

# Review of the Water Diabetes Syndrome of Racing Greyhounds

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## What is the Water Diabetes Syndrome?

The Water Diabetes Syndrome (WDS) in the greyhound appears a multi-factorial condition involving a number of separate disease entities which share a common clinical manifestation of polyuria and polydipsia.

For veterinarians who do not routinely see this condition WDS can be somewhat confusing. While the majority of cases seem to result as an acquired form of either central or nephrogenic diabetes insipidus (CDI or NDI), causes of WDS are not limited to those that trigger the polyuria/polydipsia of diabetes insipidus.

When gathering a clinical history in small animal practice, polyuria (an increase in urine production) and polydipsia (an abnormal or excessive thirst) are commonly deciphered from owner observations. However, these symptoms must be distinguished from other urinary tract symptoms of pollakiuria (the abnormally frequent passage of urine) and dysuria (painful or difficult urination) for which the list of differential diagnoses may be entirely different. In greyhound practice, trainers are generally more observant of their animals but may still fail to make the distinction between different urinary symptoms, so clarification with obtainment of an accurate clinical history is vital.

Taylor defines polyuria in a small animal as a daily urine output of greater than 50ml/kg bodyweight. Gannon reports the average racing greyhound will produce 15-35ml/kg/day of urine, but this will vary with diet, fluid intake, environmental temperature and humidity and the work programme. Likewise the urine specific gravity will also fluctuate with these factors and the presence of other solutes or disease state including water diabetes syndrome, as demonstrated in Table 1.

Taylor defines polydipsia as daily fluid intake exceeding 100ml/kg body weight. However typically greyhounds are poor voluntary drinkers normally consuming up to 0.5-1L/day depending on climate, but may be less than 100ml/day in cool climates when fluid content of their diet is high. In extreme cases of WDS, such as seen in Hyperacute WDS, affected greyhounds may reportedly drink up to 15L in the first hour.

**Table 1: Comparison of typical Urine Specific Gravities of normal Greyhounds and those affected with the Water Diabetes Syndrome (WDS).**

Urine Sample	Typical USG (g/L)
Normal greyhound 1 <sup>st</sup> morning sample	1.040 – 1.055 g/L
Normal greyhound 2 <sup>nd</sup> morning sample	1.025 – 1.030 g/L
Normal greyhound random sample	1.030 – 1.040 g/L
Expected range of WDS samples	1.001 – 1.025 g/L
Greyhound with Hyperacute WDS sample	1.001 – 1.005 g/L
Greyhound with Acute WDS sample	1.005 – 1.010 g/L
Greyhound with Chronic WDS sample	1.010 – 1.025 g/L

*Source:* Adapted from Care of the Racing and Retired Greyhound, Blythe et al

## The Kidney and Pituitary Gland - maintaining extracellular fluid volume and osmolarity

The vital roles of the kidney include regulation of blood volume, blood pressure, osmolarity of extracellular fluid, pH, conservation of nutrients and excretion of drugs and waste. The kidney receives 20-25% of total cardiac output at rest with 20% filtered through the glomerulus and into the nephron and 80% passing through to the peritubular capillaries. In order for the kidneys to concentrate urine to a USG >1.025g/L, the hypothalamic-pituitary axis must be functional and capable of producing Antidiuretic Hormone (ADH or vasopressin), more than one third of nephrons must be functional and capable of responding to ADH and a hypertonic interstitial medulla must exist.

ADH is a peptide hormone produced by the supraoptic nuclei of the hypothalamus and secreted by the posterior pituitary in response to either a decrease in effective circulating volume detected by cardiovascular baroreceptors or an increase in extracellular osmolarity detected by hypothalamic osmoreceptors. An increased secretion of ADH promotes the renal reabsorption of solute-free water in the distal convoluted tubules and collecting ducts. ADH increases cyclic adenosine monophosphate (cAMP) in the epithelial cells of the collecting ducts which as a second messenger induces a series of events ending in the insertion of luminal membrane proteins called aquaporins. Aquaporins allow osmosis of water from the lumen down a concentration gradient into the hypertonic medullary interstitium, which is then returned to the circulation via the vasa recta and peritubular capillaries, resulting in increased effective circulating volume (ultimately extracellular fluid) and urine osmolarity and decreased extracellular osmolarity and urine flow. Chronic ADH exposure (>24hrs) will increase maximal water permeability of the collecting duct epithelium.

