Table Supplemental Digital Content 5: Articles reporting patients diagnosed with EPI who are later found to be malnourished

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| Study | Exocrine Pancreatic Insufficiency (EPI) | | | | | Malnutrition | | | | Author’s conclusions | Comments |
| EPI Definition: Pancreatic Markers | Pancreatic Enzymes (serum) | Fecal Enzymes | Fecal Fat | Other tests | Definition | Anthropometrics | Clinical Indicators | Percentage affected |
| Pichler et al. 2015 | 1. Pancreatic insufficient defined as FE-1<200 μg/g. Severe deficiency in FE-1<50 μg/g  2. Ultrasound of pancreas to screen fatty replacements |  | 20/21 (95%) patients pancreatic insufficient |  | 7/21 (33%) abnormal US findings | WHO definitions of malnutrition: weight for height Z score (WHZ) of <-2  Other anthropometric parameters: WAZ, height for age Z-score (HAZ) | At baseline 7/21(33%) WAZ <-2, 9/21 (43%) HAZ <-2  Follow up: 5/13 (38%) catch up growth; 2/13 (15%) WAZ <-2, and 7/13 (54%) HAZ <-2 |  | Not reported | More 50% vitamin A, selenium deficiency despite PERT + supplements. Routine measurements needed. | No elaboration US findings |
| Kolodziejczyk et al. 2014 | 1. 72-h fecal fat quantification; reference value <4.0 g/day  2. Endoscopic retrograde cholangiopancreatography (ERCP) diagnosing and staging chronic pancreatitis (CP). Cambridge classification grades ERCP findings normal (Grade 1) to marked (Grade 4) |  |  | Mean fecal fat output among undernourished (n=38; 6.69 g) higher than in children with BMI ratio >85% (n=114; 2.27 g/day) (ns) | ERCP: Age of CP onset significantly higher group 1 (10.8, n=38) than group 2 (8.5, n=170) (p<0.05)  Mean Cambridge grade in group 1 vs group 2 ns. | BMI ratio = (BMI actual/BMI for the 50th centile) X 100 [%]  Nutritional status BMI%:  <75 = severe malnutrition  75-85 = malnutrition  86-90 = mild malnutrition  91-110 = normal  111-120 = overweight  >120 = obese  Patients divided into 2 groups: 1-clinically significant malnutrition with BMI ratio <85%, and 2 with BMI ratio >85% | 52/208 (25.0%) of CP had malnutrition:  14/52 (26.9%) mild malnutrition; 36/52, (69.2%) moderate malnutrition; 2/52 (3.8%) severe malnutrition  Clinically significant malnutrition (group 1) 38/208 (18.3%)  Mean age at disease onset significantly higher group 1 vs. group 2. (p<0.05) |  | 38/208 (18.3%) | Considerable % CP children suffer clinically significant malnutrition. Later age at CP onset predisposes to malnutrition development | Fat analysis only in 152/208 (73.0%) |
| Cohen et al. 2005 | 1. Pancreatic insufficient (PI) 72 hr. fat analyses <93% absorption or stool trypsin concentration <80 ug/g  2. Fecal elastase (FE) <15 ug/g stool = no pancreatic activity (NO-FE)  3. Percent fecal fat absorption (%CoA) 7-day weighted food record, 72 hour stool [compared between NO-FE and residual FE group (R-FE)] |  | FE<15 ug/g stool: 75/84 (89%) children = NO-FE  FE≥15 ug/g stool:  9/84 (11%) = R-FE | %CoA: R-FE 94% vs 81% NO-FE = PI, (p<0.01) |  | Weight for Age Z-score (WAZ), Adjusted height for age Z-score (AHAZ) compared between NO-FE and R-FE (CDC growth charts as reference) | Baseline: AHAZ significantly lower NO-FE group (p=0.03)  Growth over 24 months: WAZ significantly lower NO-FE group p=0.04 |  | Not reported | Some CF children misclassified pancreatic status. R-FE children better growth, absorption |  |
