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Utility of urinary markers in the assessment of renal dysfunction in familial glomerulonephritis in Dobermann dogs

Dagmara Winiarczyk[1], Łukasz Adaszek[2], Jacek Madany[1], Mateusz Winiarczyk[3], Stanisław Winiarczyk[2]

[1]Department and Clinic of Animal Internal Diseases,
[2]Department of Epizootiology and Clinic of Infectious Diseases,
Faculty of Veterinary Medicine, University of Life Sciences, 20-612 Lublin, Poland
[3]Department of Vitreoretinal Surgery, I Faculty of Medicine with Dentistry Division
Medical University of Lublin, 20-079 Lublin, Poland
genp53@interia.pl

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Abstract

Introduction: Dobermann dogs are reportedly predisposed to familial glomerulonephropathy. Proteinuria is a hallmark of canine familial glomerular diseases. The identification of glomerular abnormalities in breeds so predisposed is of great importance in improving breeding policy. Therefore, markers that allow the detection and localisation of renal damage are needed. The purpose of this study was to investigate the urinary concentrations of immunoglobulin G (uIgG), retinol-binding protein (uRBP), and Tamm–Horsfall protein (uTHP) in a family of Dobermanns with proteinuria and compare these concentrations with the corresponding values in healthy controls. **Material and Methods:** Ten dogs of the Dobermann breed with proteinuria (five with a urine protein-to-creatinine ratio (UPC) of 0.5–1 and five with a UPC >1) and twelve healthy dogs were enrolled. An ELISA was performed to measure uIgG, uRBP, and uTHP, and these proteins were quantified in relation to urinary creatinine (uCrea). **Results:** uIgG/uCr and uRBP/uCr were significantly higher in the family of Dobermanns than in the healthy dogs. A significant difference in the uTHP/uCr value was found only in dogs with a UPC of >1. **Conclusion:** IgG seems to facilitate the diagnosis of primary hereditary glomerulopathy in Dobermanns. Moreover, in affected dogs, proteinuria characterisation seems to be a promising alternative option for the detection and localisation of renal lesions.

Keywords: Dobermann dogs, proteinuria, renal dysfunction, glomerulonephritis, urinary markers.

Introduction

The Dobermann breed is inherently vulnerable to diseases caused by primary glomerulopathies, familial nephropathies, and glomerulopathies induced by immune reactions (10, 18, 27). In many animals, glomerulopathies follow an asymptomatic course, with proteinuria detected during routine health screening. Often, the only laboratory anomaly observable in these cases is proteinuria, as determined using the urine protein-to-creatinine ratio (UPC). In healthy dogs, the typical UPC is less than 0.2, and values greater than 0.5 indicate significant proteinuria. A permanently elevated urinary protein level is harmful and can lead to hypoalbuminaemia, coagulation disorders, cellular and humoral immune responses, and dysfunctions in the management of minerals and electrolytes. Proteinuria may cause direct renal damage or induce the production of inflammatory mediators such as transforming growth factor beta (TGF-β) or platelet-derived growth factor (PDGF), which may lead to kidney fibrosis and consequently end-stage renal disease. Thus, dogs of breeds that are predisposed to proteinuria should be tested for these abnormalities regardless of the occurrence of kidney disease (12). The literature contains few reports of familial nephropathies in Dobermanns; however, these diseases still occur, although their causes and pathogeneses are unknown,

and in many cases definitively diagnosing familial nephropathy is possible only after finding characteristic kidney lesions during post-mortem examinations or in biopsy samples. Wilcock and Patterson (27) reported familial nephropathy in 13 related Dobermanns, 11 of which exhibited polyuria, polydipsia, severe proteinuria, mild, non-regenerative anaemia, and elevated levels of creatinine and urea. Two other dogs did not present clinical symptoms indicating renal impairment, except for persistent proteinuria. The autopsies of the animals that died or were subjected to euthanasia indicated membranoproliferative glomerulonephritis. Similar histopathological changes were reported in 10 canines of the same breed with juvenile kidney disease. Electron microscopy studies showed clear lesions in the lamina densa of the glomerular basement membrane, with an accumulation of abnormal collagen fibres (18). The glomerular basement membrane contains a special mesh made of α3-α4-α5 chains of collagen type IV. If this mesh is not structured properly, possibly as a result of a mutation in one of the genes responsible, progressive kidney disease is initiated, which leads to chronic renal impairment (7).

