Anorexia Nervosa
From Transition to Adulthood
A challenging, multidisciplinary approach

Transition Day
Taunton, 21 November 2012

Dr C. Papastathis
Clinical Research Fellow in Endocrinology and Metabolism
Bristol Royal Infirmary
A case of end-stage Anorexia Nervosa

- 25 yr old F with severe malnutrition, electrolyte disturbances and compromised kidney function
- Meeting DSM-IV criteria for AN
- Restrictive and (in the past?), purging type
- Caloric intake ~400-600 kcal/d, excessive walking
- Lost 9kg in last month,
- Social background: former tennis player, the only child of a well-off family, presenting the first symptoms of eating disorders at adolescence

Table 1. DSM-IV diagnostic criteria for anorexia nervosa*

- Refusal to maintain body weight at or above a minimally normal weight for age and height (i.e. weight loss, or failure to make expected weight gain during period of growth leading to body weight less than 85% expected)
- Intense fear of gaining weight or becoming fat, even though underweight
- Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self evaluation, or denial of the seriousness of the current low body weight
- Amenorrhoea in postmenarcheal females (i.e. the absence of at least three consecutive menstrual cycles)

* Specified to be binge eating/purging or restricting type depending on whether there has been regular binge eating and/or purging behaviour (self induced vomiting or the misuse of laxatives, diuretics or enemas) or there has not, respectively
Physical examination

- Severe emaciation
- Weighing 27.3kg for 166cm, BMI of 9.9kg/m²
- Vital signs on admission: Alert, T:36.1°C, BP:85/57mmHg, HR:72/min, RR:15/min, SO2:98% in air
- Poor dental hygiene
- Cold extremities, acrocyanosis, cold intolerant
- Slightly tender abdomen
- Normal cardiac and lung auscultation, no oedemas, no skin or mucosa pigmentation, no masses
Psychiatric profile

- Elaborative appearance
- Denied any body dysmorphia
- Described previous purging behaviour as intention to self-harm
- Closer relationship with her mother
- Maturity fear
- Over-realistic expectations
- No evidence of psychosis, anxiety disorder or depression
# Lab findings on admission

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>7.25</td>
</tr>
<tr>
<td>Creatinine</td>
<td>149 umol/L</td>
</tr>
<tr>
<td>eGFR</td>
<td>37 mL/min/1.73 (2)</td>
</tr>
<tr>
<td>Potassium</td>
<td>5.4 mmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>114 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>83 mmol/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>16 mmol/L</td>
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<tr>
<td>Phosphate</td>
<td>1.66 mmol/L</td>
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<tr>
<td>Magnesium</td>
<td>0.79 mmol/L</td>
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<tr>
<td>Glucose</td>
<td>7.1 mmol/L</td>
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<tr>
<td>Hb</td>
<td>15 g/dL</td>
</tr>
<tr>
<td>WBC/Lymphocytes</td>
<td>18.73/0.52</td>
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<tr>
<td>Albumin</td>
<td>44 g/L</td>
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<tr>
<td>ALP/ALT</td>
<td>129 IU/L</td>
</tr>
<tr>
<td>ECG</td>
<td>SR, pointed T waves, normal QT space</td>
</tr>
</tbody>
</table>
During Hospitalisation

A Multidisciplinary approach

- Medical approach according to Royal College of Physicians recommendations
- Dietician plan and aiming to gain 0.5-1 kg/week
- Daily psychiatric evaluation, an empathic approach towards the patient, close collaboration with the family

Recommendations of Royal College of Physicians, London July 2005
Challenges

- Medical team: - re-feeding syndrome  
  - complications related to AN
- Dietician: - failure to achieve weight gain  
  - re-feeding oedemas
- Psychiatric team: - legal and ethical issues  
  - ambivalence and manipulation  
  - difficult interfamily dynamics
Re-feeding syndrome

- Electrolyte disturbances (hypokalaemia, hypophosphataemia, hypomagnesaemia)
- Acute thiamine deficiency
- Re-feeding oedemas
- Anaemia & iron deficiency
- Delayed gastric emptying & abdominal pain
- Abnormal liver function
Nutritional Rehabilitation

- Goal: 0.5-1kg/week
- Measurements according to indirect calorimetry or Harris Benedict's formula
- Prophylactic Tx for electrolyte disturbances or correction during feeding—no consensus
- Increase calorie intake gradually, supplements can be used
- Fluid balance monitoring and food chart—poor myocardial contractility and renal impairment! Water 25-30mL/Kg/day
- If patients fail to meet targets, even if oral intake is present, NG feeding is justifiable. Enteral feeding 25-30kcal/kg BW/day. High content of calories (1.7-2Kcal/mL)

2. Gentile M. Enteral nutrition for Feeding Severly Underefed Patints with Anorexia Nervosa. Nutrients 2012;4
Kidney impairment

<table>
<thead>
<tr>
<th>Clinical Manifestation/Mechanism</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Kidney Injury</strong></td>
<td>Uncertain</td>
</tr>
<tr>
<td>Reduced kidney perfusion</td>
<td></td>
</tr>
<tr>
<td>• Hypovolemia</td>
<td></td>
</tr>
<tr>
<td>• Low salt intake</td>
<td></td>
</tr>
<tr>
<td>• Purging</td>
<td></td>
</tr>
<tr>
<td>• Low cardiac outflow</td>
<td></td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>Uncertain</td>
</tr>
<tr>
<td>• Reduced kidney perfusion</td>
<td></td>
</tr>
<tr>
<td>• Rhabdomyolysis</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic Kidney Disease</strong></td>
<td>15%-20%</td>
</tr>
<tr>
<td>Chronic tubulointerstitial nephritis (hypokalemia nephropathy)</td>
<td></td>
</tr>
<tr>
<td>• Chronic hypokalemia</td>
<td></td>
</tr>
<tr>
<td>• Chronic reduced kidney perfusion</td>
<td></td>
</tr>
<tr>
<td>• Repeated urinary tract infection</td>
<td></td>
</tr>
<tr>
<td>• Laxative abuse</td>
<td></td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>Uncertain</td>
</tr>
<tr>
<td>• Diuretic abuse</td>
<td></td>
</tr>
<tr>
<td>• Binge eating with a high calcium and phosphate diet</td>
<td></td>
</tr>
<tr>
<td><strong>Nephrolithiasis</strong></td>
<td>5%</td>
</tr>
<tr>
<td>Ammonium urate stones</td>
<td></td>
</tr>
<tr>
<td>• Low urine output</td>
<td></td>
</tr>
<tr>
<td>• Paradoxical aciduria</td>
<td></td>
</tr>
<tr>
<td>• Repeated urinary tract infection</td>
<td></td>
</tr>
<tr>
<td>Oxalate stones</td>
<td></td>
</tr>
<tr>
<td>• Chronic diarrhea</td>
<td></td>
</tr>
</tbody>
</table>


