OPTIMISING NUTRITION IN CF ADULTS

DR HELEN WHITE
## Multisystem Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Nutritional Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic insufficiency</td>
<td>Nutritional status, CF related diabetes, Fat soluble vitamin status, Bone health</td>
</tr>
<tr>
<td>Increased requirements</td>
<td>Nutritional status</td>
</tr>
<tr>
<td>CFTR</td>
<td>Differing nutritional needs between Genotype</td>
</tr>
<tr>
<td>CF Related liver disease</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
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<tr>
<td>Transplantation</td>
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**Greater complexity of care in adulthood**
<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>CFTR production is stopped early and protein production becomes defective. Class 1 patients have no functioning CFTR chloride channels.</td>
</tr>
<tr>
<td>II</td>
<td>CFTR is poorly processed and is destroyed within the cell, resulting in little or no CFTR reaching the cell surface.</td>
</tr>
<tr>
<td>III</td>
<td>CFTR reaches the cell surface but does not work, unable to open properly to transport chloride.</td>
</tr>
<tr>
<td>IV</td>
<td>CFTR reaches the apical surface but the defective conduction of chloride through the channel results in poor CFTR function.</td>
</tr>
<tr>
<td>V</td>
<td>Decreased production of CFTR results in some production, but insufficient to maintain normal function.</td>
</tr>
</tbody>
</table>
REASONS FOR NEW TARGETS?

Lesser gains above BMI 22 (women), 23 (men)

Advantages reduce as BMI reaches 30

Adults
LONGITUDINAL CHANGES IN BMI

N.J. Greig, H. White, H.K. Chadwick, A. Cartwright, D.G. Peckham
Cardiovascular risk in an adult CF population: a 9 year retrospective analysis
ENERGY & MACRONUTRIENT TARGETS
DIETARY EMPHASIS ON FATS

Fat 35-40% of intake
DIFFERING ADULT POPULATIONS

Cardiovascular risk in an adult CF population: a 9 year retrospective analysis

N.J. Greig, H. White, H.K. Chadwick, A. Cartwright, D.G. Peckham

Cholesterol change over 10 years (Pancreatic sufficient versus insufficient)

Upper recommended Cholesterol limit

Cholesterol (mmol/l)

2008 2013 2017

PS PIS
WHAT TYPES OF FAT?

- Greater longevity
- Vascular endothelial dysfunction shown in children with CF (2013)
- Ischaemic heart disease reported in CF (2010)

- Greater emphasis on polyunsaturated and mono-unsaturated fats
- May also improve essential fatty acid status

- CF Trust (2016) &
- ESPEN-ESPGHAN-ECFS guidelines (2016)
Low muscle mass is consistently associated with pulmonary decline.

Protein digestion capacity is severely impaired in CF.

**Protein**
No evidence based recommendations for daily protein intake for CF (CF Trust 2016)
20% energy ESPEN-ESPGHAN-ECFS (2016)
0.83g protein/kg
High likelihood of normal lung function, targeting BMI z-score > 0

Improved further, by targeting LBM z-score > 0
SUPPLEMENTS – WHICH ONES?

Complete supplement – small volume (125ml)

Fat free supplement – no enzymes required

Complete supplement – 200ml volume

High calorie, high fat supplement (600kcal/240ml drink)
ORAL CALORIE SUPPLEMENTS – COCHRANE REVIEW (2014)

- **Limited trials**
  - **Kalnins et al (2005)**
    - 21%, 28% intake from oral calorie supplements at 1 and 3 months (mean 1.6 cans/day)
    - No change in weight or height z-score
  - **Hanning et al (2005)**
    - 25% of EAR energy intake from supplements additional to normal diet
    - No change in weight or height z-score at 6 months
    - No improvements in children with cystic fibrosis who were moderately malnourished
- ETF can improve age dependent anthropometrics
- ETF is given as a continuous overnight infusion
- Cannot recommend ETF to improve or stabilise lung function
- Recommends against FEV$_1$ being used as a contraindication to PEG or G-Tube placement
ENTERAL TUBE FEEDING - WHAT ARE THE LATEST KEY DOCUMENTS?

Consensus Report on Nutrition for Pediatric Patients With Cystic Fibrosis

*Dracy Borowitz, *Robert D. Baker, and *Virginia Stallings

Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand

Review
Enteral tube feeding for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed guidelines
Sarahanne Schwarzenberg 1,4, Sarah E. Hempstead 1, Catherine M. McDonald 1, Scott W. Powers 1, Jamie Hockbridge 1, Sharron Blair 1, Steven Freedman 1, Elaine Harrington 2, Peter J. Murphy 2, Lena Petter 1, Amy E. Schrader 1, Kyle Shiel 1, Jillian Sullivan 1, Melissa Wallenstein 1, Bruce C. Marshall 1, Amanda Radner Leonard 1
WHAT ELSE TO CONSIDER IN OPTIMISING NUTRITION