Urine flow may be increased by up to 90% in the absence or antagonised effect of antidiuretic hormone. In Diabetes Insipidus and WDS, administration of ADH is often required to maintain extracellular fluid volume and osmolarity. Treatment success depends on the ability of the nephron to respond to ADH and in cases of NDI there may be adequate systemic levels of endogenous ADH but a partial to complete defect in tubular response. Desmopressin acetate (DDAVP) is a synthetic ADH structurally similar to Vasopressin, but it has more antidiuretic activity and less vasopressor properties. While tablets exist, bioavailability is low due to gastrointestinal destruction leading to either parental or topical use. Intranasal administration is common in humans, but topical administration to either the conjunctiva (but can be an ophthalmic irritant) or the buccal mucosa (at the junction of gum and lip) is easier in animals. Antidiuretic action of DDAVP in dogs is usually seen within one hour of administration with peaks at 2-8 hours and can persist for up to 24 hours. Although the metabolism and distribution of DDAVP is not fully understood terminal half lives in humans after IV administration are from 0.4-4 hours. In comparison, the antidiuretic activity of aqueous vasopressin is 2-8 hours and the plasma half-life in humans is reported to be only 10-20 minutes.

Ability to produce concentrated urine is also dependant on the existence of a hypertonic interstitial medulla and the characteristics of the nephrons that pass through it. The ascending limb of a nephron is relatively impermeable to water, but here sodium ( $\text{Na}^+$ ) is actively transported into the interstitium at the expense of potassium ( $\text{K}^+$ ) to set up a vertical osmotic gradient within the medulla. The descending limb is permeable to water and osmosis drives water from the descending limb into the interstitium and back to the bloodstream, with active transport of  $\text{Na}^+$  from the ascending limb maintaining the osmotic gradient. Hypo-osmotic urine then flows through to the collecting duct where in the presence of ADH water will diffuse into the hypertonic medulla through aquaporins. Urea recycling is also important in maintaining a hypertonic medulla as 50% of medullary osmolarity is due to urea. Urea recycling occurs by diffusion from inner medullary collecting tubules until urine urea concentration approximates that of the medullary interstitium. Finally the hairpin loops of the vasa recta protect the concentration gradient, as the passive solute and water changes occurring as capillaries descend through the medulla are opposite as capillaries ascend given normal blood flow.

Total body  $\text{K}^+$  is regulated primarily by the kidneys with the major modifier of  $\text{K}^+$  excretion aldosterone, a mineralocorticoid produced in the adrenal cortex. Aldosterone release is triggered by decreased effective circulating volume or increased extracellular  $\text{K}^+$  and stimulates active  $\text{Na}^+$  reabsorption and  $\text{K}^+$  and  $\text{H}^+$  excretion in the distal nephron.  $\text{K}^+$  is mostly reabsorbed from filtrate in the proximal tubule and loop of henle but increased tubular flow rate reduces absorption. Mineralocorticoid therapy (e.g. Desoxycorticosterone acetate (DOCA), Desoxycorticosterone pivalate (DOCP) or Fludrocortisone) will increase  $\text{Na}^+$  reabsorption and aid in reabsorption of water in the proximal tubule reducing urine flow.

## **Classification of the Water Diabetes Syndrome**

### Hyperacute Water Diabetes Syndrome

- Rapid onset, often occurring within 1-5 minutes of race/trial
- Stress related, *includes but not limited to:*
  - Excessive environmental conditions e.g. temperature and humidity
  - Physiologically unfit for the race distance
  - Physiologically fit but excessive stress prior to or even during the race
    - Travel, kennelling, pre-race stimulation, injury, illness, interference, etc
  - Often degree of exertional rhabdomyolysis due to these stressors
- Reportedly drink up to 15L within first hour, regurgitating then drinking again
- Become dehydrated, anorectic and lose weight
- Death within 24-48 hours without rapid treatment

### Acute Water Diabetes Syndrome

- Slower onset but still rapid, occurring within 24 hours of race/trial
- Stress related as per hyperacute form with similar predisposing stressors
- Generally oral intake of 2-10L/day
- Become dehydrated and lose weight as a result but appetite is generally normal
- Death possible without treatment
- Good prognosis with successful treatment and back to normal work with 1-3 weeks

### Chronic Water Diabetes Syndrome

- Generally slower onset, occurring within 3-4 days of race/trial
- Stress related with similar predisposing stressors but more chronic forms involved
  - Environmental – kennel mates may be concurrently affected
  - Emotional – hyperexcitable during travel, kennelling, pre-race, etc
  - Chronic low grade infections
  - Chronic injury
- Generally oral intake of 1-2L/day
- Mildly dehydrated and associated weight fluctuation but appetite is generally normal
- Good prognosis with successful treatment and removal of stressors

## **Stress in the Racing Greyhound and its Role in the Water Diabetes Syndrome**

Whether it is the hyperacute, acute or chronic form of Water Diabetes Syndrome, stress is the common factor. Holloway provides an extensive list of possible causes of stress in a racing greyhound which is reproduced in Table 2. All these stressors can potentially predispose to an episode of Water Diabetes Syndrome and the reader is referred to this paper for a more detailed explanation of physiological changes seen during stress.