- Acute and chronic kidney failure due to hypok and volume depletion, prevalence 15-20% in AN
- >70% will have electrolyte abnormalities
- Higher prevalence in purging subtype
- Can progress to end-stage CKD (5.2% prevalence in a study)
- 2 major limitations: overestimation of GFR, albuminuria inappropriate due to tubular damage
Weight chart

NG feeding
Psychiatric challenges

- Consent was easy to obtain, no need to use coercion and restraint
- Collusion and manipulation—’splitting ‘ method tried by the patient, great influence on her mother & overeating
- Parental involvement and collaboration —MDT meetings twice/week with the family
- Difficult interfamily dynamics —conflict avoidance & non-expressed inculpation of father
- Dropout from Tx as inpatient (20.4-51%)
On Discharge

- Weight: 44kg, oedemas ~5kg
- BMI: 16
- Patient was eating adequately
- Multi-vitamins prescription
- Agreed on having: -regular blood tests at GP
  -appointment with STEPs nurse
After Discharge

- Diagnosed with Left Ventricular insufficiency in June 2012. Ejection Fraction 35%
- Prescription of diuretics and ACE inhibitors—new admission with severe hyperkalaemia
- Improvement of cardiac function in F/U appointment. Ejection Fraction now 40-45%
- Maintained body weight at 44kg, BMI 16, without oedemas
- Visits GP for regular electrolyte control
- Attending College
- Attendance to STEPs with nurse is uncertain
Anorexia Nervosa
A critical public health concern

- Incidence 8 new cases per 100,000 persons per year, lifetime prevalence of AN is 0.4-3.7%, increasing tendency (1)
- Commonest chronic illness in adolescence behind obesity and asthma (1)
- Interruption of normative adolescent developmental process (2)
- Co-occurrence with other psychiatric conditions and treatment is costly relative to other psychiatric disorders alone (3-4)
- Mortality 5% per decade of illness (5)
- Dropout from Tx range from 20.4% to 51% (inpatient) and from 29% to 73% (outpatient) (6-7)
- Only a few consistent predictors of treatment response exist to guide interventions (8)

2. Mullet EE et al. Under nutrition and pituitary function: relevance to the pathophysiology of some neuroendocrine alterations in AN. J Endocrinol 1992;132
5. Sullivan PF, Mortality in Anorexia Nervosa Amer J Psych. 1995 ;152
The transition process challenges (1)

- Links between CAMHS and adult medical wards are less well established.
- “Paediatric” issues (impaired growth & development) are still prominent and need paediatric expertise.
- In-patient CAMHS serve large geographical areas, served by different trusts—difficulties in developing local protocols.
- CAMHS emphasise the responsibilities of the parents, whereas, adult services focus on individual responsibility—AN in turn can become more refractory.

Junior MARSIPAN: Management of Really Sick Patients under 18 with Anorexia Nervosa.
Process, outcome and experience of transition from child to adult mental healthcare: multiperspective study

Swaran P. Singh, Moli Paul, Tamsin Ford, Tami Kramer, Tim Weaver, Susan McLaren, Kimberly Hovish, Zoobia Islam, Ruth Belling and Sarah White

Background
Many adolescents with mental health problems experience transition of care from child and adolescent mental health services (CAMHS) to adult mental health services (AMHS).

Aims
As part of the TRACK study we evaluated the process, outcomes and user and carer experience of transition from CAMHS to AMHS.

Method
We identified a cohort of service users crossing the CAMHS/AMHS boundary over 1 year across six mental health trusts in England. We tracked their journey to determine predictors of optimal transition and conducted qualitative interviews with a subsample of users, their carers and clinicians on how transition was experienced.

Results
Of 154 individuals who crossed the transition boundary in 1 year, 90 were actual referrals (i.e. they made a transition to AMHS), and 64 were potential referrals (i.e. were either not referred to AMHS or not accepted by AMHS). Individuals with a history of severe mental illness, being on medication or having been admitted were more likely to make a transition than those with neurodevelopmental disorders, emotional/neurotic disorders and emerging personality disorder. Optimal transition, defined as adequate transition planning, good information transfer across teams, joint working between teams and continuity of care following transition, was experienced by less than 5% of those who made a transition. Following transition, most service users stayed engaged with AMHS and reported improvement in their mental health.

Conclusions
For the vast majority of service users, transition from CAMHS to AMHS is poorly planned, poorly executed and poorly experienced. The transition process accentuates pre-existing barriers between CAMHS and AMHS.

Declaration of interest
None.
The transition process challenges (3)

- Research in AN and transition period is limited
- How can we better navigate the transition from paediatric to adult eating disorder programs?
- Focus on both family and patient or greater impact on patient involvement?
- How can we better work on identifying more reliable predictors of Tx response in the outpatient and inpatient setting?
- How can we improve primary care involvement?
Acknowledgements

Dr Taylor, Psychiatrist SpR, Bristol Royal Infirmary
Dr Phillippa Bailey, Nephrologist SpR, Southmead
Dr Hugh Herzig, Consultant of STEPs, Southmead
Dr Fligelstone, General Practitioner
Not sure where 16- to 19-year-olds should go

I only feel beautiful when I am hungry

Patient confidentiality at age 16 is a huge problem, and means that parents/carers are not included in care plan

My family keeps telling me to eat, but I am doing fine. The days I don't eat anything at all, are the days when I feel that I accomplished something

Unclear who to refer, when to refer and who to refer to

Skinnies look good in everything

What happens when a child reaches age 16, there does not seem to be a seamless handover
Thank you
Calcium and its relationship to bone protection, vascular and soft-tissue calcification

Is it right or harmful to give it?

Dr Chrysoula Papastathis
Clinical Research Fellow
Nov 2012
Case

A 55 yr old, postmenopausal female, asks for calcium supplementation to reduce her risk of fractures.

- FH of mother that had a hip fracture at 62
- BMI is 28
- Never smoked, does not drink, no Pmx of RA, no steroid Tx or secondary osteoporosis
- Laboratory findings: DXA scan-T score at lumbar spine is -1.8 and total hip-1.8
According to NICE guidelines, FRAX (Fracture Risk Assessment Tool) should be used to calculate the 10 year probability of fracture with BMD.

Our patient had a 11% probability of major osteoporotic fracture and an 0.8% probability of hip fracture.
What current medical concerns might influence your decision regarding calcium supplementation in this patient?

- Cardiovascular risk
- Fracture prevention
Objectives

- Who needs calcium, how much, and why?
- What are the benefits and risks of calcium supplements?
  ---Role in fracture prevention
  ---A specific focus on vascular events and calcification
Assessing Calcium Balance

- There are currently no biochemical measurements that reflect nutritional status.
- An indirect measure is skeletal health (bone mass and fracture rates).
Calcium Nomenclature

- Elemental: what is available for absorption
- All calcium from food is elemental
- Some calcium from supplements is elemental
- In NONCKD individuals calcium varies by dose—at doses of >600mg minimal gut absorption
Calcium Intake per day-Institute of Medicine Guidelines in non-CKD

<table>
<thead>
<tr>
<th>AGE (YEARS)</th>
<th>Average Requirement (mg)</th>
<th>RDA (mg)</th>
<th>Upper Level (mg)</th>
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<tr>
<td>19-50</td>
<td>800</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>MEN: 51-70</td>
<td>800</td>
<td>1000</td>
<td>2000</td>
</tr>
<tr>
<td>WOMEN: 51-70</td>
<td>1000</td>
<td>1200</td>
<td>2000</td>
</tr>
<tr>
<td>EITHER SEX&gt;71</td>
<td>1000</td>
<td>1200</td>
<td>2000</td>
</tr>
</tbody>
</table>

Why do we give Calcium?

