http://dx.doi.org/10.1590/1678-4162-12850

Arq. Bras. Med. Vet. Zootec., v.75, n.2, p.254-260, 2023

Effective treatment of a case of pregnancy toxemia in sheep - case report

[*Tratamento eficaz de um caso de toxemia de gestação em ovelhas – relato de caso*]

G. *Anteveli*[1], C.S. *Oliveira*[1], B.A. *Alves*[1], B.S. *Torres*[1], M.V.G. *Joaquim*[1], J.G.C. *Jorge*[2], E.J. *Facury Filho*[2], R.M. *Meneses*[2], A.Ú. *Carvalho*[2], T.F. *Moreira*[2]

[1]Graduate, Universidade Federal de Minas Gerais, Escola de Veterinária, Belo Horizonte, MG, Brasil
[2]Universidade Federal de Minas Gerais, Escola de Veterinária, Belo Horizonte, MG, Brasil

ABSTRACT

Pregnancy toxemia has a high mortality rate and few cases with effective treatment are reported, especially when associated with secondary diseases. Therefore, the present work reports the case of a sheep, which was referred to the veterinary hospital of UFMG, in the last month of pregnancy, presenting apathy, hyporexia and sternal recumbency. After the diagnosis of pregnancy toxemia, the fetuses were removed while still alive, but did not survive. Monitoring was started with blood gas analysis, blood glucose assessments and laboratory tests. The results were consistent with liver damage, which was justified by the condition of lipolysis. Treatment consisted of electrolyte replacement plus 50% glucose and potassium chloride, along with administration of antibiotics (ceftiofur, 5mg/kg/SID/IM/7 days), flunixim meglumine (2.2mg/kg/SID/IM first day and 1.1mg/kg/SID/IM on the second and third days) and omeprazole (4mg/kg/SID/oral). The patient had secondarily clinical laminitis, which was treated with cryotherapy and anti-inflammatory drugs, in addition to mastitis, using a single dose of intramammary antibiotics. The work demonstrated the effectiveness of the treatment of pregnancy toxemia, when performed early and intensively, associated with daily clinical and laboratory monitoring of the animal.

Keywords: cetosis, clinical laminitis, lipolysis, mastitis, sheep farming

RESUMO

A toxemia da prenhez possui alto índice de mortalidade, e poucos casos com tratamento eficaz são relatados, principalmente quando associados a doenças secundárias. Diante disso, o presente trabalho relata o caso de uma ovelha, que foi encaminhada ao hospital veterinário da UFMG, no último mês de gestação, apresentando apatia, hiporexia e decúbito esternal. Após o diagnóstico de toxemia da prenhez, os fetos foram retirados ainda vivos, porém não sobreviveram. Iniciou-se um monitoramento com análises hemogasométricas, avaliações de glicemia e exames laboratoriais. Os resultados foram condizentes com lesão hepática, a qual foi justificada pelo quadro de lipólise. O tratamento consistiu em reposição hidroeletrolítica associada à glicose 50% e a cloreto de potássio, juntamente com administração de antibióticos (ceftiofur, 5mg/kg/SID/IM/7 dias), flunixim meglumine (2,2mg/kg/SID/IM no primeiro dia e 1,1mg/kg/SID/IM no segundo e terceiro dias) e omeprazol (4mg/kg/SID/oral). A paciente apresentou secundariamente laminite clínica, a qual foi tratada com crioterapia e antinflamatórios, além de um quadro de mastite, sendo utilizado antibiótico intramamário em dose única. O trabalho demonstrou a eficácia do tratamento da toxemia da prenhez, quando realizado de forma precoce e intensiva, associado a um monitoramento clínico e laboratorial diário do animal.

Palavras-chave: cetose, laminite clínica, lipólise, mastite, ovinocultura

Corresponding author: gabianteveli21@gmail.com
Submitted: August 5, 2022. Accepted: September 2, 2022.

INTRODUCTION

Pregnancy toxemia (PT) is a multifactorial metabolic disease that affects sheep and goats, by reducing blood glucose and increasing ketone bodies (Costa and Silva, 2011; Santos *et al*., 2011; Souto *et al.*, 2019).
This condition is directly related to the increase in nutritional requirements, especially in the final third of pregnancy, particularly in twin pregnancies. In this situation, the female's organism prioritizes the use of glucose for the fetus, and if the nutritional management does not meet this demand, the female will mobilize body reserves to generate energy, initiating lipolysis (Soares *et al.*, 2009).