Morphological evaluation is considered the gold standard for characterising renal lesions and diagnosing glomerulonephropathy in dogs. However, obtaining renal tissue is invasive and not always recommended, especially in dogs with mildly elevated urine protein-to-creatinine ratios. Evaluation of certain urinary proteins (*i.e.* qualitative assessment of proteinuria) has shown promise in determining the localisation and severity of renal damage in dogs with various forms of chronic kidney disease and in detecting tubular and glomerular dysfunction earlier than conventional methods. According to several canine studies, the presence of immunoglobulin G (IgG) associated with high-molecular-weight proteins is generally attributed to glomerular lesions, while the presence of low-molecular-weight urinary proteins like retinol-binding proteins (RBP) and Tamm–Horsfall protein (THP) is supposedly linked to proximal and distal tubular dysfunction, respectively (1–4, 6, 7, 16, 17, 20, 25). IgG is usually excreted when the selective permeability of the glomerular capillary wall is severely disrupted (1, 2, 6). In dogs with different types of nephropathy, the urinary IgG (uIgG) level is evaluated to characterise the severity of proteinuria (13, 14–16).

There are studies suggesting that kidney injury was associated with a significant increase in the excretion of urinary RBP (uRBP) in dogs that had chronic renal disease compared with concentrations detected in healthy dogs (3, 8, 16, 17, 20, 25). The 21-kDa RBP circulates in plasma, where 90% of it is bound to the 55-kDa protein transthyretin. The unbound fraction of RBP is freely filtered through the glomeruli and is catabolised after reabsorption in the proximal tubules. Because of this process, only trace amounts of RBP should be excreted in the urine of healthy dogs, whereas urinary loss of RBP is expected to increase in dogs with proximal tubule disorders. Thus, RBP has been suggested as a sensitive marker of proximal tubule dysfunction in dogs (3).

THP is synthesised in the cells of the thick ascending loop of Henle and is located principally on the surface of the luminal cell membrane. In humans, vitamin A is secreted in urine as a water-soluble metabolite. In contrast, carnivores excrete vitamin A in urine as lipophilic retinol and retinyl esters. Therefore, THP is released in the urine of dogs to facilitate the excretion of retinol and retinyl esters. THP may have some immunomodulatory activity, but it is clinically important because it represents the matrix of all urinary casts (23, 24). Occasional reports have described urinary THP (uTHP) as a biomarker for distal tubular dysfunction in dogs. Its potential use is illustrated by decreased uTHP-to-creatinine ratios in dogs with CKD (21).

As urine can be easily obtained, assessment of the urinary markers seems a promising alternative option for the early detection and localisation of underlying renal lesions. The objective of this study was to assess the localisation and extent of renal damage in familial glomerulonephritis in Dobermanns using urinary markers for glomerular (uIgG), proximal tubular (uRBP), and distal tubular dysfunction (uTHP).

Material and Methods

Animals. The study was conducted on 22 dogs treated in the Clinics of the Faculty of Veterinary Medicine in Lublin. A total of 10 Dobermann dogs with suspected hereditary nephropathy were identified during proteinuria screening for a genetic predisposition to protein-losing nephropathy. The group consisted of seven females and three males (age range 2–9 years; median age 6 years), all of which were closely related and came from a single breeder. On physical examination, no symptoms were found in any of the dogs, and body temperature was within normal limits. Routine biochemical and haematological blood tests and urinalysis were performed for each dog. A feature common to them all was marked proteinuria. In the anamnesis, a history of urinary tract diseases in other animals related to this group and fatal cases was recorded. No abnormalities were identified by an abdominal ultrasound examination to evaluate renal structure and assess the liver and GI tract for alternative cause of the proteinuria. Although renal biopsies are indicated to determine the pathology underlying the protein-losing nephropathy, they were not performed due to the owner withholding consent. The presumptive diagnosis of familial glomerulonephropathy was based on the occurrence of persistent proteinuria, exclusion of extrarenal causes of proteinuria, and evidence that the Dobermann is a breed predisposed to familial glomerulonephropathy. On the basis of the UPC

