

ANOREXIA NERVOSA AND THE KIDNEY

Trina Banerjee

Outline

- ▣ Metabolic Abnormalities of Anorexia
- ▣ Etiologies of Kidney Failure
- ▣ Treatment

Metabolic Abnormalities

- ▣ Hypokalemia
- ▣ Hyponatremia
- ▣ Hypercalcemia
- ▣ Hypomagnesemia
- ▣ Hypophosphatemia
- ▣ Metabolic Acidosis

Hypokalemia: Pathophysiology

- ▣ Decreased Reabsorption of K:
 - K is reabsorbed using the H/K ATPase, which requires an acceptor for the proton in the tubular fluid
 - In anorexia the phosphate stores are low and bicarb will have been reabsorbed proximally
- ▣ Increased Secretion of K:
 - Decreased effective circulating volume results in an increase in aldosterone

Hypokalemia: Clinical Consequences

- ▣ Impaired urinary concentration:
 - Decreased collecting system responsiveness to ADH, with decreased expression of aquaporin-2, when $K < 3$ meq/L
- ▣ Increased renal ammonia production:
 - As K leaves the tubular cell H enters, causing intracellular acidosis
 - The H is then secreted leading to increased ammonia formation

Hyponatremia

- ▣ Low solute ingestion
- ▣ Impaired Osmoregulation

Impaired Osmoregulation: Evrard et al (NDT 2004)

- ▣ Case control study
- ▣ 12 patients with anorexia, 10 on antidepressants. 2 control groups: 12 women without anorexia not on antidepressants and 11 women on antidepressants
- ▣ Urine osmolarity measured at baseline and after 12 hour fast

Impaired Osmoregulation: Evrard et al cont (NDT 2004)

- ▣ Compared to women not on antidepressants, anorexics had:
 - Baseline: Identical urine urea and creatinine, identical serum ADH, higher baseline osmolarities
 - Following water deprivation: Minimal increase in ADH, minimal rise in urine osmolarity

Table 2. Biological parameters at baseline (day 1) and after water deprivation (day 2)

	Controls (n=12)		AN patients (n=12)		Patients taking antidepressants (n=11)	
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
Plasma ^a						
Urea (15–40 mg/dl)	30±2	27±2 [†]	26±3	24±3	23±2	21±2
Creatinine (0.6–1.4 mg/dl)	0.83±0.03	0.83±0.03	0.83±0.05	0.86±0.04	0.75±0.02	0.76±0.04
Na ⁺ (135–145 mEq/l)	139±0.6	140±0.4 [†]	136±0.9* [#]	138±0.7	138±0.8	139±0.3
Cl ⁻ (97–107 mEq/l)	104±0.7	106±0.7	101±1.3* [#]	103±1.3	105±0.9	106±1.0
K ⁺ (3.5–5 mEq/l)	3.9±0.3	3.8±0.2	3.9±0.2	3.9±0.2	4.0±0.2	4.0±0.2
HCO ₃ ⁻ (22–29 mEq/l)	26.5±0.6	27.2±0.4	27.3±0.9	28.4±1.4	26±0.5	25.5±0.4
Osmolality (280–300 mOsm/kg)	288±1	290±1 [†]	281±2* [#]	284±2 [†]	286±1	288±1
ADH (0–8 pg/ml) ^b	5.3±0.7	6.5±0.7 [†]	5.3±0.8	5.5±0.8	3.0±1.0	3.8±0.8
Urine						
Osmolality (mOsm/kg)	276±47	725±57 [†]	474±90	515±86	429±70	587±58 [†]

^aNormal limits are in parentheses.

^bThe ADH values were determined simultaneously in the matched AN patients and controls, and *a posteriori* in patients taking antidepressants.

Data are means±SEM; ANOVA was used for comparison between baseline values among the three groups; the paired *t*-test was used for comparison between day 1 and day 2 values in each group. *[#]*P*<0.05 AN patients vs controls (*) or patients taking antidepressants (#); [†]*P*<0.05 day 1 vs day 2 (intra-group).