| Bines et al. 2002 | 1. PI determined by stool microscopy and/or 3-day fecal fat balance |  |  | 35/46 (76%) PI |  | 1. Anthropometrics: WZ, HZ, WHZ compared to control infants and reference data | WZ and HZ significantly lower than controls (p<0.05)  WHZ significantly lower than controls (p<0.05)  PI significantly associated with lower WZ, HZ, WHZ (p<0.05) |  | Not reported | Growth impairment during first weeks of life in CF infants associated with PI | EPI cutoff values not provided  Reference data for anthropometrics not given |
| Cipolli et al. 1999 | 1. Secretin stimulation test (SST) lab values:  S. pancreatic alpha-amylase [1800 IU], Total lipase [216.7 IU],  trypsin [34.6 IU], chymotrypsin (CMT) [32 IU] (EPI = absent or lower)  2. 3 day fat balance (EPI = fat absorption <90%)  3. Fecal CMT: reference value >5 units per gram feces (EPI = <3 U/g) | 12/12 (100%) abnormally low or absent levels pancreatic enzymes  Follow up: 5/5 (100%) normal lipase values, 0/5 (0%) normal amylase, 3/5 (60%) normal trypsin and CMT | 6/7 (86%) fecal CMT values >3 U/g | - 8/8 (100%) abnormal fat balance  -Follow up: 5/6 (83%) normal fat balance |  | Height Z-score (HZ) and Weight Z-scores (WZ) WHO reference values: malnutrition if HZ and WZ<-2 | Diagnosis  11/13 (84%) HZ<-2 and WZ<-2  Follow up (n=6)  2/6 (33%) HZ<-2 and WZ<-2 |  | 11/13 (84%) | Possibility of improvement or normalization of exocrine pancreatic function with age in SD | 12/13 (92%) had SST  1 patient at follow up refused SST, abnormal fat absorption  HZ, WZ interpreted as HAZ, WAZ |
| Carroccio et al. 1998 | 1. Fecal enzymes: PI= FE-1 <200 μg/g stool], CMT <7.5 U/g]  2. S. total amylase and pancreatic amylase higher normal values 160 U/l and 83 U/l.  3. Fecal fat analyzed. Abnormal >2 SD above control value (value not given) | S. amylase value elevated in 12 children (1.2-4 fold higher than normal limit).  No correlation between fecal enzyme vs. elevated S. amylase | 14/47 (30%) low fecal enzymes 7 isolated FE-1 deficiency, 3 isolated CMT deficiency, 4 deficiency in both  Mean CMT activity significantly lower than controls (p<0.0001)  Mean FE-1 activity significantly lower than controls (p<0.0001) | 12/47 (26%) fat malabsorption  Fat malabsorption in 8/14 (57%) with low fecal pancreatic enzymes vs. 4/33 (12%) with normal enzymes (p<0.001)  Significant negative correlation steatocrit vs. FE-1 (p<0.03) |  | 1. WAZ  Italian regional standards used  2. Presence of diarrhea defined as 3 or more unformed stools per day | WAZ:  Abnormal pancreatic function test: median -0.66 (range -3.3 to 2.1)  Normal pancreatic function test: median -0.47 (range -3.8 to 2.5)  Individual results only in abnormal pancreatic function tests. Only 2 patients with abnormal WZ  (-3.3 and -3.25 ) | Diarrhea not significantly low pancreatic enzymes vs. normal: 4/14 (29%) vs. 4/33 (12%), (p>0.05) | \*Incomplete data  Abnormal pancreatic function group:  2/14(14%) z-score below -3 | Abnormal pancreatic function tests frequent HIV, contributes to steatorrhea | High serum amylase attributed to salivary amylase 10/12 patients)  Individual WAZ only in 14/47 patients |