It is well understood that stress of any form can within minutes cause an enhanced secretion of adrenocorticotrophic hormone (ACTH) and subsequently cortisol. In periods of severe or prolonged stress, endogenous cortisol production is high enough to produce typical glucocorticoid-induced changes in the leukogram – leukocytosis, neutrophilia, monocytosis, lymphopenia and eosinopenia. These cortisol-induced changes are consistent with a previous study of haematology from 50 greyhounds with the chronic form of

WDS by Gannon. They were found in general to have a leukocytosis, a neutrophilia with a neutrophil to lymphocyte ratio in excess of 2:1, monocytosis, eosinopenia and varying degrees of anaemia suggesting chronic low grade infections and a greyhound under stress.

**Table 2: Causes of Stress in the Racing Greyhound**

<b>Environmental</b>	<b>Emotional</b>
Overcrowding	Emotional
Poor sanitation	Fighting
Intestinal parasites	Prerace excitement
Infectious diseases	Transport
Giardia	Competition for food
Ehrlichia	Need for exercise
Babesia	Sexual competition
Lyme disease	Overwork
Heartworm	
Poor nutrition	
Poor vaccination practices	
Poor quarantine practices	
Poor husbandry techniques	
Racing injuries	
Temperature and humidity	
Poorly maintained kennels	
Iatrogenic injury	

*Source: Stress and Performance - Related Illness in Sporting Dogs SA Holloway*

### **Potential causes of Water Diabetes Syndrome**

- Central Diabetes Insipidus
  - Results from a complete or partial deficiency in ADH synthesis or secretion.
  - Mostly idiopathic but can result from pituitary tumours, head trauma or from congenital lesions.
  - Many drugs inhibit ADH release including phenytoin, alcohol and glucocorticoids.
- Endogenous glucocorticoids
  - Endogenous glucocorticoids such as cortisol produce a polyuria with compensatory polydipsia by interfering with ADH action on the distal tubule and collecting duct as well as reducing the sensitivity of osmoreceptors and therefore appropriate release of ADH from the posterior pituitary. Any stressor previously mentioned which triggers a rise in endogenous cortisol can trigger an episode of WDS. Extreme environmental conditions, excessive stress and stimulation pre-race, physically unfit for the race, chronic infections or chronic injuries are the most common stressors.
  - Any injury of the musculoskeletal system will increase endogenous cortisol. Hauler reported an increased frequency of myositis in the origin of the left lateral vastus in affected greyhounds with palpable pain in the left medial gluteal, origin of the left lateral vastus, lower biceps femoris and lateral semitendinosus.
- Exogenous corticosteroid administration
  - Corticosteroids used for treatment of musculoskeletal injuries or as pre-race stimulants will like endogenous corticosteroids produce a polyuria with compensatory polydipsia.
- Hypokalaemia
  - PU/PD associated with hypokalaemia results from impaired renal responsiveness to ADH and is supported by excellent response in some WDS cases to K+ supplementation alone.