Hypercalcemia and Hypomagnesemia

- ▣ Increased bone breakdown from acidosis, results in hypercalciuria
- ▣ High calcium turns off the calcium sensing receptor in the thick ascending tubule shutting off ROM-K, leading to magnesium wasting

Hypophosphatemia

- ▣ During starvation, tissue breakdown can cause total depletion of phosphate
- ▣ Clinical Consequences:
 - Cardiac:
 - ▣ Low ATP decreases contractility of the heart
 - Pulmonary:
 - ▣ Low ATP causes diaphragmatic weakness
 - Hematologic:
 - ▣ Anemia because RBCs don't get enough ATP
 - ▣ Immune dysfunction because leukocytes don't get enough ATP
 - Rhabdo
 - Seizures

Metabolic Acidosis

- ▣ Increased production of ketones:
Starvation ketosis

- ▣ Decreased phosphate buffer in the tubular fluid to excrete acid

Etiologies of Kidney Failure

- ▣ Volume Depletion
- ▣ Rhabdomyolysis
- ▣ Hypokalemic Nephropathy

Hypokalemic Nephropathy: Clinical Presentation

- ▣ Polyuria, metabolic alkalosis, proteinuria
- ▣ If short term can be reversed
- ▣ If long term causes progressive renal dysfunction

If long term causes progressive renal dysfunction

- ▣ Acute:
 - Over at least 1 month chronic hypokalemia produces vacuolar lesions in the proximal and distal tubule, which can be reversed by K repletion
- ▣ Chronic:
 - Renal tubular cell hypertrophy
 - Medullary collecting ducts and the thick ascending limb with tubular atrophy, interstitial macrophage infiltration, and fibrosis
 - Hypertrophy of the juxtaglomerular apparatus

Pathophysiology

▣ Acute:

- The vacuolization of the proximal tubule cells causes obstruction of the tubule

▣ Chronic:

- Prolonged hypokalemia can lead to interstitial fibrosis, tubular atrophy, and cyst formation most prominent in the renal medulla.
- Correcting hypokalemia can decrease the number and size of cysts, but tubulointerstitial lesions and renal insufficiency associated with it may be irreversible.

Hypothesis I: Increased ammonia Production, increased complement

- ▣ Toler et al:
 - Study I to observe the effect of NaHCO₃ and NaCl in a rat model of potassium deficiency
 - Sprague Dawley rats maintained on a K deficient diet for 3 weeks and randomized them to either NaCl or NaHCO₃
 - Control animals got a normal K diet and NaHCO₃
 - Study I the rats treated with NS has hypertrophied kidneys, while the rats with NaHCO₃ had less hypertrophy

Table III. Renal NH₃ Metabolism of Rats in Study I

	KDEF	KDEF + HCO ₃	Control
Renal vein NH ₃ (μM)	392* ±110 (6) [‡]	214 [§] ±28 (6)	179 ±57 (8)
Urinary NH ₃ excretion rate (μmol/min)	2.29* ±0.70 (6)	0.89 [§] ±0.29 (6)	1.49 ±0.49 (8)
NH ₃ production rate (μmol/min)	3.11* ±1.30 (6)	1.33 [§] ±0.47 (6)	1.84 ±0.56 (8)

* $P < 0.05$ vs. control.

[‡] n

[§] $P < 0.05$, KDEF + HCO₃ vs. KDEF.

Table II. Renal Functional Parameters of Rats in Study I

	KDEF	KDEF + HCO ₃	Control
Urine output (ml/24 h)	83* ±19 (8) [‡]	46 [§] ±15 (8)	29 ±9 (8)
Urinary total protein excretion (mg/24 h)	39* ±21 (15)	20 [§] ±6 (15)	17 ±7 (16)
Urinary low molecular weight protein (<10,000 mol wt) excretion (mg/24 h)	7* ±2 (12)	4* [§] ±2 (11)	2 ±1 (12)
GFR (ml/min)	0.74* ±0.28 (10)	0.91* ±0.29 (8)	1.27 ±0.14 (10)
Renal plasma flow (ml/min)	4.67 ±2.31 (10)	4.69 ±2.06 (8)	4.89 ±0.67 (10)

* $P < 0.05$ vs. control.