| Carroccio et al. 1995 | Pancreatic function assessed SST:  Lipase (range 300-6000, median 800; units/ml/min/kg)  CMT (range 42-850, median 80; units/ml/min/kg  Phospholipase (range 4-150, median 12; units/ml/min/kg)  Severe EPI = enzymatic secretion <10% of normal value |  | No significant differences between groups  Group A (treatment): 8/20 (40%) subnormal enzyme output 1 or more enzymes  Group B (placebo): 7/20 (35%) subnormal enzyme output 1 or more enzymes  3/20 (15%) patients in both groups had severe EPI (6/40, 15%) |  |  | Anthropometrics: [body weight, height, weight/ height (W/H ratio)] Italian regional standards used | Increase in W/H ratio  Group A significant after 30 days (p<0.02)  Group B significant after 60 days (p< 0.03)  Patients with EPI:  Group A (treatment): significantly higher weight vs. Group B (p<0.008) |  | Not reported | Pancreatic enzyme therapy useful in first 30 days after celiac diagnosis |  |
| Carroccio et al. 1994 | Pancreatic function assessed SST:  Lipase (range 300-6000, median 800; units/ml/min/kg)  CMT (range 42-850, median 80; units/ml/min/kg  Phospholipase (range 4-150, median 12; units/ml/min/kg)  Severe deficiency = <10% enzyme output |  | No statistical significance:  -6/52 (12%) low phospholipase  -4/52 (8%) low CMT  14/52 (27%) low lipase: celiac groups statistically lower than control (p<0.009)  15/52 (29%) presented pancreatic deficiency based on enzyme output  4/52 (8%) had severe EPI |  |  | Body (W/H) ratio American National growth curves, no malnutrition definition | Control group had significantly higher W/H ratio than celiac patient groups (p<0.05)  No W/H difference EPI and PI patients |  | Not reported | Mild/ moderate PI frequent in celiac patients, independent of nutrient status | -Lipase reported as 600 but is in fact 6000 |
| Bronstein et al. 1992 | 72-h fecal fat collection, pancreatic sufficient (PS) <15% fat malabsorption at diagnostic visit (~6 weeks) and as <10% fat malabsorption at 6 and 12 month visits |  |  | Diagnosis: 23/39 (59%) PI  6 and 12 month visit: PI, 79% at 6 months, 92% at 12 months (n not given)  7/49 (14%) PS in first year  Only PI had significant fat balance ratio (p<0.05) |  | 1. Anthropometrics:  Weight and length data expressed as Z scores below 50th percentile American growth standards  Change in weight calculated as [(WAZ at diagnosis- birth weight z score) / months in age at diagnosis]  Weight gain (gm/day)  2. Serum Albumin lower limit ≤2.8 gm/dl | Diagnosis:  -Weight gain (gm/day) (n=29) lower in PI (p=0.05)  -WAZ (n=29) lower in PI  (p=0.05)  Fecal fat excretion inversely correlated with WAZ (p=0.005) and weight gain (p <0.005) | Frequency of hypoalbuminemia not significantly different (5/15, 33%, PI and 1/11, 9%, PS)  Albumin (n=26) higher in PS (p<0.01) | Not reported | PI in CF infants significant impact on growth and nutrition | Only select patients compared |
| Hill et al. 1982 | 1. PI based on PST:  lipase, colipase, trypsin no reference values given  2. Fecal fat: upper normal limit =7% | 14/14 (100%)EPI  Lipase <2% of mean normal secretion in all steatorrheic patients.  Colipase and trypsin higher in 5 patients without steatorrhea compared to 3 patients with steatorrhea |  | 12/14 (86%) children steatorrhea.  Follow up 5/12 (42%) still had steatorrhea |  | Growth percentiles | Weight percentiles on admission:  <3 n=7  <10 n=2  >25 n=1  >50 n=1  no values n=3  Height percentiles on admission:  <3 n=7  <10 n=2  >25 n=2  >50 n=0  no values n=3 |  | Not reported | Fat absorption improves in majority SD patients, associated marginal improvement lipase | Follow up timeframe not consistent |