analysis, the group of related dogs was divided into two subgroups A and B. Subgroup A consisted of four females and one male, aged 4 to 9 years. These patients did not have azotaemia (creatinine level <125 μmol/L), yet the UPC level in this group was over 1. Subgroup B consisted of three females and two males, aged 5.5 to 9 years, with no azotaemia and UPC values in the range of 0.5–1. Twelve healthy dogs were included as a control group (two female and three male Dobermanns, two female boxers, one male flat-coated retriever, one male German shepherd, one male and one female Labrador retriever, and one female pug), weighing from 8 kg to 41 kg (median 32.7 kg) and aged 2 to 10 years (median 6 years). They were considered healthy based on physical examination, complete blood cell count, plasma biochemistry profile, and urinalysis. The control group was chosen to be age-matched with the study group.

Sample collection and processing. The clinical study involved the collection of blood and urine samples in both groups. Each blood sample was collected using a closed vacuum system into a test tube containing EDTA and subjected to haematological analysis in an Exigo Vet analyser (Boule, Spånga, Sweden). The serum obtained after centrifugation at 3,000 rpm for 15 min at 4°C was analysed in a BS-130 automatic biochemical analyser (Mindray, Shenzhen, China). The chemistry panel included alanine transferase, aspartate aminotransferase, total bilirubin, urea, creatinine, alkaline phosphatase, glucose, albumin, total protein, amylase, and γ-glutamyltransferase. Morning urine was collected midstream in containers containing a protease inhibitor (20 μL per 5 mL of urine; Protease Inhibitor Cocktail, Roche Diagnostyka, Warsaw, Poland) and divided into portions, one of which was subjected to complete routine urinalysis with sediment examination and quantitative assessment of proteinuria using the UPC. Urine total proteins and creatinine were determined using commercial kits on an automated chemistry analyser (Mindray BS-130). The UPC was calculated using the following formula: UPC = urine protein (mg/dL)/urine creatinine (mg/dL). The UPC was measured twice, in two samples collected after a two-week interval. UPC levels exceeding 0.5 were considered to indicate proteinuria. The specific gravity was determined on the basis of measurements with a refractometer. The whole sample preparation procedure was performed within one hour from material collection.

Blood pressure was measured using the Doppler method. The measurements were made using an Ultrasonic Doppler Flow Detector, Model 811 (Parks Medical Electronics, Inc., Aloha, OR, USA). Blood pressure was measured after the patient was acclimatised in the clinic, and the average of three measurements was used. Systolic pressure values exceeding 160 mmHg were considered to indicate hypertension.

The kidney ultrasound scan was performed on a MyLab machine (Esaote, Genoa, Italy) using a microconvex 3–9 MHz transducer.

Urinary markers. Quantification of urinary markers was performed on supernatant by immunoassays (uIgG, uRBP, and uTHP, Immunology Consultants Laboratory, Portland, OR, USA) as validated previously by other research groups (3, 15, 25). The absorbance was measured at a wavelength of 450 nm using a SpectraMax M2 ELISA plate reader (Molecular Devices, Sunnyvale, CA, USA). A four-parameter logistic non-linear regression curve-fitting model (MasterPlex Software, Hitachi Solutions, Tokyo, Japan) was used to generate the standard curve and calculate the concentrations of uIgG, uRBP, and uTHP. The resulting concentrations were normalised to the urinary creatinine (uCr) concentrations and expressed as ratios in mg/g.