- Calcium is an essential nutrient
- It is important for the mineralisation of bone
- It theoretically increases bone density and decreases fractures
- Role of calcium in reducing postmenopausal bone loss is highly controversial
Mechanism by which Calcium Increases Bone Mineral Density

Calcium increases bone mineral density because it is a weak antiresorptive and slightly modifies bone formation.
Alkaline Phosphatase: Change From Baseline to Year 5

![Bar graph showing change in ALK-P(U/L) for Placebo and Calcium groups with a p-value of <0.0001.]

ALK-P = alkaline phosphatase.

Calcium is good for your bones....

Right?
Calcium Intake and Bone Mineral Density


FIG. 1. Total hip BMD by calcium intake (corrected for measurement error) in individuals with a 25(OH)D status <50, 50-74, or 75+ nM. (A) Values for the measurement error corrected calcium intake in quartiles among women: lowest <566 mg/d; second = 567-671 mg/d; third = 672-825 mg/d; top = 826-2143 mg/d. p value for trend across categories of 25(OH)D concentrations was <0.0001 while controlling for calcium intake, age (10-yr age categories), race/ethnicity (white, black, Mexican American), body mass index, height, total calorie intake, estrogen use among women, physical activity, smoking, and socio-economic status. (B) Values for the measurement error-corrected calcium intake quartiles among men: lowest <626 mg/d; second = 627-761 mg/d; third = 762-962 mg/d; top = 963-2152 mg/d. p value for trend across categories of 25(OH)D concentrations was 0.0001 while controlling for calcium intake, age (10-yr age categories), race/ethnicity (white, black, Mexican American), body mass index, height, total calorie intake, physical activity, smoking, and socio-economic status.
Relative Risk of Hip Fracture by Calcium Intake
Bischoff-Ferrari HA. Am J Clin Nutr 2007;96:17980-1790

FIGURE 3. Pooled analysis for categories of calcium intake and hip fracture risk in the women from the prospective cohort studies. The reference intake categories in the various studies ranged from 280 to 554 mg total Ca/d.
Effect of Calcium + Vitamin D on Preventing Fractures

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reid et al.</td>
<td>0.40 (0.39-1.98)</td>
<td></td>
</tr>
<tr>
<td>Cheethamy et al.</td>
<td>0.86 (0.81-2.48)</td>
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<tr>
<td>Rucker et al.</td>
<td>0.87 (0.76-1.00)</td>
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<tr>
<td>Riggs et al.</td>
<td>0.59 (0.51-1.17)</td>
<td></td>
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<tr>
<td>Peacock et al.</td>
<td>0.81 (0.75-1.43)</td>
<td></td>
</tr>
<tr>
<td>Fujita et al.</td>
<td>0.51 (0.30-1.09)</td>
<td></td>
</tr>
<tr>
<td>Record et al.</td>
<td>0.64 (0.67-1.16)</td>
<td></td>
</tr>
<tr>
<td>Reid et al.</td>
<td>0.62 (0.59-1.24)</td>
<td></td>
</tr>
<tr>
<td>Prince et al.</td>
<td>0.57 (0.53-1.28)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.39 (0.33-1.00)</td>
<td></td>
</tr>
<tr>
<td>Chapuy et al.</td>
<td>0.75 (0.61-0.91)</td>
<td></td>
</tr>
<tr>
<td>Dawson-Hughes et al.</td>
<td>0.49 (0.29-0.90)</td>
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</tr>
<tr>
<td>Chapuy et al.</td>
<td>0.85 (0.54-1.12)</td>
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</tr>
<tr>
<td>Larsen et al.</td>
<td>0.84 (0.72-1.00)</td>
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<tr>
<td>Harwood et al.</td>
<td>0.48 (0.29-0.78)</td>
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<tr>
<td>Record et al.</td>
<td>0.84 (0.77-1.16)</td>
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<tr>
<td>Pothous et al.</td>
<td>0.96 (0.79-1.33)</td>
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<td>Jackson et al.</td>
<td>0.87 (0.72-1.03)</td>
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<tr>
<td>Overall</td>
<td>0.57 (0.77-0.97)</td>
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</tbody>
</table>

Calcium only
Calcium and Vitamin D

Calcium may not be very helpful, but causes no harm.....

Right?
Calcium supplementation and Bone Mineral Density

CONCLUSIONS

Among healthy postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones. (ClinicalTrials.gov number, NCT00000611.)
Women's Health Initiative Study

- Supplementation of up to 1000mg calcium, 600 IU Vit D
- Use of BP, calcitonin, SERMs

36,282 pm women
50 to 79 years

1000mg calcium
400D3
Some women on E/P
7-yr f/u

No intervention
Some women on E/P
7-yr f/u

Calcium Intake and Cardiovascular events
Bolland MJ et al. BMJ 2008;336:262-269

Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial

**Conclusion** Calcium supplementation in healthy postmenopausal women is associated with upward trends in cardiovascular event rates. This potentially detrimental effect should be balanced against the likely benefits of calcium on bone.
BMJ study

1471 pm women
55 and older
No clinical evidence of CKD

1000mg calcium titrate
(in addition to dietary intake)
5-yr f/u

Placebo
(in addition to dietary intake)
5-yr f/u
Effect of Calcium on MI
Bolland MJ et al. BMJ 2008;336:262-269

Kaplan-Meier survival plot showing proportion of healthy postmenopausal women assigned to calcium supplementation or placebo that had a verified myocardial infarction during the study. Included are events self reported by participants and those from the national database of hospital admissions and review of death certificates (P=0.14 when compared by log rank test)
Bolland MJ et al. BMJ. 2010;341:

Effects of Calcium Supplements on Risk of Myocardial Infarction and Cardiovascular Events: Meta-Analysis

- 15 trials, 3.6 yrs follow-up
- Primary end points: MI, stroke, sudden death
- Secondary end points: all cause mortality
Meta-Analysis: Relative Risk of Myocardial Infarction

(95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron 1999</td>
<td>13</td>
</tr>
<tr>
<td>Grant 2005</td>
<td>29</td>
</tr>
<tr>
<td>Grant 2005 Vit D</td>
<td>26</td>
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<tr>
<td>Prince 2006</td>
<td>13</td>
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<tr>
<td>Reid 2006</td>
<td>17</td>
</tr>
<tr>
<td>Lappe 2007</td>
<td>1</td>
</tr>
<tr>
<td>Reid 2008</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>13</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2 = 0\%$, $P = 0.98$