The animal starts the condition with apathy, hyporexia, dehydration, congested mucous membranes and in a few hours, with the worsening of the hypoglycemic condition, it may show neurological signs such as amaurosis, tremors, behavioral changes, and death (Rook, 2000; Brozos *et al*., 2011; Santos *et al.*, 2011; Mota *et al*., 2015). The high morbidity and lethality, which can reach 80% of the cases, may also be related to immunosuppression and the systemic inflammatory process caused by PT, which can predispose to other diseases, such as mastitis, edema, and laminitis (Rook, 2000; Barbagianni *et al.*, 2015).

To date, there are few reports of reversal of cases of pregnancy toxemia, especially when they are accompanied by secondary diseases, demonstrating the need to deepen the knowledge about the treatments for this disease.

The aim of this study is to report a case of pregnancy toxemia in a sheep, which was associated with mastitis and laminitis, whose treatment was effective.

CASE REPORT

On 06/04/2021, a pet sheep of the Dorper breed, approximately 2 years and six months old, arrived at the ruminant clinic sector of the UFMG veterinary hospital. The farm worker reported that for about 5 days the sheep was apathetic and remained in sternal recumbency for long periods. The owner administered dexamethasone three days before bringing her to the hospital. About a week before showing clinical signs, the animal was trimmed.

In December 2020, the same sheep had been admitted to the veterinary hospital due to a rectal prolapse. At that moment, the ewe had a body score of 5.0 on a scale of 1 to 5, and a reduction in the supply of concentrated feed was recommended. When questioning about the current nutritional management, it was reported that the ewe no longer received concentrated ration, only cabbage leaves and hay, and the mineral supplement was offered *ad libitum*. Regarding reproduction, it was mentioned that in the previous year she got pregnant, but miscarried.

The patient was apathetic, in sternal recumbency, weighing 75kg, and despite being 10kg less than the last hospitalization, her body score was 5.0 (score from 1 to 5) as can be seen in Figure 1. Ocular, oral and vaginal mucous membranes were congested and there was a dehydration between 6 to 8%. Associated with this, the patient had dyspnea, abdominal contractions, and bloody vaginal discharge. Therefore, labor was suspected. When performing vaginal palpation, a dilated cervix was noticed, which made it possible to perform obstetric maneuvers. It was possible to remove the two premature fetuses of approximately 4 months of gestation. After parturition, the ewe was maintained on oxygenation due to severe mixed dyspnea. Blood glucose assessments were performed using the Accu-check® device and ketone bodies using ketovet® (Table 1). To monitor electrolyte imbalances, blood gas analysis was used using the i-STAT® automatic device (Table 2). In addition, blood collection was performed to assess leukogram and liver and kidney functions. These last exams revealed neutrophilia (Table 3) and increased AST and GGT enzymes, associated with a decrease in blood urea and glucose.

The hydroelectrolytic replacement of seven liters of Ringer's lactate was started by rapid drop, associated with 0.5 ml/kg of 50% glucose, 12 mL of potassium chloride and 0.5 mg/kg of calcium subcutaneously. A maximum of 3 mL of potassium chloride and 5 ml of 50% glucose per liter of lactated Ringer's was added.

Antibiotic therapy was performed with ceftiofur 5 mg/kg (SID, IM, for seven days), and for anti-inflammatory effect, flunixim meglumine 2.2 mg/kg on the 1st day (SID, IM) and 0.5 mg/kg on the 2nd and 3rd days (SID, IM).

A few hours after the beginning of the treatments, the patient presented an increase in the temperature of the four hooves, sensitivity to palpation, and appeared to be in pain when standing still, remaining most of the hours in sternal recumbency, which was suggestive of clinical laminitis. In addition, she had sole and white line hemorrhages.

The mucous membranes became more congested, and the sheep was apathetic. To try to reverse the situation, a single dose of dimethylsulfoxide was used at a dose of 1mg/kg intravenously and cryotherapy in the hooves was applied for two hours.

Figure 1. Dorper ewe named Dolly after labor in sternal recumbency, with a body condition score of 5 (0-5) and with a Betahydroxybutyrate result of 2.3 mmol/L.