- Polyuria of any kind will lead to a progressive hypokalaemia. Activation of the renin-angiotensin-aldosterone system leads to retention of Na<sup>+</sup> and active excretion of K<sup>+</sup>, particularly in hot weather and during dehydration. Glucocorticoids increase K<sup>+</sup> excretion.
- The most recognized clinical signs associated with hypokalaemia are muscular weakness and PU/PD but hypokalaemia polymyopathy occurs at serum [K<sup>+</sup>] <3.0 mEq/L and can result in overt muscle damage. Hypokalaemia also reduces arterial dilatation causing a relative ischemia predisposing to exertional rhabdomyolysis.
- In rats, K<sup>+</sup> depletion results in increased renal ammoniogenesis that may activate complement and contribute to tubulointerstitial disease. Renal interstitial nephritis and fibrosis occurred in cats fed a diet containing low K<sup>+</sup>.
- Pyelonephritis or bacterial endotoxin
  - Resolution of polyuria particularly in chronically affected cases in response to antibiotics lends support to a bacterial endotoxin component in WDS.
  - The most common bacteria encountered in canine urinary tract infections are *Escherichia coli*, and *Staphylococcus* spp. Others include *Streptococcus* spp., *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Klebsiella*, *Enterobacter* spp. and, *Enterococcus* spp.
  - E. coli's endotoxin mediated effect has long been established in pyometra. Endotoxin can affect urine concentrating ability either by causing injury and interference to Na<sup>+</sup> and Cl<sup>-</sup> reabsorption in the loop of henle affecting the medullary osmotic gradient or by directly affecting ADH action on collecting ducts.
  - Infection and inflammation of the renal pelvis can also destroy medullary hypertonicity and the countercurrent concentrating mechanism.
  - Fever, renal pain, inflammatory CBC, inflammatory urine sediment and positive urine culture are typical for pyelonephritis.
- Hypercalcaemia (NDI)
  - Elevated serum Ca<sup>++</sup> inactivates transport of Na<sup>+</sup> and Cl<sup>-</sup> into the renal medulla affecting medullary hypertonicity and can eventually precipitate in renal tubules.
- Hyperthyroidism (NDI)
  - Greyhounds are traditionally considered hypothyroid so is an unlikely cause for WDS.
  - However, thyroxine supplementation can cause a polyuria and compensatory polydipsia while also increasing the actions of catecholamines and sympathomimetics potentially increasing endogenous glucocorticoid production.
- Liver failure/insufficiency
  - This is unlikely in a fit animal but degrees of hepatic insufficiency could contribute through reduction in medullary hypertonicity and delayed clearance of drugs including cortisol.
- Psychogenic polydipsia
  - Polydipsia with compensatory polyuria.
  - Learned behaviour in dogs with exercise restricted environments or subject to stress.
  - Neoplastic or traumatic lesion in thirst centre can produce similar polydipsia.
- Excessive electrolyte supplementation
  - Overzealous supplementation of electrolytes by trainers particularly post-race in hot weather can stimulate the thirst centre via osmoreceptors with a compensatory polyuria. USG tends to be higher than other forms of WDS.
- Other exogenous drugs
  - Kidney tonics or flushes administered by trainers are generally diuretic based and induce a polyuria with compensatory polydipsia.
  - Drugs such as phenytoin and alcohol can inhibit ADH release.
- Renal Medullary Solute Washout
  - Can occur secondary to reduced protein intake or as a sequel to any disease causing polyuria, as increased tubular flow rate results in decreased reabsorption of Na<sup>+</sup> and urea recycling. A

reduction in the osmotic gradient of the renal medulla develops and even in the presence of ADH, urine concentration is limited to the maximum osmolarity of the medulla.

### Treatment options

In all cases of Water Diabetes Syndrome it is important to establish as best as possible the initial stressor/s that trigger a clinical episode in order to prevent future recurrences. However presented with a clinical case, stabilisation of the animal is more important.

- IV fluid therapy
  - Replace deficits to maintain tissue perfusion within 4 hrs in acute cases or over 12-24 hrs in chronic cases (remember ongoing losses and maintenance).
  - 0.9% NaCl or Ringers over solutions containing lactate such as Lactated Ringers if acidotic.
  - Potassium Chloride (KCl) supplementation is beneficial as diuresis promotes hypokalaemia.
    - K<sup>+</sup> should not be infused IV at a rate > 0.5 mEq/kg/hr because arrhythmias may occur at higher administration rates.
    - E.g. If 40mEq KCl is added to 1L 0.9% NaCl then 12ml/kg/hr is maximal fluid rate.
  - Sodium Bicarbonate (NaHCO<sub>3</sub>) if animal has concurrent metabolic acidosis or if serum bicarbonate is less than 16mEq/L.
    - mEq Replacement dose = bodyweight (kg) x 0.3 x bicarbonate deficit (desired bicarbonate i.e.. 22-28mEq/L – measured bicarbonate)
    - ½ mEq Replacement dose IV over 20-30 mins other ½ mEq over next 2-4 hrs
- Antidiuretic Hormone
  - Desmopressin Acetate (DDAVP or Minirin®)
    - Minirin® Injection 4 µg/ml or Minirin® Drops 100 µg/ml
    - SVC use Minirin® 1ml every 8-12 hours SC or IM
    - Blythe et al recommends 3 Minirin® drops q4-6hrs
  - Vasopressin (Pitressin®)
    - Pitressin® Injection 20 pressor units/ml
    - Blythe et al recommends 0.2ml IM every 4-8hrs to effect
- Mineralocorticoids
  - May be useful in retaining fluid by active Na<sup>+</sup> absorption and assist in re-establishing or maintaining medullary osmotic gradient following polyuria but should supplement K<sup>+</sup> to minimise hypokalaemia.
  - Desoxycorticosterone acetate i.e. DOCA
    - Decort20® (20mg/ml) 1ml IM (Recommended racing withhold 48hrs)
    - 0.2-0.4mg/kg IM SID (Ettinger)
  - Fludrocortisone
    - Florinef® 0.1mg PO q8-12h for 5d then q24h for 7-10d (Blythe et al)
    - 0.015-0.02mg/kg PO SID (Ettinger)
  - Desoxycorticosterone pivalate i.e. DOCP
    - Percorten-V® (25mg/ml) 1.7-2.2mg/kg every 21-30d for control of Addison's
    - 1.1mg/kg has been used in WDS
- Adrenocorticotrophic hormone (ACTH)
  - Cooper discusses 3 types of WDS - ADH responsive, DOCA responsive & ACTH responsive.
  - Synthetic ACTH does reliably increase serum [aldosterone] (which is a more potent mineralocorticoid than DOCA) with peaks within 60 minutes of administration but serum [cortisol] is also significantly increased making its use seem contraindicated in WDS.