$1.27 (1.01-1.59)$ $P = 0.038$

Favors Calcium  Favors Placebo

Meta-Analysis: Balancing Heart and Bone effects of Calcium Supplements: Numbers needed to treat for 5 years

- Treatment of 1000 people with calcium for 5 years:
  --Causes: 14 MIs, 10 strokes, 13 deaths
  --Prevents: 26 fractures
Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events.
### Vitamin D Supplementation and CV Risk

<table>
<thead>
<tr>
<th>Study, Year (reference)</th>
<th>Vitamin D</th>
<th>Placebo</th>
<th>Relative Risk (95% CI)</th>
<th>Relative Risk (95% CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events n,</td>
<td>Total n</td>
<td>Events n,</td>
<td>Total n</td>
</tr>
<tr>
<td>Trivedi et al. 2003 (32)</td>
<td>477</td>
<td>1345</td>
<td>503</td>
<td>1341</td>
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<tr>
<td>Prince et al. 2008 (35)</td>
<td>5</td>
<td>151</td>
<td>6</td>
<td>151</td>
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<tr>
<td>Pooled</td>
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# Calcium Supplementation and CV Risk

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Calcium</th>
<th>Placebo</th>
<th>Relative Risk</th>
<th>Relative Risk</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Baron et al. 1999 (36)</td>
<td>62</td>
<td>464</td>
<td>57</td>
<td>466</td>
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<tr>
<td>Prince et al. 2008 (35)</td>
<td>56</td>
<td>730</td>
<td>51</td>
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<tr>
<td>Bolland et al. 2008 (33)</td>
<td>60</td>
<td>732</td>
<td>50</td>
<td>739</td>
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<tr>
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# Vitamin D and Calcium Supplementation and CV Risk

<table>
<thead>
<tr>
<th>Study, Year (reference)</th>
<th>Vitamin D + Calcium</th>
<th>Placebo</th>
<th>Relative Risk (95% CI)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events n, Total n</td>
<td>Events n, Total n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazier et al. 2005 (39)</td>
<td>6, 95</td>
<td>5, 98</td>
<td>1.21 (0.37-3.97)</td>
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</tr>
<tr>
<td>Hsia et al. 2007 (34)</td>
<td>499, 18176</td>
<td>475, 18106</td>
<td>1.04 (0.92-1.18)</td>
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<td>Bolland et al. 2008 (33)</td>
<td>60, 732</td>
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<td>1.21 (0.84-1.74)</td>
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<td>1.04 (0.92-1.18)</td>
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</tbody>
</table>

Risk of Cardiovascular Events with Calcium/Vitamin D: A Re-Analysis of Data from the Women's Health Initiative

MJ Bolland, A Grey, GD Gamble, IR Reid
University of Auckland

Bolland MJ et al. BMJ. 2011;342:d2040
Meta-Analysis of CaD Effect on Cardiovascular Events

- 3 trials
- n = 20,090
- 465 incident MI
- 477 incident strokes
- 911 MI/strokes
- Mean duration: 6.2 years (weighted by study size)

Relative Risk:

- **Myocardial infarction**
  - Grant 2005
  - Lappe 2007
  - WHI 2007
  - Test for heterogeneity: P = 0%, P = 0.94
  - Relative Risk: 1.21 [1.01-1.44]
  - Weight (%): 81

- **Stroke**
  - Grant 2005
  - Lappe 2007
  - WHI 2007
  - Test for heterogeneity: P = 0%, P = 0.99
  - Relative Risk: 1.20 [1.00-1.43]
  - Weight (%): 75

- **Myocardial infarction or stroke**

  Test for heterogeneity: P = 0%, P = 0.94
  Relative Risk: 1.18 [1.02-1.32]
  Weight (%): 78

WHI: no personal calcium use.
Balancing Heart and Bone Effects of Calcium Supplements+Vitamin D

- Treatment of 1000 people with calcium for 5 years:
  --Causes: 4 MIs, 4 strokes, 2 deaths
  --Prevents: 3 fractures

Bolland MJ et al. BMJ. 2011;342:d2040
Mechanism:
Serum Calcium is associated with Vascular Disease
Carotid Plaque Thickness Is Related to Serum Calcium

Mean Plaque Thickness (mm)

Lowest

Highest

Calcium Quintile

2.05-2.12 mmol/L

2.28-2.60 mmol/L

*P<0.002

Data from 1194 men and women aged 68 ± 9 years.
Relationship between Serum Calcium and CV events in MORE study


<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)/SD</th>
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<tbody>
<tr>
<td>Combined (stroke, MI, death)</td>
<td>1.17 (1.01-1.35)</td>
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<tr>
<td>Stroke</td>
<td>1.22 (0.99-1.49)</td>
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<td>Coronary Heart Disease</td>
<td>1.12 (0.92-1.37)</td>
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<tr>
<td>Death</td>
<td>1.18 (0.94-1.48)</td>
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</tbody>
</table>
How might Calcium Supplementation Cause Heart Disease?

- Within calcium cohorts, high normal serum calcium levels are associated with:
  - Carotid artery plaque thickness
  - Abdominal aortic calcification
  - Incidence of CHD/stroke
  - Mortality

Bolland MJ et al. J Bone Miner Res. 2010;341:c6331
Simin Y et al. Int J Cardiol. 2011; 149:335-340
Guidelines on Calcium Intake

- Calcium intake values have been lowered in response to the recent data.
- The new RDA for calcium is 1000mg/dl for men aged 19-70yrs and women aged 19-50yrs, and 1200mg/dl for women>50yrs and men>70yrs, for general HEALTHY population.
- No more than 1200mg of calcium/day from diet and supplements for HEALTHY population.
1. There are numerous large studies of calcium plus Vit D that have shown NO increased risk of CV events.

2. Persons currently taking calcium supplements should not necessarily discontinue their use. Rather they should discuss the decision to use these agents with their health provider, and understand that the food remains the best source of calcium. Supplements should be used only when adequate dietary intake of calcium cannot be achieved.

3. The beneficial effects of calcium are found with relatively low doses. More is not necessarily better.

4. In almost every modern study of osteoporosis treatment, adequate calcium and Vit D were required for medications to have anti-fracture efficacy.