- High energy/high protein diet
- Oral dietary supplements
- Enteral tube feeding
- Enzyme therapy
- Vitamin supplementation (A,D,E,K)
- Co-morbidities – cystic fibrosis related diabetes, bone disease
- Pregnancy
- Transplantation
- New therapies
CYSTIC FIBROSIS RELATED DIABETES - THE BASIC DEFECT

- Pancreatic β cell dysfunction, fatty infiltration and fibrosis
- Causes decreased but not absolute insulin deficiency
- Diabetic ketoacidosis is rare
- Develops insidiously
- Patients may be asymptomatic
- Often first presents where insulin resistance is increased
  - Acute pulmonary infection
  - Chronic severe lung disease
  - Glucocorticoid therapy
  - Immunosuppression regimens (post-transplant)
AT WHAT STAGE DOES IT BEGIN TO OCCUR

Prevalence of Common Complications by Age in 2014

- Progressive with age
- Annual screening for CFRD ≥ 10 years, using OGTT
- Poor sensitivity of HBA1c
<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort (n)</th>
<th>Findings for CFRD</th>
</tr>
</thead>
</table>
| Finkelstein et al, 1988 | 448        | Increased mortality  
Worse nutritional status and lung function                                         |
| Koch et al, 2001      | 7756       | Worse nutritional status and lung function  
(greatest discrepancies at puberty)                                                   |
| Sims et al, 2005      | 2640       | Worse pulmonary disease in females                                                 |
| Marshall et al, 2005  | 8247       | Worse nutritional status, increased pulmonary exacerbations, increased liver disease |
| Adler et al, 2008     | 8029       | Greater risk of CFRD in females  
Worse pulmonary function and liver function. CFTR class effect                     |
| Moran et al, 2009     | 872        | Worse lung function (males) but  
Gender gap in mortality is narrowing  
No nutritional differences  
Pulmonary and nutritional differences do not differ by fasting glucose status      |
CRUCIAL CHANGES TO CARE

- Annual screening using the oral glucose tolerance test
- Early instigation of insulin therapy

**Oral Glucose Tolerance Test**

The pathologist will give you:
75 ml glucose drink

Then ask you to:
Wait 2 hours

Take blood and test glucose levels
## NUTRITIONAL GAINS ASSOCIATED WITH INSULIN TREATMENT

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moran et al, (2009)</td>
<td></td>
<td></td>
<td>2% ↑BMI</td>
<td>↑</td>
</tr>
<tr>
<td>White et al (2009)</td>
<td></td>
<td></td>
<td>3.3% ↑BMI</td>
<td>5.9% ↑BMI</td>
</tr>
<tr>
<td>Nousia Avanitarkis et al, (2001)</td>
<td>16.6% ↑BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rafii et al, (2005)</td>
<td>2.4% ↑BMI</td>
<td>6.9% ↑BMI</td>
<td></td>
<td></td>
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DIETARY RECOMMENDATIONS … CHANGE?

Update on cystic fibrosis related diabetes Kelly A, Moran A [Journal of Cystic fibrosis 2013:12;318-331]

- Consuming simple CHO in combination with complex CHO, protein and fat may limit the glucose excursion

CF Trust Nutritional management of Cystic Fibrosis (2016)

- Type I /II advice inappropriate
- Some people may be taught CHO counting
- If they do not CHO count regular meals should be encouraged containing complex CHO and limiting simple CHO to mealtimes

Insulin initiation and dose adjustments should be done conservatively - to avoid hypoglycemia.
LEWIS ET AL (2015)
DIABETES – RELATED MORTALITY IN ADULTS WITH CYSTIC FIBROSIS

Diabetes related mortality in adults with cystic fibrosis:
Role of genotype and sex
Am J Resp & Critical Care Med 2015:191(2);194-200

In 5th decade 83% women and 64% men with a severe genotype had CFRD
TREATMENT CONSIDERATIONS FOR PREVENTING LOW BONE MINERAL DENSITY

- Disease severity
  - Age
  - Gender
  - Delayed puberty

- Nutrition
  - Weight/BMI
  - Vitamin D, K
  - Calcium deficiency

- Iatrogenic
  - Cumulative corticosteroid use
  - Genotype
  - Physical inactivity
  - Immunosuppression

Increased prevalence of bone mineral density
## A NUTRITIONAL PROBLEM

### Requirements for normal bone mineralisation

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Function</th>
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<tbody>
<tr>
<td>Adequate bone mass</td>
<td>(especially during the growth spurt)</td>
</tr>
<tr>
<td>Protein</td>
<td>Osteoid formation</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Calcium absorption and phosphate utilisation</td>
</tr>
<tr>
<td>Calcium, phosphate and Magnesium</td>
<td>Bone calcification and mineralisation</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Carboxylation of osteocalcin</td>
</tr>
</tbody>
</table>
RISK FACTORS FOR VITAMIN D DEFICIENCY IN CF