Statistical analysis. Statistical analysis was performed using the Mann–Whitney U test, a non-parametric test for independent samples. The independent variables were uIgG/uCr, uTHP/uCr, and uRBP/uCr. Variables were added one by one (forward step), and the model was refitted until the p values were statistically significant ($p < 0.05$). The statistical analyses were performed using Statistica 10.0 software (StatSoft, Poland).

Results

The haematology, serum biochemistry, and renal ultrasound findings were unremarkable in all the Dobermanns. The urinary parameters of renal function revealed proteinuria with normal urinary sediment and a specific gravity of 1.030 (Table 2). Hypertension was diagnosed in all dogs, and the average systolic pressure was 175 (172–189) mmHg.

No dogs from the control group were diagnosed with proteinuria. Haematology and biochemistry results were within the normal physiological ranges and renal ultrasound findings were unremarkable in all dogs.

The levels of the biomarkers uRBP/uCr, uTHP/uCr, and uIgG/uCr are presented in Tables 3 and 4. IgG was undetectable in healthy dogs, and the average uIgG/uCr value in the whole experimental group was 460.4. In subgroup B, there was a statistically significant increase in the uIgG/uCr value to 50.5, and this value sharply increased to an average value of 742.77 in subgroup A. In healthy dogs, the average uRBP/uCr value was 0.2 mg/g, while in the whole experimental group, this average was 2.82 mg/g, increasing to 15.8 mg/g in subgroup A. The average uTHP/uCr value in healthy dogs was 0.26 and was not significantly higher at 0.7 on average in the whole group of Dobermanns. The uTHP/uCr value increased significantly to 1.52 in subgroup B but decreased to 0.093 in subgroup A.

Table 1. Results for blood biochemical parameters in sick Dobermann dogs and healthy dogs (expressed as mean and range)

Variable (reference range)	Dobermann dogs (n = 10) Mean (range)	Healthy dogs (n = 12) Mean (range)
Alanine transferase (u/L) (3–50)	43 (35–49)	47 (21–101)
Aspartate aminotransferase (u/L) (1–37)	18 (24–38)	28 (18–46)
Total bilirubin (mg/dL) (≤ 0.60)	0.36 (0.27–0.47)	0.2 (0.1–0.5)
Urea (mg/dL) (20.0–45.0)	35.9 (24.6–36.6)	37.7 (27.5–59.7)
Creatinine (µmol/L) (88–150)	114.9 (79.6–141.4)	106.1 (53–150.3)
Alkaline phosphatase (u/L) (20–155)	137 (98–150)	122 (110–143)
Glucose (mg/dL) (70–120)	98 (80–118)	117.2 (66–136)
Albumin (g/dL) (3.30–5.60)	3.54 (3.34–3.80)	3.7 (3.3–4.5)
Total protein (g/dL) (5.50–7.00)	6.26 (5.23–6.90)	6.7 (2.2–8.6)
Amylase (u/L) (388–1800)	595 (422–743)	602 (498–703)
Gamma glutamylotransferase (u/L) (5–25)	18 (12–24)	14 (8–23)

Table 2. Results for routine urinary parameters of renal function in sick Dobermann dogs and healthy dogs (expressed as mean and range)

Variable	Dobermann dogs (n = 10)	Healthy dogs (n = 12)
uCr (mg/dL)	74.1 (20.0–149.6)	135.64 (53.91–212.82)
Specific gravity	1.03 (1.02–1.03)	1.03
UPC	1.3 (0.5–2.3)	<0.5

UPC – urine protein-to-creatinine ratio

Table 3. Concentrations of urinary markers in sick Dobermann dogs and healthy dogs (expressed as mean and range)