Table 1. Results of glycemia and beta-hydroxybutyrate of a sheep with pregnancy toxemia

Exams	06/apr	07/apr	10/apr	11/apr	Reference values
Glycemia (mg/dL)	42	65	50	42	50-80
Betahydroxibutyrate (mmol/L)	2.3	1.7	0.5	0.7	< 0.8

Reference values adapted from Radostits *et al.* (2007) and Kaneko *et al.* (2008).

Table 2. Blood gas analysis results of a ewe with pregnancy toxemia soon after induced labor (04/06) and in the following days

Data	04/06/2021	04/07/2021	04/08/2021	04/11/2021	04/14/2021	Reference values
Ph	7.33	7.4	7.44	7.51	7.57	7.32-7.54
PCO2	26.5 mmHg	29.6 mmHg	35.4 mmHg	27,8 mmHg	28 mmHg	37-46
Beecf	-12	-5	0	-1	4	0-6
HCO3	14.0 mmol/L	19.2 mmol/L	24.5 mmol/L	22.2 mmol/L	25.9 mmol/L	20-25
TCO2	15 mmol/L	20 mmol/L	26 mmol/L	23 mmol/L	27 mmol/L	21-28
Na	147 mmol/L	145 mmol/L	154 mmol/L	147 mmol/L	142 mmol/L	139-152
K	2.9 mmol/L	3.1 mmol/L	3.5 mmol/L	3.2 mmol/L	4 mmol/L	3.9-5.4
iCa	1.27 mmol/L	1.07 mmol/L	1.55 mmol/L	1.46 mmol/L	1.47 mmol/L	1.0-1.2
Hct	31%	24%	23%	20%	23%	27-45
Hb	10.5 g/dl	8.2 g/dl	7.8 g/dl	6.8 g/dl	7.8 g/dl	8-16

Reference values adapted from Constable (1999), Kaneko *et al.* (2008) and Pugh and Baird (2012).

Table 3. Biochemical tests on 04/06, 04/08 and 04/13 of a ewe with pregnancy toxemia

Bioquímico	04/06/2021	04/08/2021	04/13/2021	Reference values
Urea (mg/dL)	42.92	24.57	11.8	17.12-42.8
Creatinine (mg/dL)	1.22	1.34	0.58	1.2-1.9
ALT (U/L)	33.6	48.5	24.9	4-38
AST (U/L)	458.25	563.2	1557.5	60-280
GGT (U/L)	145.9	114.3	186.5	20-52
Total protein (g/dL)	6.02	4.71	5.5	6.0-7.9
Albumine (g/dL)	2.35	1.87	2.83	2.4-3.0
Globulines (g/dL)	3.67	2.74	2.65	3.5-5.7

Reference values adapted from Kaneko *et al.* (2008).

On the morning of 04/07/2021, the patient began to have constant spasms and the mucous membranes remained congested and dehydration remained at 6% to 8%. Despite this, the hooves were less hot and painful to the touch. Because the feces were dark, she was suspected of abomasal ulcer formation. As a result, omeprazole at a dose of 4 mg/kg was added to the treatment.

Blood gas analysis revealed metabolic acidosis, hypocalcemia, and hypoglycemia (36 mg/dl). To reverse the imbalances, calcium replacement was started at 1mg/kg, divided between the intravenous and subcutaneous routes. The same hydroelectrolytic replacement protocol as the previous day was also maintained, however, the volume was according to the calculation of replacement, maintenance, and continuous losses of the day. On 04/08/2021, the blood gas analysis showed the continuity of metabolic acidosis, but with an increase in bicarbonate. Despite the hypoglycemia, glucose rose to 50 mg/dL and calcium replacement from the previous day was efficient.

Regarding the biochemical exam, there was a reduction in urea and creatinine, a significant increase in AST and GGT enzymes and hypoproteinemia in relation to previous exams. Despite laboratory findings, electrolyte replacement and antibiotic therapy were maintained.

On 04/14/2021, close to the patient's clinical discharge, she had a swollen udder, with painful sensitivity to touch, especially the left gland, characterizing grade 2 clinical mastitis. When milking, a small amount of thick, yellowish, and odorless milk was observed, similar to sheep colostrum. To interrupt lactation and prevent a worsening of the condition, a single application of intramammary antibiotics based on cephalonium was used for drying.

