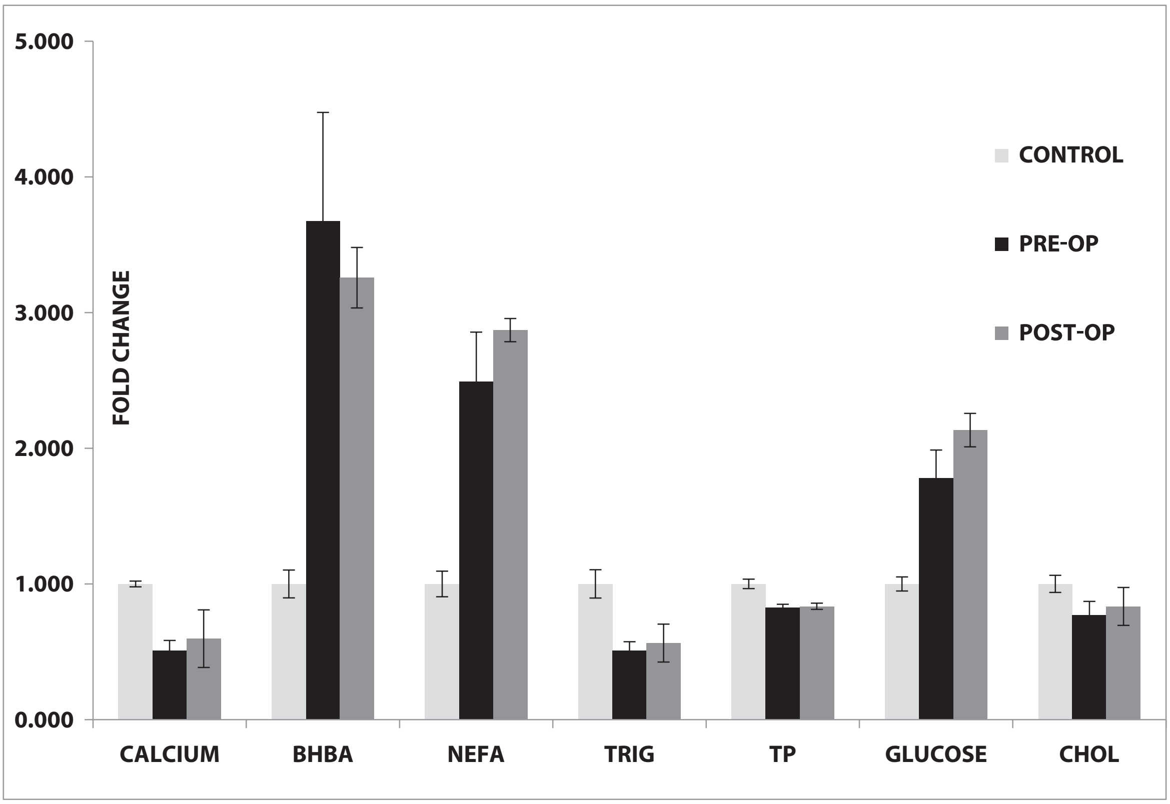

Figure 1. Biochemical parameters changes before and after the operation in cows with LDA

Table 2. Hormonal changes before and after the operation in cows with LDA

Parameter	Control *(n=8)* $\bar{x}$±*sd*	Pre-op *(n=8)* $\bar{x}$±*sd*	Post-op *(n=8)* $\bar{x}$±*sd*	*p*
Ghrelin (ng/L)	170,61±53,73[a]	298,04±76,14[b]	287,08±113,60[b]	0,012
Leptin (ng/mL)	2,03±0,51[a]	1,24±0,34[b]	2,02±0,73[ac]	0,013
Irisin (ng/mL)	3,98±1,65[a]	6,43±2,81[b]	11,93±4,17[c]	0,001
Insulin (μIU/L)	4,17±0,52[a]	5,19±0,53[b]	3,83±1,25[a]	0,003

