Anorexia Nervosa and The Refeeding Syndrome

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Case: HD

- HD is a 20 yo woman with longstanding restrictive anorexia nervosa who was admitted to ACUTE at Denver Health after six months of continuous hospitalization on the East Coast, and worsening health.
Case: HD

• Background
  – August: Started college losing weight, tried to eat, developed refeeding hypoglycemia and had seizure
  – At a large Delaware hospital, PICC line placement gave her an air embolism, and overaggressive IV glucose kept her in their ICU for days of “raging refeeding syndrome”
  – Transferred to a large NJ hospital PICU
Case: HD

• Background
  – The NJ PICU to floor transfer was complicated by abrupt cessation of IV glucose, causing immediate re-transfer to PICU after second hypoglycemic seizure
  – Transferred to another hospital nearer her home, where an NG was placed because no surgeon was willing to place a PEG
    • Her NG came out and no one noticed all night. Was transferred to the PICU with third bout of severe hypoglycemia
    • Later, a physical therapist told her to walk, and having been in bed for days, she promptly syncopated on rising
Case: HD

- **Background**
  - HD lost weight from August to December
  - Each hospitalization was further complicated by edema so severe she could not walk
  - There was no provision of psychiatric support during these hospitalizations
  - HD was admitted to ACUTE when her inpatient MDs felt she was too complex for them and called Children’s Hospital, who recommended Denver Health’s ACUTE program based on the patient’s age and severity
Case: HD

- On admission to ACUTE:
  - 5’1”, 50.8 lbs, representing 48% of ideal body weight and a BMI of 9.8 kg/m²
  - On exam, vitals signs: 36.8 C, pulse 78, RR 16, BP 101/69, 96% on RA
  - Profoundly emaciated, with facial lanugo hair growth, alert, oriented, generally weak. Lungs clear, heart regular, abdomen scaphoid with normal bowel sounds, non-tender, significant skeletal muscle atrophy, with a flat affect.
  - Labs on admission:

<p>| | | | |</p>
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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>132</td>
<td>96</td>
<td>9</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>3.9</td>
<td>27</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Phos 3.8 mg/dL

AST 39 U/L (10-40)
ALT 52 U/L (7-45)
Albumin 4.1
HD is started on 1000 oral kcals/day, glucose are checked every 4 hours, telemetry is started, and labs are checked daily

- DEXA scan shows Z-score of -2.2; echo is unremarkable
- Within a week of admission, LFTs have more than tripled, and on hospital day 19 the AST is 331 U/L and ALT is 625 U/L, with an INR of 1.39. A RUQ ultrasound is unremarkable. Six days later a repeat ultrasound with dopplers is also unremarkable.
- Viral serologies and a full autoimmune panel are negative
Case: HD

- A liver biopsy is performed on hospital day 21, which finds no inflammation, only evidence of autophagy
  - HD fails a swallow evaluation that day due to worsening weakness
- She remains unable to increase her oral kcal intake, so a PEG tube is planned.
  - Her weight falls nine pounds to 44.6 lbs (20kg), BMI 7.8
- On hospital day 22, she desaturates acutely and is found to have a NIF of zero and a phosphorous of 1.9 mg/dl
  - Transferred to PICU
Case: HD

- A surgical PEG is placed successfully just prior to transfer
- At the time of transfer on hospital day 22, labs show:

  - Phos 1.9 mg/dL
  - AST 3832 U/L (10-40)
  - ALT 3219 U/L (7-45)
  - Bilirubin normal
  - Albumin 2.8
  - INR 2.08
Case: HD

• The patient shows evidence of severe sepsis, with a positive UA, fever, and tachycardia. Pseudomonas grows out of the urine and the blood
• The patient is placed on oxygen with intermittent “easy pap” in the PICU and does not need intubation
• PEG feeds are started, as the patient lacks the strength to swallow without aspirating
• Nadir weight comes the day after ICU admission: 43.3 lbs, with a BMI of 7.7 kg/m²
Case: HD