On 04/18/2021, the animal was alert, standing, in good physical condition. Despite the ruminal movements that presented a frequency of 2 complete movements in five minutes, the other general parameters were within the reference value for the species and the ewe fed normally. The patient did not have mastitis and at the end

of antibiotic and anti-inflammatory treatment, she was allowed to be discharged from the clinic.

DISCUSSION

Currently, few reports in the literature describe the recovery of patients with PT. The detailed history, symptoms and complementary exams were essential for early diagnosis, which enabled rapid treatment, contributing to clinical improvement.

With information about a trimming prior to the onset of signs, it was suspected that this was an important stressor that may have caused hyporexia, and that, associated with the fact that the nutritional management did not have a good energy source, predisposed the onset of signs of pregnancy toxemia.

The use of dexamethasone three days before arrival at the veterinary hospital probably induced labor. However, as the lambs were premature, they died soon after. It was decided to start a treatment with antibiotics and anti-inflammatory drugs in the ewe, as excessive manipulation to remove the fetuses increased the probability of retained placenta and uterine infections.

Before starting hydroelectrolytic replacement, blood glucose and BHB were measured, which diagnosed hypoglycemia (42mmol/dL) and ketonemia (2.3mmol/dL), respectively, confirming pregnancy toxemia. In pregnant ewes, fetuses can capture glucose through insulin-independent receptors and, with this, can stimulate lipolysis and increase the production of ketone bodies (Rook, 2000; Santos *et al.*, 2011). In ewes pregnant with twins, this glucose uptake is even greater (Raoofi *et al*., 2013).

Even with the removal of the fetuses and the administration of 50% glucose after the blood glucose measurement, the process of returning glucose and BHB to physiological limits was not immediate. It was only on the third day of treatment that BHB concentrations were within the normal range. This may have occurred, because even with the increase in plasma glucose, if there is insulin resistance, the body remains in a catabolic state, mobilizing fat (Rook, 2000). Therefore, it is important to maintain the glucose infusion to encourage insulin levels to remain high for longer periods.

The postpartum blood gas analysis showed that the ewe had decreased bicarbonate (14.0mmol/dL) and potassium (2.9mmol/dL), with the presence of metabolic acidosis and mild responsive respiratory alkalosis. Acidosis is possibly caused by the excess of ketone bodies in the bloodstream and by the reduction of bicarbonate, which was consumed (Kasari, 1999). In addition, with muscle fatigue and tissue hypoxia, the body may have increased anaerobic glycolysis and produced lactate, which may be related to a reduction in the patient's pH (Kasari, 1999).

According to Sweeney (1999), low potassium concentration may be associated with reduced food intake, as the diet is the main source of this mineral. In addition, the author highlighted the importance of the relationship between potassium and insulin, which contributes to the entry of electrolytes into the intracellular environment. Thus, when replacing the patient's glucose, potassium chloride was also administered to avoid an increase in hypokalemia in the extracellular environment.

On the second postpartum day, the ewe remained in recumbency for long periods, with muscle tremors. When performing blood gas analysis, maintenance of hypokalemic metabolic acidosis was observed, but with an increase in hypocalcemia. The reduction of calcium may be related to the production of colostrum (Souto *et al*., 2013). Therefore, it is demonstrated that metabolic acidosis, hypoglycemia, hypokalemia, and hypocalcemia may be present in PT. Thus, for the efficiency of the treatment, they must be diagnosed, and then reversed, which is probably essential for the recovery of blood glucose and reduction of ketone bodies.

Clinical signs suggestive of laminitis started within hours of delivery. Laminitis can be secondary to acidosis, infectious processes, and toxemia (Gelasakis *et al*., 2019). By releasing vasoactive substances, vasodilation occurs in the chorion, which can cause congestion and active inflammation, with increased permeability and the onset of hemorrhages (Ossent and Lischer, 1998). When specifically examining the hooves, white line hemorrhages were noted, suggesting a

previous subclinical laminitis. In human medicine, the relationship between leptin, which is a hormone released by adipose tissue, has already been observed to be directly related to the stimulation of a chronic inflammatory process (Wisse, 2004). In horses, the release of adipokines has already been reported, which are cytokines released by adipose tissue and may be involved in a chronic systemic inflammatory process, usually causing subclinical laminitis (Paz *et al.*, 2013). Interestingly, studies in cows show that in periods of high fat mobilization, such as periparturient, there is lower release of adipokines, which is inversely proportional to lipolysis (Kabara *et al*., 2014). Despite not having a similar study in sheep, with high body score, adipokines may have predisposed to chronic inflammation, leading to the installation of subclinical laminitis. However, an acute inflammatory process may have been initiated with the high concentrations of ketone bodies during PT, predisposing to clinical laminitis.