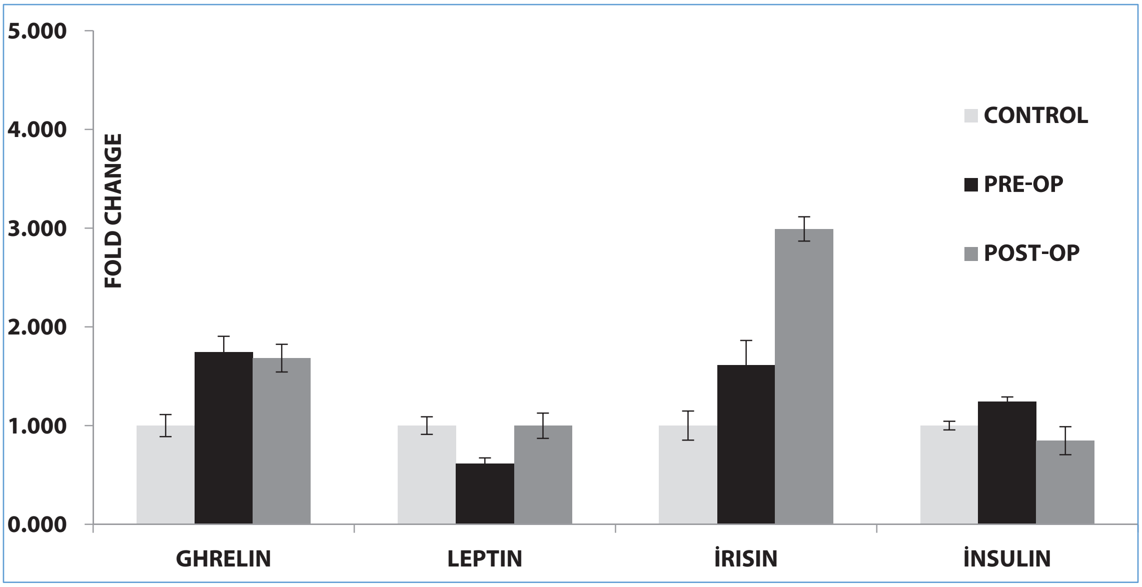

Figure 2. Hormonal changes before and after the operation in cows with LDA

There is a statistically significant difference between columns with different superscripts ($p<0.05$).

Discussion

LDA is the displacement of gas-filled abomasum from where it is anatomically located slightly dexterous on the abdominal ventral wall to the left and dorsal wall of the abdomen at varying degrees. It is considered a digestive system disease that causes significant economic losses, especially during the postpartum period in high-yield dairy cattle (1,2,3) Among disease predisposing factors; are nutrition, race, genetic predisposition, twin or difficult birth, lactation, ketosis, fatty liver, insulin resistance, hyperglycemia, hypocalcemia, retention secundinarum, endometritis, mastitis and foot diseases (4, 14). In the abomasum displacement, metabolic alkalosis occurs as a result of ruminoreticular reflux of HCl. As blood pH and bicarbonate levels rise, hypochloremia and hypokalemia occur together with hypoglycemia (15, 16). Serum calcium level falls because of a decrease in uptake and absorption (15, 17). In this study, the fact that serum calcium level falls in animals with LDA compared to healthy animals confirms the hypothesis. Liver functions are evaluated by measuring parameters such as AST, GGT, total protein, albumin, and globulin (18). In addition, because of decreased food consumption and decreased albumin synthesis in the livers of cattle suffering from LDA, serum total protein, albumin, and globulin were found to be significantly decreased (19, 20). The total protein level of animals with LDA was lower.

When ration was applied during the transition period of dairy cattle; as the development of the fetus can't compensate for milk production and increased metabolic activity, a negative energy balance occurs (21). As peripartum negative energy balance plays role in the pathogenesis of the abomasum displacement, it is considered the most important reason for LDA (22). When a negative energy balance occurs, an energy deficit is met by unsaturated fatty acids (NEFA) produced as a result of hydrolysis of triglycerides in adipose tissue (21). It was reported that serum triglyceride concentration significantly falls due to impaired circulation in liver parenchyma in the abomasum displacement (23). In cattle with LDA, serum beta-hydroxybutyric acid (BHBA) and NEFA concentrations were high (22, 24, 25), and cholesterol level was low (24, 26). It was reported that in the abomasum displacement glucose and lipid metabolism are impaired and consequentially the amount of increased BHBA and NEFA due to fatty liver, energy imbalance, and endotoxemia (26). In this study, serum BHBA and NEFA levels were increased compared to healthy animals, and their levels did not change considerably in the postoperative period.

In this study, it was reported that serum cholesterol and triglyceride levels were lower in cattle with LDA because of disorders in lipid metabolism and the presence of fatty liver. Because of negative energy balance, the stored fat reserve in the body results in excessive fat accumulation in liver cells and fatty liver and decreased lipoprotein synthesis (19). In this study, serum triglyceride levels decreased significantly in animals with LDA compared to healthy animals. In addition, it has been determined that glucose levels increased because of toxemia and stress in LDA (26), and even in dead cattle glucose level was twice as higher than in surviving cattle (24). In this study, serum glucose levels in cattle with LDA were higher compared to healthy cattle. Additionally, although serum glucose levels increased after the operation, they didn't reach statistical significance.

In some studies, it was reported that blood glucose and insulin levels increased because of stress in the abomasum displaced cattle, and abomasal motility decreased in cattle with high blood insulin, glucose, and glucagon levels (27, 28). High glucose and insulin levels might be related to stress in cattle with the abomasum displacement. Pravettoni et al in their study suggested that high serum insulin level is associated with the abomasum displacement in cattle and insulin resistance might be an etiological factor for the abomasum displacement (29). In studies, it was reported that insulin secretion decreases and this might be related to insulin resistance in individuals in the postoperative period (30). As a matter of fact, in this study serum insulin levels were higher in cattle with the abomasum displacement than in healthy animals, and after the operation insulin levels were lower ($P<0.05$), and this might be related to insulin resistance in animals with LDA.