- Over the following 19 days, the patient makes slow but steady improvement.
  - She transfers back to the floor on hospital day 48 and is able to resume oral feeds in addition to her PEG. At discharge she is consuming 2800 kcal/day of a balanced oral diet alone.
  - Her weight at the time of discharge is 56 lbs, almost 13 lbs above her nadir weight, with a BMI of 10.9 kg/m².
  - Her labs at discharge show a normal chemistry, albumin 2.6, ALT 48 U/L, AST 21 U/L, WBC 3.3 k/ul, hct 26%, and Plt 991 k/ul.
Case: HD

- She is discharged to the Eating Recovery Center in Denver on hospital day 47, where she stays for many months.
- To date, she maintains a normal body weight and has graduated college.
Acute Comprehensive Urgent Treatment for Eating Disorders at DHMC

ACUTE

- Anorexia nervosa diagnosed at <85% of IBW (BMI 17.5)

% of IBW

40% 50% 60% 70% 80% 90% 100%

Inpatient treatment

Outpatient treatment

Severe

Mild

Moderate

A.C.U.T.E

Level One Care for ALL

(Severe-Extreme)
Severe Anorexia Nervosa

BMI

<table>
<thead>
<tr>
<th></th>
<th>NHANES-4</th>
<th>DSM-IV A.N.</th>
<th>ACUTE @ DH (7.7-14.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>29</td>
<td>17.5</td>
<td>11.7</td>
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</table>
ACUTE at DHMC
Severe Anorexia Nervosa

• Weight only 40-60% of IBW (BMI 7.7-12)
• Little physiologic reserve
• Languish in and out of acute care hospitals over months to years
• Many patients are transferred to DHMC via air-ambulance
Clinical Findings (*LFT’s*)
& Bone Density

- Average age: 25
- Abnormal LFT’s (AST/ALT): 76%
- Abnormal LFT’s peaked Day 4
- Hypoglycemia: 50%
- Osteoporosis: 34% (worst Z score: -4.6)
- Osteopenia: 50%
Medical Stabilization (Results)

- No deaths, seizures, cardiac arrests and only 5% readmission rate
- 100% gained weight
- 90% refed with progressive oral KCAL
- 10% refed with TPN or enteral (PEG/PEJ)
- Average KCAL at discharge: 3000 KCAL
Cardiac (Anorexia)

- Increased risk of sudden death
- Clean coronaries on post-mortem
- ??QT prolongation → Torsade De Pointes, → sudden death (the old)
Cardiac (Anorexia)

• Myofibrillar atrophy with loss of left ventricular mass
• Attenuated BP response to exercise
• Hypotension
• Bradycardia due to exaggerated parasympathetic output
• Mitral valve prolapse
# Lipids in Anorexia

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>BMI</td>
<td>15.35</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>179.3 mg/dL</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>104.1 mg/dL</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>65.5 mg/dL</td>
</tr>
<tr>
<td>Beta-Carotene (8-20 mg/dL)</td>
<td>57.0 mg/dL</td>
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QT Dispersion

- $QT_D$ is measured as the difference between the longest and shortest QT interval from a single ECG lead
- Increased variation in QT segment length might represent differences in ventricular repolarization and result in an increased risk of ventricular arrhythmias
Heart Rate Variability (HRV)

- Moment to moment fluctuations in heart rate, over time and frequency domains, mediated by autonomic input to the sinus node
- These variations reflect the underlying stability of autonomic function, and susceptibility to potentially serious cardiac arrhythmic events
Correlations and Predictions of Low HRV

- ↑ Sudden death in CHF and CAD
  - (ARIC study, Framingham)
- ↑ Mortality following MI
  - (GISSI-2)
- No direct evidence ↑ HRV improves survival, BUT ↑ HRV with:
  - ACE-I and carvedolol in CHF & MI
Cardiac Repolarization in Severe Anorexia Nervosa (DH-ACUTE)

- 34 Denver Health patients with median BMI of 12.9 (8.5-14.3)
- Mean HR: 54
- Mean QTc (Fridericia): 0.421 sec (nml)
- No correlation between QTcF and either admission BMI or REE
## Resting ECG Data $QT_D$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AN</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>$51.3 \pm 2.8$</td>
<td>$61.7 \pm 3.5$</td>
<td>$0.04$</td>
</tr>
<tr>
<td>QRS</td>
<td>$0.089 \pm 0.032$</td>
<td>$0.093 \pm 0.021$</td>
<td>$0.09$</td>
</tr>
<tr>
<td>$QT_C$</td>
<td>$0.415 \pm 0.11$</td>
<td>$0.419 \pm 0.64$</td>
<td>$0.60$</td>
</tr>
<tr>
<td>QT Dispersion</td>
<td>$66.67 \pm 6.15$</td>
<td>$26.00 \pm 2.67$</td>
<td>$0.001$</td>
</tr>
</tbody>
</table>