As soon as the first clinical signs of laminitis were observed, cryotherapy was started to reduce vasodilation and dimethylsulfoxide was administered. On the following day, the patient did not have high hoof temperature and sensitivity to touch, demonstrating the effectiveness of the treatment and probable interruption of the cause.

The occurrence of clinical mastitis in sheep must have been favored by the reduced immunity experienced by animals with PT (Lacetera *et al.*, 2001; Barbagianni *et al.*, 2015). Therefore, it is common for animals that undergo PT to present infectious diseases.

In the biochemical exam, a continuous drop in urea, creatinine, and globulins was observed, with a progressive increase in ALT, AST and GGT enzymes. Total proteins, as well as albumin, decreased on 02/08/2021, but increased again in the last evaluation. Santos *et al.* (2011) and Souto *et al.* (2019) also found increased liver enzymes in most sheep with PT. The increased oxidation of NEFA and the accumulation of triglycerides in hepatocytes favor liver overload, which results in an increase in enzymes and, consequently, a reduction in some of their products (Kabakci *et al*., 2003; Souto *et al*., 2019). However, the reduction in albumin and total proteins may also be related to blood loss, as the drop is intensified soon after delivery.

On 04/18/2021, although ruminal movements were still reduced in relation to the reference value, the patient was active, with appetite and no other systemic alterations. Antibiotic therapy had already been completed, leaving only the cleaning of the rectovaginal fistula, which was almost completely healed. To reduce costs and with the clinical evolution of the animal, discharge was authorized.

PT, when clinically present, usually leads to death in sheep and fetuses (Santos *et al*., 2011). However, in the case reported, some factors contributed to the patient's clinical improvement.

With the beginning of the signs, the owner used dexamethasone, which stimulated the beginning of labor (Brozos, 2011). Thus, when arriving at the hospital, the sheep already had cervical dilatation, not needing a surgical intervention and the use of anesthetic drugs. With the removal of the lambs, fetal glucose consumption ceased, allowing an increase in blood glucose (Soares *et al*., 2009).

The use of blood gas analysis and devices for measuring blood glucose and BHB facilitated daily monitoring, as it was possible to assess the patient's deficits and initiate hydroelectrolytic replacement. In addition, the daily clinical examination allowed the early diagnosis of clinical laminitis, grade 2 mastitis and rectovaginal fistula, with immediate treatment with antibiotics and anti-inflammatory drugs, which was also essential for the patient's clinical improvement.

CONCLUSION

Pregnancy toxemia is a disease that requires urgent and intensive care, which consists of daily monitoring of the animal through clinical and laboratory tests, evaluating the need for hydroelectrolytic replacement, the use of antibiotic therapy and anti-inflammatory drugs.

REFERENCES

BARBAGIANNI, M.S.; MAVROGIANNI, V.S.; KATSAFADOU, A.L. *et al*. Pregnancy toxemia as predisposing factor for development of mastitis in sheep during the immediately post-partum period. *Small Ruminant Res*., v.130, p.246-151, 2015.

BROZOS, C.; MAVROGIANNI, V.S.; FTHENAKIS, G.C. Treatment and control

of peri-parturient metabolic diseases: pregnancy toxemia, hypocalcemia, hypomagnesemia. *Vet. Clin. Food Anim.*, v.27, p.105-113, 2011.

CONSTABLE, P.D. Clinical assesment of acid-base status. *Vet. Clin. North Am. Food*

Anim. Pract., v.15, p.447-471, 1999.

COSTA, R.L.D.; SILVA, A.E. Toxemia da prenhez em ovelhas. *Pubvet*, v.5, p.1-12, 2011.

GELASAKIS, A.I.; KALOGIANNI, A.I.; BOSSIS, I. Aetiology, risk factors, diagnosis and control of foot-related lameness in dairy sheep. *Animals*, v.9, p.1-17, 2019.