[‡] n

[§] $P < 0.05$, KDEF + HCO₃ vs. KDEF.

Toler et al: Study II

- ▣ Study II to determine the effect of ammonia of complement levels
- ▣ In Study II the cortexes of normal rats were taken and the Same amount of ammonia was added to them that is found in hypokalemic rats and goat anti rat C3 was applied
- ▣ Large amount of C3 deposition

Hypothesis II

- ▣ Vasoconstriction
- ▣ Alternation in growth factors and cytokines: including VEG-F, IGF-1, IGFBP-1, Angiotensin II, MCP-1, and TGF-Beta
- ▣ Decreased angiogenesis

Siritaj et al: JASN 2008

- ▣ 34 male Sprague Dawley rats were initially given a normal K diet for 5 days, and then randomized to either normal K (16) or low K (18) diets
- ▣ Rats were euthanized at week 2, week 4, and week 12
- ▣ VEGF and eNOS were measured by Western Blot and MCP-1 and TNF-alpha were measured by ELISA

Siritaj et. al: Cont.

- ▣ Low K rats had:
 - Renal hypertrophy
 - Higher Cr at all time points, and an increased P/Cr at week 12
 - Higher collagen III at 12 weeks
 - Increased MCP-1, which increased further at every time point, more macrophage infiltration
 - TNF alpha higher, eNOS and VEGF lower
 - Increased capillary loss