QT Dispersion and Metabolic Rate (DH-ACUTE)

P=0.004

### Heart Rate Variability (DH-ACUTE)

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=16)</th>
<th>Controls (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pNN50 (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td>13 ± 16%</td>
<td>22 ± 12%</td>
</tr>
<tr>
<td>24 h</td>
<td>12 ± 3%*</td>
<td>31 ± 15%</td>
</tr>
<tr>
<td>Daytime</td>
<td>11 ± 6%*</td>
<td>26 ± 14%</td>
</tr>
<tr>
<td>Nighttime</td>
<td>13 ± 11%</td>
<td>46 ± 25%</td>
</tr>
<tr>
<td><strong>SDNN (ms)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>134 ± 24*</td>
<td>201 ± 53</td>
</tr>
<tr>
<td>Daytime</td>
<td>102 ± 26*</td>
<td>148 ± 37</td>
</tr>
<tr>
<td>Nighttime</td>
<td>80 ± 10*</td>
<td>149 ± 66</td>
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*significantly different than controls
QT Dispersion and HRV in Anorexia Nervosa (Summary)

- Measures of HRV were decreased in patients with AN compared to controls
- $QT_D$ was greater in AN compared to controls
- $QT_D$ correlates with metabolic rate
- May be markers of increased cardiac risk
NHLBI Study (2013 – proposed)

- Longitudinal evaluation with high-frequency digital electrocardiography and assessment of LV mass
- Longitudinal evaluation of cardiac hypotrophy and role of autophagy
- Correlate with different inflammatory markers
- Assess during stages of progressive weight restoration
Refeeding Syndrome

• Classic study by Keys in 1940’s (“Minnesota Experiment”)
• Seen with unintentional refeeding experiments involving victims of WWII. Once released they were given candy by soldiers and precipitously died. Those given chocolate milk survived??
• These severe complications of refeeding rediscovered with introduction of TPN
• Anorexia nervosa serves as a sobering model for the possible calamity inherent in refeeding severely malnourished patients and manifests with peripheral and pulmonary edema, CHF, hypophosphatemia and death
Refeeding Hypophosphatemia

**Phosphorous – The Key**

**Refeeding Syndrome**

- Tissue Hypoxia
- Myocardial Myopathy

- Increased Demand for Phosphorous to provide phosphorylated intermediates of Glycolysis and high energy compounds like ATP

- 2,3-DPG
- ATP
- Glycolysis

- Hypophosphatemia

- Intraacellular Influx of Phosphorous

- Insulin Secretion

- Normal Serum Phosphorous

- Renal Excretion of Phosphorous & Muscle Catabolism

- Carbohydrates

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Consequences of Hypophosphatemia

- RBC dysfunction (hemolysis)
- Rhabdomyolysis (↑ CPK)
- CNS dysfunction (Seizures)
- Myocardial failure
- Respiratory paralysis (diaphragm doesn’t move)
Timing of Hypophosphatemia

- DKA ~ 12 hours
- ETOH Re-Feeding ~ 24-48 hours
- Hyperalimentation ~ 24-48+ hours
- Anorexia Nervosa ~ 24-72+ hours

(Generally at risk for it for first few weeks of consistent refeeding)
Recommendations to Avoid the Refeeding Syndrome

1. Recognize the “patient at risk”
2. Carefully test for and correct electrolyte abnormalities **before** initiating nutrition support (PO, PEG or TPN)
3. Judiciously restore circulatory volume
4. Increase caloric delivery slowly
5. Carefully monitor electrolytes especially over the first 1-2 weeks, including: Phosphorous and Potassium
6. “A little nutrition support is good, too much may be lethal”
Refeeding Syndrome

National Institute for Clinical Excellence (NICE) Guidelines for Management of Refeeding Syndrome:

**Patients at risk for refeeding syndrome**

<table>
<thead>
<tr>
<th>One or more of the following: -OR-</th>
<th>Two or more of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>· BMI &lt; 16 kg/m²</td>
<td>· BMI &lt; 18.5 kg/m²</td>
</tr>
<tr>
<td>· Unintentional weight loss of &gt;15% in the previous 3-6 months</td>
<td>· Unintentional weight loss of &gt;10% in the previous 3-6 months</td>
</tr>
<tr>
<td>· Little or no nutritional intake for &gt;10 days</td>
<td>· Little or no nutritional intake for &gt; 5 days</td>
</tr>
<tr>
<td>· Low levels of potassium, phosphorus, or magnesium before refeeding</td>
<td>· History of alcohol abuse or drugs including insulin, chemotherapy, antacids, or diuretics</td>
</tr>
</tbody>
</table>

*National Institute for Health and Clinical Excellence. Guideline for the Management of Refeeding Syndrome (Adults), 2009*
ACUTE Patients Hospital Course

- 70% developed hypophosphatemia within 72 hours of admission
- Fall in phosphorous not correlated with admission BMI, bump in LFT’s or glucose
- Fall in phosphorous correlated with Kcal consumed (p=0.008)
- Mean days and amount of phosphorous required: 13 days and 16,500 mg
- Nadir pulse occurred by day 7 in 70% of patients
- Hypothermic for 50% of hospital days (<35° C)
Refeeding Syndrome

- **Refeeding edema (swelling)**
  - Does not refer to swelling in patients who get intravenous fluid or who stop purging
  - This is swelling in patients with AN-R, is seen within the first few days of refeeding and lasts for a few weeks
  - With a low sodium diet, leg elevation, and slow progression of calories, it will go away on its own
Refeeding Syndrome

• But can you really predict who will get it?
  – January 2012 in *IJED*
  – 45% of our patients developed refeeding hypophosphatemia...but no clinical features predicted which patient was most at risk
  – Assume anyone who meets the NICE criteria is at risk
  – Typically after 6 days without low phos, patients are safe if no halt in kcals
Refeeding Syndrome

- Prevention is always best!
- In patients at risk for refeeding syndrome:
  - Start calories around the resting metabolic rate
  - Advance slowly, watching phosphorous levels
  - Replace phosphorous when it falls and check frequently
**Phosphorous Repletion**

**Intravenous**
- Severe hypophosphatemia (<1.8 mg/dl) = 0.16 mmol/kg
- Moderate hypophosphatemia (1.9-2.6 mg/dl) = 0.8 mmol/kg

**Oral**
- K-phos tablets 500mg – 1000mg BID-TID
  (Watch for diarrhea)
Pathophysiology of Refeeding Edema in Anorexia Nervosa

• Not due to albumin – oncotic pressure
• Hyperinsulinemia $\rightarrow \uparrow$ distal tubular sodium reabsorption-retention
• Or, refeeding syndrome
Idiopathic Cyclical Edema

- Many reports demonstrating that diuretic abuse may actually be the primary factor in initiating some cases
- Reflex edema following their usage due to stimulation of Renin-Angiotensin-Aldosterone system
- Treatment is to taper diuretics, restore volume, restrict salt and be patient
Nutrition

• Metabolic rate or total energy expenditure (TEE) has four components:

1. Sleeping energy expenditure (SEE)
2. Resting energy expenditure (REE)
3. Dietary-induced thermogenesis
4. Activity-induced thermogenesis
• Absolute REE is low in underweight A.N. patients
• REE increases substantially (20% increase in REE/5kg) with refeeding
• Accurate prediction of the calorie level to promote weight restoration is needed especially in later steps of weight gain (>4,000 Kcal/d)
• Leptin does not contribute either to the reduced REE in prefed A.N. patients or to the increase in REE during refeeding
• Majority of predictive formulas overestimate REE in the early refeeding stages of anorexia nervosa
Plateau Effect

• During the course of refeeding the number of Kcal needed to gain weight increases and REE increases (>4000 Kcal/day)

• Clinical observations consistently suggest that anorectics gain weight with great difficulty

• Calculations for caloric needs necessary to assure weight gain and are continuously upwardly adjusted