KABAKCI, N.; YARIM, G.; YARIM, M *et al*. Pathological, clinical and biochemical investigation of naturally occuring pregnancy toxemia of sheep. *Acta Vet.*, v.53, p.161-169, 2003.

KABARA, E.D.; SORDILLO, L.M.; HOLCOMBE, S.; CONTRERAS, A. Adiponectin links adipose tissue function and monocyte inflammatory responses during bovine metabolic stress. *Comp. Immunol. Microbiol. Infect. Dis.*,v.37, p.49-58, 2014.

KANEKO, J.J.; HARVEY, J.W.; BRUSS, M.L. *Clinical biochemistry of domestic*

animals. 6.ed. San Diego: Academic Press. 2008. 916p.

KASARI, T.R. Metabolic acidosis in calves. *Vet. Clin. North Am. Food Anim. Pract.* v.15, p.473-486, 1999.

LACETERA, N.; BARNABUCCI, U.; RONCHI, B.; NARDONE, A. Effects of subclinical pregnancy toxemia on immune responses in sheep. *Am. J. Vet. Res.*, v.62, p.1020-1024, 2001.

MOTA, T.A.M.; SOUTO, R.C.; MENDONÇA, C.L. *et al*. Níveis séricos de triiodotironina (T3) e tiroxina (T4) em ovelhas com toxemia da prenhez. *Arch. Vet. Sci.*, v.20, p.49-55, 2015.

OSSENT, P.; LISCHER, C. Bovine laminitis: the lesions and their pathogenesis. *Farm Anim. Pract.*, v.20, p.415-427, 1998.

PAZ, C.F.R.; PAGANELA, J.C.; SANTOS, C.A *et al*. Relação entre obesidade, insulina plasmática e posicionamento da falange distal em equinos da raça Crioula. *Arq. Bras. Med. Vet. Zootec*., v.65, p.1699-1705, 2013.

PUGH, D.C.; BAIRD, C.B. *Sheep and goat medicine*. 2.ed. Missouri: Saunders. 2012. p.596-600.

RADOSTITS, O.M.; GAY, C.C.; HINCHCLIFF, K.W.; CONSTABLE, P.D. *Clínica veterinária:* um tratado de doenças dos bovinos, ovinos, suínos, caprinos e equinos. 9.ed. Edinburgh: Saunders, 2007. p.1307-1316.

RAOOFI, A.; JAFARIAN, M.; SAFI, S.; VATANKHAH, M. Fluctuations in energy-related metabolites during the peri-parturition period in Lori-Bakhtiari ewes. *Small Ruminant Res.*, v.109, p.64-68, 2013.

ROOK, J.S. Pregnancy toxemia of ewes, does, and beef cows. *Vet. Clin. North Am. Food Anim. Pract.*, v.16, p.293-317, 2000.

SANTOS, F.C.O.; MENDONÇA, C.L.; SILVA FILHO, A.P. Indicadores bioquímicos e hormonais de casos naturais de toxemia da prenhez em ovelhas. *Pesqui. Vet. Bras.*, v.31, p.974-980, 2011.

SOARES, F.A.P.; BORBA NETO, A.V.; GUIMARÃES, J.A. *et al*. Metabolismo de indicadores preditivos da toxemia da prenhez em ovelhas dorper no terço final da gestação, parto e pós-parto. *Ciênc. Anim. Bras.*, v.1, p.197-203, 2009

SOUTO, R.J.C.; AFONSO, J.A.B.; MENDONÇA, C.L. *et al*. Achados bioquímicos, eletrolíticos e hormonais de cabras acometidas com toxemia da prenhez. *Pesqui. Vet. Bras.*, v.33, p.1174-1182, 2013.

SOUTO, R.J.C.; AFONSO, J.A.B.; MENDONÇA, C.L. *et al*. Biochemical, endocrine, and histopathological profile of liver and kidneys of sheep with pregnancy toxemia. *Pesqui. Vet. Bras.*, v.39, p.780-788, 2019.

SWEENEY, R.W. Treatment of potassium balance disorders. *Vet. Clin. North Am. Food Anim. Pract.*, v.15, p.609-617, 1999.

WISSE, B, E. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J. Am. Soc. Nephrol*., v.15, p.2792-2800, 2004.