5. Elderly individuals and others with impaired renal function who take calcium supplements may be at higher risk of cardiovascular problems.
Conclusions

- Calcium is thought to be beneficial to bone by reducing bone resorption.
- Effects of calcium on fracture reduction remain uncertain—certainly there is no evidence that more calcium is better.
- Calcium supplements increase risk of vascular events.
- Aim for total calcium intake of ~1g/d.
- Food sources are preferred.
- Use interventions with proven anti-fracture efficacy if fracture prevention is the goal.
Thank you
Vitamin D and pregnancy

Dr Chrysoula Papastathi

B.R.I.
Vitamin D and pregnancy

- Physiology
- Epidemiology
- Pregnancy
- Neonate
- Bone mass

- Insulin action and secretion
- Lung and immune development
- Treatment and supplementation
Low serum [Ca++]

CaSR

Increased calcium reabsorption

Increased [Ca++] absorption

Bone resorption

PTH

1,25(OH)₂D

25(OH)D

Increased calcium reabsorption

Into serum

Increased [Ca++]
Dietary reference for vitamin D

- Increased maternal vitamin D binding protein
- Cod-liver oil safe and effective
- n=7 osteomalacic women who improved on Rx
Vitamin D requirement during pregnancy and lactation

- Current recommendation 200 IU/day
- Poor evidence
- May be as high as 6000 IU/day

Hollis 2007 JBMR 22(S2):V39-44
Epidemiology

• Vitamin D insufficiency common
• Especially in those with reduced skin exposure in northern latitudes
High prevalence of vitamin D deficiency in non-western women in the Netherlands

- 25(OH)D 358 Hague women 12/40
- Turkish 15.2±12nmol/l
- Moroccan 20±14nmol/l
- Western 53±22nmol/l
- Relation to deprivation
- Recommend screening

Van de Meer Am J Clin Nutr 2006 84:350-3
Prevalence of vitamin deficiency by ethnic group at St Mary's London (n=180)
Neonate

• Neonatal hypocalcaemia with tetany
Maternal vitamin D deficiency and neonatal hypocalcaemic convulsions

- Maternal vitamin D insufficiency common, especially in some groups
- Cause of neonatal hypocalcaemia in addition to rickets in infancy and childhood
- Correlation between maternal vitamin D status and neonatal hypocalcaemia and rickets in childhood

Camadoo 2007 Nut J 6:23
Vitamin D, PTH and calcium levels in pregnant women and their neonates

- Australia N=971 25[OH]D<25nmol/L
- 15% women (30/40) and 11% neonates (n=98)
- Maternal vitamin D insufficiency associated neonatal vitamin D insufficiency
- Varied by season
- Dark skin OR 2.7, veil OR 21.7
- Birth weight lower def 3245(545) v suf 3453(555)

Bowyer 2009  Clin Endo 70 372-77
Pregnancy

• Hypertension and preeclampsia
• Caesarean section
Maternal vitamin D deficiency increases risk of preeclampsia

• PET; Implantation and vascular effect of placental, oxidative stress, endothelial dysfunction
• 55 singleton PET cf 219 controls
• $25(\text{OH})\text{D} \ 45 \text{ v } 53 \text{ nmol/L}$
• Higher $25(\text{OH})\text{D}$ associated lower risk PET

Bodnar 2007 JCEM 92:3517
Vitamin D and hypertension in pregnancy

- Canadian study n=78
- Two or more readings > 140/90
- $25(\text{OH})\text{D}<50\text{nmol/L}$ 13 control v 29% BP
- Low maternal circulating vitamin D associated hypertension in pregnancy

Ringrose 2011 Clin Invest Med 34:E147
Plasma vitamin D levels in early onset severe preeclampsia

- EOSPE = 50, v 100 controls
- $25(\text{OH})D$ 18 v 32 ng/mL
- $<20\text{ng/mL}$ 54% PET v 27% control

Robinson 2010 AJOG 203:366
Vitamin D supplementation and reduced risk of pre-eclampsia

- 23,423, estimated nutrient intake
- **15-20ug/d cf 5ug/d OR 0.76 (0.60-0.95)**
- Consistent protective effect vitamin D on PET development
- Long chain n-3 fatty acids

Haugen 2009 Epidemiology 20:720-6
Association between vitamin D deficiency and primary Cesarean section

- N=253, 17% cesarean
- Inverse association CS and 25(OH)D
- 28% CS 25(OH)D<37.5nmol/l
- 14% CS 25(OH)D>37.5nmol/l
- Logistic regression (ethnicity, age, education, insurance, alcohol)
- 25(OH)D<37.5nmol/l have OR 3.84 (1.71-8.62) of primary cesarean

Merewood 2009 JCEM 94:940-5
Bone mass

• Growth *in utero*
• Low bone mineral mass as child and adulthood
Vitamin D and fetal bone

- Mineralisation of fetal skeleton poor indicator of maternal vitamin D status
  Congdon 1983 BMJ 286:1234-5

- Low Vitamin D with incomplete fetal ossification may explain increased incidence of craniotabes in winter months
  Reif 1988 APS 77:167-8
Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study

• 198 Southampton children
• 31% insufficient, 18% deficient
• Low maternal 25(OH)D assn age 9
  – Whole body bone mineral content $r=0.21$
  – Lumbar spine bone mineral content $r=0.17$
• Estimated UVB exposure and supplement
  Javaid 2006 Lancet 367:36
Low maternal vitamin D status and fetal bone development: Cohort study

- 424 pregnant women Southampton
- HR 3D U/S femur length and cross section at 19 weeks

2010 Mahon JBMR 25:14-9

Fig. 2. Maternal vitamin D concentrations for the cohort (n = 424).
Maternal [vitamin D] associated small for gestational age births

• 111 SGA, 301 control
• U shaped association 25OHD and SGA risk, lowest 60-80nmol/L
• $<37.5 \text{ OR } 7.5 \ (1.8-31.9)$
• Not in black women
• Complex relationship VDR

Bodnar 2010 JN 140:999
Vitamin D and insulin secretion and action

• T2DM and metabolic syndrome associated with vitamin D insufficiency
• GDM similar association
Hypovitaminosis D associated impaired glucose tolerance and diabetes

- Insulin secretion and insulin sensitivity
- Most but not all studies
  
  Chiu 2004 Am J Clin Nutr 79:820
  Pittas 2010 Diab Care 33:2021
  Scragg 2004 Diab Care 27:2813
Maternal vitamin D deficiency, ethnicity and gestational diabetes

• 307 women
• Ln 25(OH)D negatively correlated PTH, FPG, HOMA IR
• **OR GDM 1.92 (0.89-4.17) if 25(OH)D<50**

Clifton-Bligh 2008 Diab Med 25:678
Correlation between vitamin D3 deficiency and insulin resistance of pregnancy

- 741 Tehran women, screen OGTT HOMA
- Total 25(OH)D <25nmol/L 70.6%

Maghbooli 2008 DMRR 24:27
Maternal 25(OH)D concentrations and risk for GDM

• 57 GDM, 114 controls
• GDM **24.2 v 30.1 ng/ml** (p<0.001)
• After adjustment for age ethnicity FH BMI
• 33% GDM, 14% controls <20 ng/ml
• Each 5 ng/ml assn 1.29* risk GDM

Zhang 2008 PLoS ONE 3:e3753
Maternal vitamin D status in gestational diabetes mellitus

• 54 GDM, 39 IGT, 111 control
• 83% GDM cf 71% control group vit D, 20ug/mL
• 2.66 risk deficient status

Soheilykhah 2010 nutr Clin Prac  25;524
Vitamin D insufficiency is common in Indian mothers but is not associated with gestational diabetes