• Mechanism unknown: ↑ anxiety, ↑ T₃
Indirect Calorimetry vs. Harris-Benedict

Measured REE

Harris-Benedict Predicted REE
Weight Restoration

- Goal is to achieve 90% - 100% of IBW
- Rate of weight gain: 1-1.5 lbs/week (outpt) and 2-3 lbs/week (inpt)
- Increase Kcal by 300-400 every 3-4 days
- No further increases once adequate rate of weight gain being achieved
Cortisol in Anorexia Nervosa Patients vs Healthy Controls

Whiskers [5-95th percentile]

* = P=0.003 vs healthy ctrl patients

Leptin Levels in Anorexia

* p < 0.05 versus AN
Hypoglycemia

- 58% prevalence
- Severe hypoglycemia: 12%
- Resolution of hypoglycemia: Day 8
- Highly elevated LFTs do predict hypoglycemia (OR: 9.78, p=0.02)
- 20% with hypoglycemia but normal LFT
Severe Anorexia Nervosa (RX)

- Leg elevation
- Strict activity restrictions
- Daily electrolyte and phosphorous checks
- Regular LFT and CBC
- INR checks – vitamin K
- DVT risk - ??

Severe Anorexia Nervosa (*Nutrition*)

- Alternative modes of weight restoration
  - PEG
  - PEJ
  - TPN

- Each of these needs thoughtful deliberation before initiation and occasional use of the legal system
Enteral vs TPN

- Little attention accorded to innovation in nutritional rehabilitation for the treatment of anorexia (no RCT’s)
- Staged oral refeeding remains the standard, but may need additional help
- PEG – NG feedings, or via PEJ
- Supplemental nocturnal tube refeeding successfully used
- Has been challenged clinically and ethically
TPN

- Strict case selection
- Tunneled central catheter
- D-20, amino acids 15%, Intralipids 20%
- Start at 600-800 Kcal/d, and ↑ by 300 Kcal q 3-4 days
- Goal is 60% Kcal from carbohydrate and 40% from fat
- Goal weight is: 90-95% of IBW
- Usual course is 12-18 weeks
Severe/Extreme Anorexia Nervosa RX: Dietary

- Early weight gain may be delayed
- Smaller Kcal increases
- Low salt diet
- Close attention to tele monitor
- 1:1 sitter for safety
- Daily PT (strengthening)
- Abdominal x-rays
Hepatitis (Elevated Liver Function Tests)

- Hepatitis of starvation....or of refeeding?
  - Patient with severe malnutrition may develop hepatitis (transaminitis-↑AST/ALT) which is related either to apoptosis (cell death) or to autophagy (cell self-consumption)
  - This recovers with refeeding
  - However, anorectic patients may also develop steatohepatitis (fatty liver) of refeeding early on in weight restoration treatment very different: “Turn it on or turn it down!” This requires slowing of the refeeding rate.
  - How to tell which is which?
Liver Function and Glucose

• Check serial ultrasounds if LFTs continue to rise
  – If starvation mediated:
    • LFTs may continue to rise days into refeeding
    • Ultrasounds will show normal size, not enlarging liver
    • Push forward with refeeding
  – If refeeding mediated:
    • Ultrasounds will show enlarging, steatotic (“fatty”) liver
    • Reduce rate of refeeding for a few days
Cachexia

- Condition associated with a variety of serious diseases including cancer, AIDS, and CHF
- Complex disruption of several systems leading to anemia, low albumin, and activation of acute phase reactants, and inflammatory cytokines (TNF, IL-6)
- Traditional markers of nutritional status (alb, RBP & transferrin) are normal in anorexia nervosa

Anorexia Nervosa

• Anorectic patients paradoxically die with near-normal albumin levels which does not change much during weight restoration

• Other potential markers: transferrin, prealbumin, $C_3C_4$ and RBP
Case: HD: Albumin

Albumin: The harbinger of illness. Starts to fall on HD # 22

Transferred to PICU

Transferred back to floor
Prealbumin – Albumin Paradox

• Prealbumin is low, but albumin is normal
• Different catabolism – excretion
• TNF (“Cachexia”) lowers albumin
• Prealbumin indicative of hepatic reserve rather than nutritional state
Refeeding Syndrome

- Anorexia nervosa serves as a sobering model for the possible calamity inherent in refeeding severely malnourished patients and manifests with peripheral and pulmonary edema, CHF, hypophosphatemia and death