Variable	Doberman Pinscher dogs (n = 10)	Healthy dogs (n = 12)
uRBP/uCr (mg/g)	2.82 (0.27–10.3)*	0.23 (0.08–0.41)
uTHP/uCr (mg/g)	0.7 (0–3.7)	0.2 (0–0.45)
uIgG/uCr (mg/g)	460.4 (34.02–2410.81)*	0

uRBP – urinary retinol-binding protein; uTHP – urinary Tamm–Horsfall protein; uIgG – urinary immunoglobulin G; uCr – urinary creatinine
* $p \leq 0.05$

Table 4. Concentration of urinary markers in sick Dobermann dogs divided into subgroups (expressed as mean and range)

Variable	Subgroup A (n – 5)	Subgroup B (n – 5)
uRBP/uCr (mg/g)	15.8 (2.6–ALD)*	0.38 (0.27–0.43)
uTHP/uCr (mg/g)	0.093 (0–0.093)	1.52 (0.39–3.7)*
uIgG/uCr (mg/g)	742.77 (34.02–2410.81)*	50.5 (0–85.17)

uCr – urinary creatinine; uIgG – urinary immunoglobulin G; uRBP – urinary retinol-binding protein; uTHP – urinary Tamm–Horsfall protein; ALD – above the limit of detection
* $p \leq 0.05$

Discussion

A presumptive diagnosis of familial nephropathy in 10 dogs was made on the basis of proteinuria, the close relationships between the dogs self-evident in their origin from a single dog breeder, and the history of urinary tract disorders in other dogs from the same breeder that developed polyuria and polydipsia, leading to death or euthanasia. Additional tests (abdominal ultrasound examination, complete urinalysis, neurological examination, and haematological and biochemical blood analysis) enabled the exclusion of extrarenal proteinuria. According to the International Renal Interest Society grading criteria, the dogs were classified as suffering stage 1 chronic kidney disease (nonazotaemia, proteinuria, and hypertension). In the current study, hypertension was diagnosed in all the experimental Dobermanns. To the authors' knowledge, correlation between blood pressure and familial nephropathy in the Dobermann has not been reported. Another study (4) investigating pathophysiology in familial nephropathy in a different breed demonstrated that along with glomerular hypertrophy and hyperfiltration, glomerular hypertension may occur as a compensatory response to acquired or congenital nephron paucity and may result in podocyte injury and

adaptive focal segmental glomerulosclerosis in protein-losing nephropathy. However, in our study, we cannot confirm these findings due to renal histopathological examination not having been carried out.

The assessment of kidney damage leading to proteinuria was performed by measuring the urinary excretion of RBP, uromodulin (THP), and IgG. Early identification of glomerular abnormalities is of major importance in breeds predisposed to familial glomerulopathy, in order to improve breeding policy. The gold standard for evaluating the nature and severity of canine glomerular lesions is histopathological examination of kidney biopsies. Nevertheless, this is an invasive and costly procedure, especially as a screening test. Therefore, non-invasive urinalysis is an attractive option for screening dogs at risk. Even if information regarding values for urinary marker ratios in healthy dogs is available from comparative studies (3, 16, 17, 20, 25), no reference intervals (RI) have been established that could be used as threshold values to screen dogs at risk for glomerular disease. To the best of our knowledge, there is no scientific evidence showing the differences among breeds in the levels of urinary markers. We therefore decided to determine specific RI for urinary marker ratios, by including healthy, non-proteinuric dogs (Dobermanns and other breeds). Although the number of non-proteinuric dogs was small and might have produced questionable thresholds, the values used in the present study were nevertheless comparable to those previously published for healthy dogs (13, 14–17).

The increase in the urinary level of IgG is caused by major damage to the glomerular filtration membrane, which increases its permeability (1, 2, 6). The differences in the uIgG/uCr ratios between the experimental group of Dobermanns and the group of healthy dogs were statistically significant and indicated a significant impairment of glomerular function. In the healthy dogs, the IgG levels were not measurable; however, in the Dobermanns with moderate proteinuria and a UPC of 0.5–1, the IgG levels were significantly elevated, and in those with a UPC > 1, the IgG levels were more than 10 times higher than those in the subgroup with moderate proteinuria. This drastic increase demonstrated an impairment of the glomerular filtration function, which also provided indirect additional evidence for the diagnosis of hereditary nephropathy in that particular group. These results are in accordance with another study in dogs showing that increased uIgG/c in apparently healthy Dogue de Bordeaux dogs with proteinuria and in some dogs with borderline proteinuria correlated with the presence of glomerular lesions (13).