- Chronic stress suppresses ACTH production through negative feedback from elevated cortisol levels. Blythe et al suggests ACTH may be of short term benefit in maintaining performance over a stressful period so ACTH may reduce the chances of WDS occurring e.g. Synacthen® (Tetracosactrin) 0.25mg SC/IM SID for 3 days then twice weekly for 2-4 weeks.
- Controlled oral fluids
  - As a guide, every 6hrs on Day 1 supply 2L, on Day 2 supply 1L, on Day 3 supply 1/2L and by day 4 oral intake should be <1L/24hrs.
  - Preferably restrict to isotonic solutions rather than water.
  - Be aware that deprivation of oral fluid may agitate and further stress already stressed animals and if not correctly managed lead to hypernatraemia.
- Electrolytes
  - Isotonic oral fluids such as Vitrate® or Lectade®.
  - Oral potassium supplementation – Slow K®, Beta K®, etc.
- Antibiotics
  - Warranted if bacterial infection suspected from urine or blood test and ideally based on result of culture and sensitivity.
  - Empiric antibiotic choices should be excreted kidneys in their active form and be broad spectrum. E.g. Amoxicillin-clavulanate, Cephalexin, Enrofloxacin, Trimethoprim-sulfa.
- Treat musculoskeletal injuries
- Minimise stress
  - Anxious dogs will benefit from a quiet environment with minimal stimuli but may benefit from calming drugs during WDS or in future prior to stress e.g. Reserpine 0.25mg IM for 3 days (recommended racing withhold 96hrs) or Tryptophan 400mg BID PO (no withhold).
  - Rest for minimum 7 days depending on severity of illness and speed of recovery.
- Anabolic steroids
  - Withholding periods now an issue for all anabolic steroids except ethyloestrenol in bitches
  - Can use ethyloestrenol at 0.05mg/kg/day PO in bitches (30kg dog 0.4ml Nitrotain® or 3 Oestrotain® tablets) to oppose the catabolic effects of cortisol e.g. muscle wastage.
  - Same dosage in dogs with observance of suggested racing withhold of 2 weeks which is likely to be shorter than the convalescence from illness.
  - Clinical judgement to be used when prescribing other anabolic steroids e.g. Stanozolol. In severe cases particularly with concurrent metabolic acidosis a parental anabolic may be necessary. Suggest cautious use of anabolic steroids in racing greyhounds with the documented recommendation made to trainers that an elective test is taken through GRV prior to future competition.
- Haematinics if indicated by haemogram
  - Iron, Vitamin B12, Folic Acid and Vitamin B Complex will increase RCC & Hb.
- Immune stimulants
  - Vitamins C & E, glutamine, etc will increase WCC.
- Thiazide diuretics
  - Not a common treatment but ironically have been used in animals with congenital NDI, as thiazide diuretics will increase proximal tubule reabsorption of Na<sup>+</sup> reducing tubular flow and urine output. Reduces urine output by 20-30% in cases of congenital NDI.
  - Chlorothiazide 10-20mg/lb q12hr or hydrochlorothiazide 1-2mg/lb q12hr (Ettinger).
- Dietary modification
  - Additional fat and carbohydrate in the diet will have a protein sparing effect

## Conclusion

The Water Diabetes Syndrome in racing greyhounds is still a complicated and perplexing condition, but one which can be successfully treated particularly when underlying stressors can be identified and prevented in future.

Successful treatment, like any other, comes back to first principles. Obtaining an accurate history, performing a thorough physical examination including musculoskeletal examination and performing a minimum database of haematology, biochemistry and urinalysis will ensure the clinician can at least confirm their diagnosis, but can aim treatment at correcting derangements from normal.

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