- Reduced absorption Lark et al, 2001
- Inadequate supplementation
- Non adherence to therapy
- Reduced stores due to depleted fat mass
- Reduced sunlight exposure because of illness and medications
- Low vitamin D binding proteins Speeckaert et al, 2008
- Mg deficiency causes functional vitamin D deficiency (renal 25 OHD to 1,25(OH)₂D)
## Vitamin D Insufficiency Persists in CF

<table>
<thead>
<tr>
<th>Geographical Location</th>
<th>Reference (Year)</th>
<th>Insufficiency/Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Grey et al, 2008</td>
<td>88% insufficient</td>
</tr>
<tr>
<td>USA</td>
<td>Green et al. 2008</td>
<td>46% insufficient</td>
</tr>
<tr>
<td>France</td>
<td>Sermet-Gaudelus et al, 2008</td>
<td>90% insufficient</td>
</tr>
<tr>
<td>UK</td>
<td>Conway et al., 2008</td>
<td>78% insufficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15.0% deficient</td>
</tr>
<tr>
<td>Russia</td>
<td>Asherova et al, 2008</td>
<td>41.7% insufficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.6% deficient</td>
</tr>
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TRENDS IN BMD STATUS

- Vitamin D intakes had increased by 53%

- Contributing factors may include steroid use, low BMI, inadequate calcium and vitamin D intake, and poor nutrient absorption, as well as effects of gene mutation on bone cells
VITAMIN D SUPPLEMENTATION

- > 1 years 1,000-5,000 IU Vitamin D$_3$/day
- Aiming for minimum of 50nmol/L

ECFS, 2011
CONTINUED DEBATE

Target serum level >20 or >30ng/ml (50-75nmol/l) – mixed guidance

Timing (Possible improved absorption with food and enzymes)

Vitamin D2 or Vitamin D3? - Vitamin D3 (Cholecalciferol)

Intervals (no evidence for bolus versus daily dosing)

UV lamps (no recommendation)
Vit D measured by total serum 25(OH) D as it is associated with health outcomes, is the primary circulating form of Vit D and accounts for Vit D from diet & sunlight.

Assess during the winter months (winter levels shown to be only 70% of summer values).

Repeat intervals following changes in treatment should be undertaken at 3 months.
CALCIUM

- Should be assessed at least annually (ESPEN-ESPGHAN-ECFS Guidelines)
- Daily calcium intakes should be at a minimum to achieve dietary intake recommended by the EFSA

<table>
<thead>
<tr>
<th>Age</th>
<th>Dietary reference values</th>
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<tbody>
<tr>
<td>0-6 months</td>
<td>200mg</td>
</tr>
<tr>
<td>7-11 months</td>
<td>280mg</td>
</tr>
<tr>
<td>1-3 years</td>
<td>450mg</td>
</tr>
<tr>
<td>4-10 years</td>
<td>800mg</td>
</tr>
<tr>
<td>11-17 years</td>
<td>1150mg (1300mg 9-18yrs)</td>
</tr>
<tr>
<td>18-25 years</td>
<td>1000mg</td>
</tr>
<tr>
<td>&gt;25 years</td>
<td>950mg</td>
</tr>
</tbody>
</table>

Calcium intake for people with CF: recommendations guided by EFSA
VITAMIN K

- Sub clinical as assessed by increased PIVKA II- almost universal in CF Conway et al, 2005; Rashid et al, 1999; Becker et al, 1997; Wilson et al, 1997
- Increased % of undercarboxylated osteocalcin (Glu-Oc) Fewtrell et al, 2008; Grey et al, 2008; Nicolaidou et al, 2006; Conway et al, 2005; Aris et al, 2003
- Associated with increased bone turnover
- Reduced markers of bone mineral accrual
European Cystic Fibrosis Bone Mineralisation Guidelines

‘If height is $\geq 1$ SD below age and sex matched healthy controls, BMD Z scores should be adjusted for height or statural age to avoid overestimating deficits in BMD in people with short stature’

Stress the importance of serial height adjusted measurements

Sermet-Gaudelus et al, 2011

ECFS, 2011

Initial scan age 8-10 years

- Normal LS Z score: Rescan every 5yrs
- LS Z score -1 to -2: Rescan every 2yrs
- LS Z score $<-2$: “CF related low BMD” Rescan every yr
Greater complexity of nutritional management and emergence of new therapies

- Diet, oral supplementation, enteral tube feeding
- Pancreatic enzyme therapy introduction
- Vitamin Supplementation (Vitamin A, D, E, K)
- Cystic fibrosis related diabetes, osteoporosis, management of pregnancy, post-transplantation.... and others

- Improvements in nutritional status over the last 10 years aligned with earlier and more aggressive interventions across all aspects of nutritional management
- .....The future for our adult populations?