In healthy dogs, the low molecular weight RBP protein (21 kDa) is excreted in trace amounts. Elevated urinary RBP levels are a consequence of impaired glomerular filtration function or reduced tubular reabsorption caused by damage to the cells of the proximal tubule (16, 17, 20, 25). Thus, uRBP is considered a useful indicator of minor lesions in the proximal tubule; RBP excretion precedes increases in the urine protein and serum creatinine level above the reference values (3, 8). As has been reported, the increased level of uRBP in dogs with X-linked hereditary nephropathy can be detected approximately two months before the onset of azotaemia, while the uRBP/uCR value increases as the disease progresses (17). Moreover, positive correlations between the uRBP level and the serum creatinine level, the glomerular filtration rate and the presence of interstitial fibrosis in the kidney biopsy samples were observed in the group of dogs with nephropathy (16). Our study also showed a significant increase in the uRBP/uCr values in the group of dogs with familial nephropathy, while in the subgroup of them with a UPC 0.5–1, this increase was not statistically significant. Therefore, this indicator may be useful in the diagnosis of primary glomerulopathies with advanced pathological lesions.

Uromodulin is a glycoprotein synthesised exclusively in the epithelial cells of the descending limb of the Henle loop and the distal part of the convoluted tubule. Under physiological conditions, THP is present in the urine of healthy dogs (11, 22). Decreased excretion of THP in the urine is related to a dysfunction of the distal tubule of the Henle loop, which is considered a marker of chronic kidney disease (5, 9, 19, 26). In our study, the average uTHP/uCr value of 0.7 for all studied dogs with familial nephropathy was non-significantly higher than the average value for healthy dogs. However, in the subgroup with a UPC 0.5–1, the uTHP/uCR value was significantly higher (1.52), while in the group with considerable proteinuria (UPC > 1), the value was only 0.093, below the average value for the group of healthy dogs. Thornely *et al.* (26) determined that in people with chronic kidney diseases, the total secretion of THP decreases as the number of nephrons decreases, although the secretory activity of a single nephron unit increases. As a result, in patients with early-stage disease and a normal glomerular filtration rate, the daily secretion of THP is higher than that in healthy individuals. This relationship was also observed in our study; in the group of Dobermanns with a UPC 0.5–1, the uTHP/uCr value was significantly higher than that in healthy dogs. However, in the group with UPC > 1, this value decreased below the average for healthy dogs. This pattern confirms the dynamics of the increases and decreases in uTHP/uCr during the course of this kidney disease, if we assume that the dogs with a UPC 0.5–1 were in an earlier or less-advanced developmental stage of this nephropathy.

In summary, this study's principal contribution is providing a better understanding of the pathogenic phenomena underlying the renal dysfunction in hereditary nephropathy in Dobermanns. The studied group of dogs exhibited glomerular, proximal tubular, and distal tubular dysfunction. Notably, changes in the urinary RBP, THP, and IgG levels, indicating nephron

damage, occurred even before the appearance of azotaemia, as the mean serum creatinine values did not exceed the upper limit. IgG, RBP, and THP seem to facilitate the diagnosis of primary hereditary nephropathies in living animals, especially those with advanced glomerular lesions. Nevertheless, longitudinal studies of the quantitative and qualitative characteristics of proteinuria, combined with renal histopathological description, are required to complement the present result in order to assess the true prevalence of glomerular lesions within the breed.

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Animal Rights Statement: The study was conducted in accordance with the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (Revised Directive 86/609/EEC – Directive of the European Parliament and of the Council on the protection of animals used for scientific purposes).

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