- 559 Mysore women, 7%GDM
- 66% 25(OH)D<50nmol/L, 31%<28nmol/L
- Not associated GDM, fetal growth, or [insulin]

Farrant 2008 EJCN 63:646-52
Serum 25-(OH) D concentrations are lower in women with GDM

• A greater proportion of women with GDM have lower 25OHvitD concentrations compared to ethnic matched controls.
• Age, BMI, parity matched controls
• African Caribbean, Arab-Mediterranean, South Asian, Caucasian

Newlands 2011 abstract,
Immune and lung development

• Wheeze
• Infection
Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3yr of age

- 1194 mother child pairs total vit d preg
- 16% recurrent wheeze at 3yr
- **Lowest v highest quartile vit D OR 0.39[0.25-0.62] rec wheeze**
- Diet or supplement
- 12 potential confounders

Camargo 2007 AJCN 85:788-95
Cord blood vit D status impacts innate immune responses

• Antimicrobial peptide gene expression TLR induced cathelicidin expression
• Vit D and neonatal microbial responses need further investigation
• Cord 25(OH)D effect on TLR induced cathelicidin production altered in vitro monocyte responses

Walker 2011 JCEM 96:1835
Maternal and child’s vitamin D supplement use, childhood lung function. KOALA

• 436 Dutch children
• No association Vit D levels, supplementation in childhood and pregnancy
• Lung function in children 6-7

Cremers Thorax 2011 66:474-80
Does vitamin D deficiency supplementation in infancy reduce the risk of pre-eclampsia

- Vitamin D increases Th2 over Th1 helper cytokines
- N= 2969, PET 2.3%
- Risk of PET 0.49 (0.26-0.92) in those vitamin D supplemented in first year of life

Hypponen 2007 EJCN
Vitamin D treatment

• Safety
• Treatment
• Supplementation
• Little evidence on hard outcomes
Hypercalcaemia when calcium given to mother with secondary hyperparathyroidism with pregnancy induced gut sensitivity to vitamin D
Vitamin D supplementation during pregnancy

- 350 women
- 400, 2000, 4000 IU/d vitamin D3
- Mean and % sufficient highest for 4000
- No difference on safety

Hollis 2011 JBMR 26:2341
advise women of the importance of vitamin D intake during pregnancy and breastfeeding (10 mcg, 400IU/d). Ensure women at risk of deficiency are following this advice.”

Routine antenatal care 2006 NICE CG 6
Vitamin D supplementation in pregnancy

- 320 Asian Indian mother
- 1200IU/d v 600,000 twice
- vitamin D Rx associated greater birth weight in one study not second

Myra 1981 GOI 12:155-61
Myra 1988 IJMR 88:488-92
Vitamin D supplementation in pregnancy

- 34 French women randomised to 1000IU/d v placebo 3rd Trimester
- Cord 25(OH)D higher but [Ca]= with Rx
- Day 4 [Ca] higher
- PTH=

Delvin 1986 JP 109:328-34
Vitamin D supplementation in pregnancy, controlled trial of 2 methods

• 68 French women randomised to 1000IU/d v 200,000IU v placebo once 3rd Trimester

• Cord and day 4 25(OH)D higher in Rx groups, day 4 calcium =

Mallet 1986 OG 68:300-4
Vitamin D deficiency in non European pregnant women: an intervention study

• 160 ethnic minority pregnant women screened, if deficient given vitamin D (800IU/d)
• 50% were deficient. 25(OH)D increased by delivery, no change in PTH.
• 25(OH)D still low >>1600IU/d,
• 81% had normal PTH at baseline

Datta 2002 BrJOG 109:905-8
Vitamin D deficiency and supplementation during pregnancy

C. K. H. Yu*, L. Sykes*, M. Sethi†, T. G. Teoh* and S. Robinson†

*Department of Obstetrics and Gynaecology and †Department of Metabolic Medicine, Imperial College School of Medicine, St Mary’s Hospital, London, UK
Endocrine Society Clinical Practice Guideline

• Pregnant and lactating women receive at least 600IU/d of vitamin D

• Recognise at least 1500-2000IU/d may be needed to maintain blood level above 30ng/ml

Holick 2011 JCEM 96:0000
Increasing requests for costly vitamin D measurement

- Widespread testing asymptomatic people
- Will test alter treatment
- Need economic evidence base

Sattar 2012 Lancet 379(9811)95-6
RCOG Guidance

- Don’t screen
- >800IU/day for all
- 4-6000IU/day appear safe
- 20,000 IU/week safe as treatment
- Treatments for non-classical vitamin D actions indications as yet unproven
Hyperlactataemia in DKA

Dr Chrysoula Papastathi
May 2012
Grand Medical Round
The increasing practice of measuring lactates at A&E, requires an evidence-based interpretation.

At present, clinicians may associate high lactate in DKA as an indicator of illness severity, but is this assumption valid?

How much do we know about it?
Case discussion of April, 20yrs

- T1DM since the age of 4
- Poor glycaemic control, Hba1c 118 (13%), mean glu value 21.4mmol/lt.
- Microcomplications +ve, on lisinorpil.
- Recurrent episodes of DKA (almost 1 every month), without obvious precipitating factors.
- Depression, very difficult social background.
<table>
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<th>HCO3</th>
<th>PO2</th>
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<td>HOUR</td>
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</table>
QUESTIONS

● How frequent is hyperlactataemia and lactic acidosis in DKA?

● What is the significance of hyperlactataemia in DKA? Is it associated with negative outcome?

● Which are the underlying pathophysiological mechanism(s) of the raise of lactate levels in DKA?

● When do the lactate levels return to normal?

● Are the lactate concentrations on ABG reliable?
History

• 1780 ---- Lactic acid was first isolated from sour milk by Scheele.

• 19th century ---- Diabetic ketoacidosis
  Urine of diabetic patients turned a purple color on the addition of ferric chloride – Acetoacetate

• 1925 ---- Clausen, identified lactic acidosis as a cause of acid-base disorder.

• 1961 ---- Huckabee, first expounded the clinical syndrome of lactic acidosis and described its association with critical illnesses.

• 1976 ---- Cohen and Wood, clinical and biochemical aspects of lactic acidosis.
Hyperlactataemia versus Lactic Acidosis

- The normal blood lactate concentration in unstressed patients is 0.5-1 mmol/L.
- Patients with critical illness can be considered to have normal lactate concentrations of less than 2 mmol/L.
- Hyperlactataemia is defined as a persistent, mild to moderate (2-4 mmol/L) increase in blood lactate concentration without metabolic acidosis.
- Lactic acidosis is characterized by persistently increased blood lactate levels (usually >5 mmol/L) in association with metabolic acidosis with PH<7.35.
Physiology

- Lactate is produced in all tissues.
- Skeletal muscle, brain, gut, red blood cells, and renal medulla are responsible for the majority of the production.