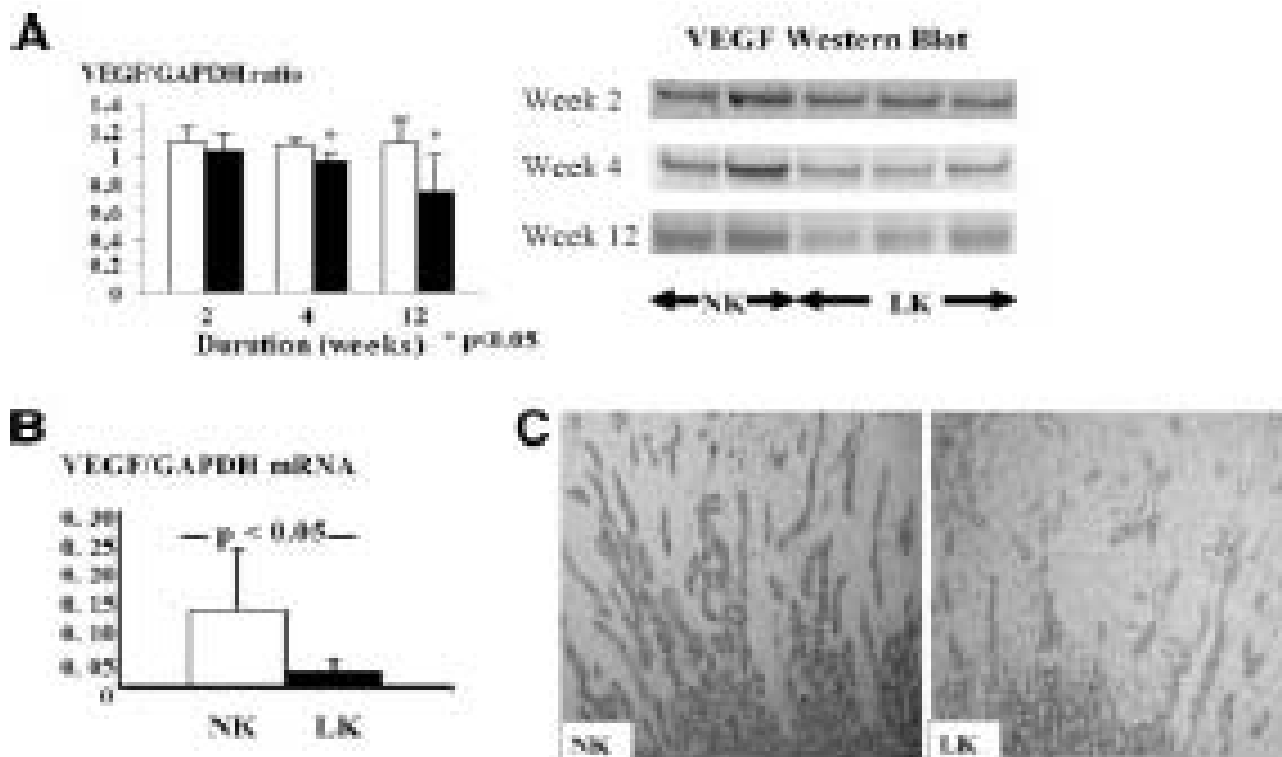


Figure 6. Reduction of renal VEGF mRNA and protein expressions in the hypokalemic rats. (A) VEGF protein represented by Western Blot which was reduced at weeks 4 and 12 of hypokalemic nephropathy (normal K^+ rats; NK represented with white bars and low K^+ rats; LK represented with black bars). (B) VEGF mRNA expression at week 12 of low K^+ diet (C) Renal tubular VEGF expression at week 12 of the study demonstrated by immunohistochemistry (200x)

Treatment: Refeeding

- ▣ Types
- ▣ Dangers
- ▣ Practicality

Types of Refeeding

- ▣ Oral refeeding:
 - Preferred
- ▣ Indications for TPN:
 - Failure of weight gain with standard oral feeding
 - Life threatening weight loss
 - Worsening psychological state
- ▣ PEG

Dangers: Refeeding Syndrome

- ▣ Cardiovascular
- ▣ Hypokalemia
- ▣ Hypophosphatemia
- ▣ Hypomagnesemia
- ▣ Gastrointestinal

Cardiovascular

- ▣ Heart mass is reduced during anorexia
- ▣ Increased circulation during refeeding
- ▣ Heart failure may result

Hypokalemia

- ▣ Increased glucose load causes insulin release, which caused K to shift into cells
- ▣ Potassium will also be incorporated into tissues as the catabolic state switches to the anabolic state

Hypophosphatemia

- ▣ Increased glucose load causes insulin release which causes phosphate to shift into cells

- ▣ Increased glucose load causes insulin release which causes phosphate to shift into cells

Hypomagnesemia

- ▣ Magnesium may be incorporated into newly formed tissue

Gastrointestinal

- ▣ LFTs:
 - Early in refeeding LFTs may rise. Initially the AST and ALT, followed by the alkaline phosphatase, and then the bilirubin. There is no clinical significance
- ▣ Motility:
 - Constipation
 - Diarrhea:
 - ▣ Atrophy of the intestinal mucosa may have diarrhea early in refeeding

Practicality: IBW

Calculation:

- Female: 100lbs for 5 feet, five lbs for every inch more than 5 feet tall
- Male: 106lbs for 5 feet, 6 lbs for every lb over
- ▣ Patients may be calculated as mild, moderate, or severe depending on whether they are 10, 20, or 30% below IBW
- ▣ Pt is acceptable when within 10% of IBW, or when menstruation

Practicality: Caloric Requirement

- ▣ Basal metabolic rate is Based on the Harris-Benedict Formula:
 - $6.55 + (9.6 * \text{body weight in kg}) + (1.8 * \text{height in cm}) - (4.7 * \text{age in years})$
- ▣ Total Energy Expenditure (TEE)
 - Multiplied by a factor of 1.2 to 2 to achieve the total energy expenditure

Practicality: Caloric requirement cont

- ▣ Intake levels usually start at 600-1000kcal/day and are increased by 300-400kcal every 3-4 days
- ▣ Initially anorectics are metabolically inefficient, and the amount of calories required for weight gain may vary between 1800 and 4500kcal

Practicality: Monitoring

- ▣ CV status should be check several times a day
- ▣ Mag/Phos/K should be checked at least daily