When energy balance is re-established in lactating cattle; leptin supports energy metabolism together with IGF-I and insulin (31). Leptin was discovered by Zhang et al. in 1994 (32). Leptin, isolated from fat tissue is a peptide hormone with 16kDa weight and its main function is known to regulate body weight (33). In studies, it has been reported that leptin is a satiety hormone that prevents food intake and increases energy consumption. In a study conducted with rats, it was determined that leptin concentration falls during lactation, and with cessation of milk yield leptin concentration and adiposity significantly increase (34). In other studies, it has been concluded that there is a close relationship between the leptin hormone and nutrition and the reproductive system and acts as a mediator between energy metabolism and the reproductive system (32). In cows, there is a linear relationship between plasma leptin level and body condition scores. An increase in body fat mass and feeding with energy reach foods increase leptin levels (35). In a study with dairy cattle, it was reported that plasma leptin concentration before birth is the most important marker of body adiposity (36). In addition, it was determined that there is a positive relationship between energy balance and leptin concentration in cattle. Evidence supporting this idea exists in rodents and humans, with insulin increasing and growth hormone decreasing plasma leptin (31). Leptin demonstrates its effects on energy metabolism by stimulating insulin, IGF-I, glucose, and thyroid hormones (T3, T4) positively and growth hormone and free fatty acids negatively (31). In this study with the abomasum displaced cattle with negative energy balance, a decrease in leptin levels supports the above findings. In addition, we found that leptin levels increased after the operation. In studies, it was reported that leptin acts as an acute phase reactant during non-infectious stress responses (like abdominal surgery) (37). The reason for this postoperative increase is thought to be an acute phase response.

Leptin acts as a ghrelin antagonist and its serum concentration in cattle with negative energy balance decreases compared to those without it (7).

Ghrelin is a 28 amino acid peptide hormone first isolated from rat stomachs (38). Animal studies have revealed that ghrelin has significant effects on gastrointestinal motility. Ghrelin in rodents accelerates gastric emptying (39, 40)

In a study, it was determined that plasma ghrelin level is higher in lactating cattle than in non-lactating. Again in this same study, ghrelin was effective in increasing growth hormone, especially in early lactating cattle (41). In another study, plasma ghrelin levels that increased before feeding in scheduled feeding sheep did not have any effect on voluntary food intake but had an effect on growth hormone that increased after feeding (42). In another research with cattle and goats, it was determined that plasma ghrelin levels significantly decreased 1 hour after feeding in cattle and they rose again to prefeeding levels in a later period. While, in goats, ghrelin application significantly increased plasma growth hormone levels in a dose-dependent manner (43). These results show that ghrelin affects the regulation of feeding in domestic animals (44). In a recent study, motilin, ghrelin, and gastrin serum concentrations increased and leptin concentration decreased in AD-affected Holstein Friesian cattle. It is thought that the impaired abomasum motility because of abomasum displacement causes gastric emptying by causing feedback metabolism of these hormones (6). In this study, ghrelin levels before the operation in cattle with LDA increased compared to healthy animals. On the other hand, ghrelin levels after the operation decreased compared to levels before the operation, which supports the findings of Öztürk et al (6)'s study.

The irisin hormone regulates energy metabolism and is found in different tissues like the brain, fat, and liver. Irisin hormone is produced as a result of proteolytic degradation of FNDC5. Despite comparative structural configuration and amino acid variations of FNDC5, FNDC5 structures in humans, water buffalos, and cattle are quite similar (45). Although there are no studies to demonstrate irisin hormone effects in ruminants, in a study conducted with buffalos, irisin hormone was shown to play role in the control of energy metabolism, folliculogenesis, and spermatogenesis for the first time (45). There is no study to explore serum irisin levels in the abomasum displacement and related metabolic disorders. In this study, serum irisin levels increased in cattle with LDA before the operation compared to healthy cattle and continued to increase after the operation. In a study about abdominal pain and irisin levels, in individuals with abdominal pain irisin levels were shown to increase significantly (46). Therefore, this increase found in this study might be related to pain in the abdominal area. Irisin hormone is generally secreted from muscles, so this increase in the post-operative period might be related to muscle injury.

Conclusion

In conclusion, it is thought that increased serum ghrelin, insulin, and irisin hormone levels in cattle with LDA might be used as biomarkers for LDA diagnosis, and postoperatively increased leptin levels might be considered as acute phase response and irisin levels as a pain response. On the other hand, decreased serum insulin levels in cattle after the operation suggested that it may be related to the insulin resistance state caused by the left displacement abomasum.

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Conflict of Interest: There is no conflict of interest issue.

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