- Normal arterial blood lactate $\sim 0.620$ mmol/L.
- Normal venous lactate is $\sim 0.997$ mmol/L.
- Lactic acid exists in 2 optical isomeric forms, L-lactate and D-lactate.
GLUCOSE  
\[ \rightarrow \]  
GLYCOGEN  
\[ \rightarrow \]  

GLUCOSE 6-P  
\[ \rightarrow \]  

FRUCTOSE 6-P  
\[ \rightarrow \]  

PHOSPHOFRACTOKINASE  
\[ \rightarrow \]  

FRUCTOSE-1,6-BISPHOSPHATE  
\[ \leftrightarrow \]  

TRIOSE PHOSPHATES  
\[ \rightarrow \]  

PHOSPHOENOLPYRUVATE  
\[ \rightarrow \]  

PYRUVATE KINASE  
\[ \rightarrow \]  

PYRUVATE  
\[ \rightarrow \]  

ANAEROBIC METABOLISM  
\[ \rightarrow \]  

OXIDATION IN CITRIC ACID CYCLE  
\[ \rightarrow \]  

PYRUVATE  
\[ \rightarrow \]  

LACTATE DEHYDROGENASE  
\[ \rightarrow \]  

LACTATE
Metabolic aspects of Lactate Production

• Lactate / pyruvate ~ 20:1.

• Under basal conditions, lactate production is ~0.8 mmol/kg body weight/h or ~1300 mmol/day for a 70-kg person.
Fates of Lactate

- Diffuses out of the cells and is converted to pyruvate and then **aerobically metabolizes to carbon dioxide** and ATP. The heart, liver, and kidneys use lactate in this manner.

- Alternatively, hepatic and renal tissues can use lactate to produce glucose via **gluconeogenesis**. The metabolism of glucose to lactate by one tissue, such as red blood cells, and conversion of lactate to glucose by another tissue, such as the liver, is termed the **Cori cycle**.

- Liver takes up approximately 60% of the circulating lactate. The ability of the liver to consume lactate is concentration-dependent and decreases as the level of blood lactate increases. It is impaired by several other factors, including acidosis, hypoperfusion, and hypoxia.

- Excretion by the kidney.

- The rate of lactate clearance can reach **320 mmol/L/h**.
Coricyle Liver kidney

Glucose → Glycogen

NAD

PFK ± alkalosis

NADH

Pyruvate → Lactate

NAD

Cytosol

Mitochondria

2 ATP

H⁺ ADP

O₂

Acetyl CoA

PDH ± dichloroacetate

CO₂ + H₂O
The Cori Cycle

Liver

Glucose → 2 Pyruvate → 2 Lactate

6 ATP

Muscle

2 Pyruvate → 2 Lactate → Glucose

2 ATP
Pathogenesis of Lactic Acidosis

- The anaerobic metabolism of glucose produces only lactate, ATP, and water. No protons are produced.

\[
D \text{ glucose} + 2 \text{ ADP} + 2 \text{ Pi} = 2 \text{ lactate} + 2 \text{ ATP}
\]

- The acidosis occurs when ATP is hydrolyzed to adenosine diphosphate (ADP) and inorganic phosphate (Pi).

\[
2 \text{ ATP} = 2 \text{ ADP} + 2 \text{ Pi} + 2 \text{ H}^+ + \text{energy}
\]

- Every mole of glucose metabolized anaerobically, 2 moles of lactate and 2 moles of hydrogen ion are produced.

\[
D \text{ glucose} = 2 \text{ lactate} + 2 \text{ H}^+ + \text{energy}
\]

- Lactate leaves the cell in exchange for a hydroxyl anion (OH-). The source of extracellular OH- is the dissociation of water into OH- and H+. Extracellular H+ combines with lactate leaving the cell, forming lactic acid, while intracellular OH- binds to H+ generated during the hydrolysis of ATP to form water.

- Lactic acidosis occurs whenever production of lactate exceeds its utilisation.
High anion gap and PH

**ANION GAP**

- Traditionally, lactic acidosis has been associated with an elevation in the anion gap.
- In one report, 50% of patients with serum lactate levels between 5.0 and 9.9 mmol/L, levels associated with a mortality of >80%, had an anion gap of <16 mmol/L.
- Hypoalbuminemia. Reduction in serum albumin by 10 g/L reduces the normal value for anion gap by 2.5 mmol/L.

**PH**

- Concomitant respiratory or metabolic alkalosis.
- The arterial pH can be an insensitive indicator of lactic acidosis.
- The pH may therefore be normal or even elevated.
Etiologies

Cohen and Woods (1976) divided lactic acidosis into two types: type A and type B.
Type A lactic acidosis refers to conditions in which oxygen delivery is inadequate.

**Decreased oxygen delivery**

- Hypotension
- Volume depletion
- Blood loss
- Cardiogenic shock
- Septic shock
- Severe anaemia
- Severe hypoxaemia
- Carbon monoxide poisoning

**Increased oxygen demands**

- Exercise
- Seizures
Type B lactic acidosis occurs in settings of normal blood pressure and oxygen delivery

- Systemic Inflammatory Response Syndrome (SIRS)
- Diabetes Mellitus
- Malignancy
- Total parenteral nutrition
- Thiamine deficiency
- **Congenital lactic acidosis** glucose-6-phosphatase deficiency (von Gierke disease), fructose-1,6-diphosphatase deficiency, pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, oxidative phosphorylation deficiency, and methylmalonic aciduria.
- Mitochondrial myopathies, MELAS syndrome
- HIV infections
- Malaria
- Toxins/ Drugs
- D-Lactic acidosis
<table>
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<th>Drugs and Toxins</th>
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</table>
ASSAYS

• In the past, lactate assays were difficult and tedious.

• Newer autoanalyzers can rapidly and accurately measure lactate levels within minutes. Either arterial blood or a mixed venous sample is preferable, because the peripheral venous specimen may reflect regional, rather than systemic, lactate concentrations.

• The blood specimen should be immediately transported on ice and analyzed without delay, because blood cells continue to produce lactate in vitro and falsely elevate the concentration.

• Microdialysis technique has been used to quantify lactate levels in interstitial fluid in humans. McLean et al, J of Applied Physiol. 1999.
FACTS

- DKA affects nearly 8 per 1000 persons with diabetes annually and is associated with a mortality of less than 5%. *Wilson JF. In clinic. Diabetic ketoacidosis. Ann Intern Med 2010.*

- DKA patients in ICU are less ill, and have lower disease severity scores, mortality, and shorter length of ICU and hospital stay than non-DKA patients. *Freire et al, J Crit Care 2002*

● Elevations of blood lactate concentration are not uncommon in patients with hypovolemia, hypotension, and hyperventilation, which are abnormalities often found in patients with DKA. *Fulop et al Arch Intern Med 1976.*

● Lactic acid may contribute to the metabolic acidosis in patients with true diabetic ketoacidosis, but the blood lactate concentrations in these patients are not usually very high. *Watkins et al Br Med J 1969.*

● Measuring blood lactate concentration easily establishes the diagnosis of lactic acidosis (>5 mmol/L) because DKA patients seldom demonstrate this level of serum lactate. *Kitabsci et al, Diabetes Care 2001.*
Prevalence and significance of lactic acidosis in diabetic ketoacidosis.


- Retrospective, observational study of 68 patients with DKA
- Lactate levels were measured only once on less than 3 hours of admission in patients with documented DKA.
- 46 pts (68%) had lactic acidosis (lactate, >2.5 mmol/L), and 27 (40%) of 68 had a high lactate (>4 mmol/L). The median lactate was 3.5 mmol/L.
- There was no association between lactate and ICU length of stay (LOS) or overall mortality.
- Lactate correlated negatively with blood pressure (r = -0.44; P < .001) and positively with glucose (r = 0.34; P = .004).
<table>
<thead>
<tr>
<th>Patient characteristics, stratified by initial lactate levels</th>
<th>Lactate &lt; 4 (n = 41)</th>
<th>Lactate ≥ 4 (n = 27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>39.2 ± 17.0</td>
<td>49.7 ± 18.1</td>
<td>.018&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gender</td>
<td>36.6%, male</td>
<td>22.2%, male</td>
<td>.286</td>
</tr>
<tr>
<td></td>
<td>63.4%, female</td>
<td>77.7%, female</td>
<td></td>
</tr>
<tr>
<td><strong>Data and vital signs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>622.6 ± 247.5</td>
<td>813.4 ± 310.8</td>
<td>.007&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bicarbonate MEq/L</td>
<td>9.7 ± 4.5</td>
<td>8.2 ± 3.9</td>
<td>.284</td>
</tr>
<tr>
<td>Anion gap</td>
<td>29.2 ± 6.0</td>
<td>36.1 ± 6.3</td>
<td>&lt;.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>pH</td>
<td>7.11 ± 0.15</td>
<td>7.09 ± 0.13</td>
<td>.635</td>
</tr>
<tr>
<td>(n = 25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, min mm Hg</td>
<td>115.6 ± 27.4</td>
<td>103.7 ± 31.6</td>
<td>.003&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diastolic BP, min mm Hg</td>
<td>57.9 ± 17.2</td>
<td>49.7 ± 18.3</td>
<td>.065</td>
</tr>
<tr>
<td>APACHE II</td>
<td>14.6 ± 5.9</td>
<td>19.7 ± 7.0</td>
<td>.002&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Comorbid diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (53.6%)</td>
<td>12 (44.4%)</td>
<td>.621</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>4 (9.8%)</td>
<td>3 (11.1%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2 (4.9%)</td>
<td>4 (14.8%)</td>
<td>.206</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4 (9.8%)</td>
<td>1 (3.7%)</td>
<td>.641</td>
</tr>
<tr>
<td><strong>Precipitant for DKA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication noncompliance</td>
<td>19 (46.3%)</td>
<td>10 (37%)</td>
<td>.466</td>
</tr>
<tr>
<td>Infection</td>
<td>11 (26.8%)</td>
<td>8 (29.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0%)</td>
<td>1 (3.7%)</td>
<td>.397</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (26.8%)</td>
<td>8 (29.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>6 (14.6%)</td>
<td>2 (7.4%)</td>
<td>.463</td>
</tr>
<tr>
<td>Metformin use</td>
<td>4 (9.8%)</td>
<td>0 (0%)</td>
<td>.146</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

<sup>a</sup> Represents statistical significance using Wilcoxon rank sums for nonnormal variables and the Student t tests for normal variables and Fisher exact tests for categorical variables.
Conclusions 1

- Current evidence show that elevated lactate concentrations are common in DKA and do not seem to be associated with worse clinical outcomes i.e. LOS in ICU and ICU mortality.
- Further prospective studies are needed to confirm these first data as well as epidemiological studies for prevalence.
Conclusions 2

● There is currently no explanation for the phenomenon: hyperlactataemia persists after fluid resuscitation in our patient, so theory of volume depletion and subsequent hypoxia is challenged. *Altered glucose metabolism in DKA-role of epinephrine? Activation of glycolysis for energy generation, as for stress conditions?*

● There are no data concerning when lactate levels return to normal in DKA and to what extent hyperlactataemia contributes to protracted acidemia in DKA. In our patient, hyperlactataemia persisted and increased over the hours, PH was refractory to treatment but we do not know the levels of ketones.

● What is the significance of this transient increase in lactate levels in DKA? Is this a common feature in all DKA patients, or different groups with different outcomes?

" Lactic acid may contribute to the metabolic acidosis in patients with true diabetic ketoacidosis, but the blood lactate concentrations in these patients are not usually very high.

In some patients the ketoacidosis is replaced by a lactic acidosis during treatment. This usually occurs in association with a serious underlying disorder and is associated with a poor prognosis.

A transient increase in blood lactate concentration was in fact observed in most patients after the beginning of treatment, but the significance of this finding is uncertain".
Recommended Approach

- Careful history to evaluate the underlying pathophysiologic cause that contributed to lactic acidosis. No distinctive features are specific for hyperlactatemia.
- Correcting the underlying cause of lactic acidosis.
- Optimizing tissue oxygen delivery by cardiopulmonary support.
- Avoid solutions containing lactate and vasoconstrictor Tx.
- Evidence so far indicates that alkali therapy is not beneficial, it may, in fact, cause harm. The use of bicarbonate in patients with severe metabolic acidosis and arterial pH less than 7.15 should be reserved to maintain the pH above 7.15 until the underlying process is corrected.
- NaHCO3 required = \((\text{bicarbonate desired} - \text{bicarbonate observed}) \times 0.4 \times \text{body weight (kg)}\).
Complications of bicarbonate therapy

- Bicarbonate combines with hydrogen to form H2CO3, which dissociates into CO2 and H2O. CO2 rapidly diffuses into cells and can worsen intracellular acidosis.
- Increase in lactate generation in lactic acidosis and cardiac depression in animals.
- Volume expansion.
- Hypocalcaemia.
- Hypernatraemia – IV NaHCO3 (8.5%).
Alkalinizing Agents, Haemofiltration and Thiamine

- **Dichloroacetate** is the most potent stimulus of pyruvate dehydrogenase. Dichloroacetate may inhibit glycolysis and, thereby, lactate production.

- **Carbicarb** is a new buffering agent with potential use in metabolic acidosis. It is an equimolecular mixture of sodium bicarbonate and sodium carbonate. Carbicarb has a buffering capacity similar to sodium bicarbonate but does not generate carbon dioxide.

- **Dialysis** may be a useful mode of therapy when severe lactic acidosis exists in conjunction with renal failure or congestive heart failure. Dialysis would allow bicarbonate infusion without precipitating or worsening fluid overload. Therefore, dialysis would correct acidosis by restoring the buffer pool.

- **Thiamine** can be administered safely to patients with lactic acidosis, particularly in the absence of an obvious alternate etiology.

- The treatment for D-lactic acidosis is NaHCO$_3$ to correct acidemia and antibiotics to decrease the number of organisms producing D-lactate.