Table Supplemental Digital Content 6: Articles reporting patients diagnosed with malnutrition who are later found to have Exocrine Pancreatic Insufficiency

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| Study | Malnutrition | | | Exocrine Pancreatic Insufficiency (EPI) | | | | | | Author’s Conclusions | Comments |
| Definition | Anthropometrics | Clinical Indicators | EPI definition: Pancreatic Markers | Pancreatic Enzymes (serum) | Fecal Enzymes | Fecal Fat | Other tests | Percentage affected |
| Bartels et al. 2016 | Severe acute malnutrition (SAM) defined WHZ <-3 SD and/or a mid-upper arm circumference (MUAC) of < 115 mm (non-edematous) and/or presence of bilateral edema (edematous malnutrition) | WHZ ≤-3 =51/89 (58%)  MUAC <11.5 cm =45/89 (50.6%) | 56/89 (63%) had edematous SAM  33/89 (37%) had non edematous SAM | 1. FE-1 <200 μg/g stool = EPI, Levels <100 μg/g stool =severe EPI  2. S. trypsinogen in a random subset: abnormal >57 ng/mL  3.S. pancreatic amylase with upper limit set at 110 U/l | Amylase:  17/80 (21%) increased levels (ns between groups)  High levels of trypsinogen 11/39 (28%) patients.  Non-edematous = 9/20 (45%); Edematous 2/19 (11%) (p= 0.03) | EPI on admission: 71/77 (92.2%) EPI and 59/77 (77%) severe EPI  Edema patients significantly lower FE-1 levels vs non-edematous group (22 μg/g of stool vs. 80 μg/g of stool, (p=0.009)  47/48 (98%) of edematous group EPI vs 24/29 (83%) of non-edematous group (p=0.03),  Severe EPI 42/48 (88%) vs 17/29 (59%) in non-edematous (p=0.006)  3 days post stabilization:  EPI  38/46 (83%) edematous  20/24 (83%) non-edematous  Severe EPI  28/46 (61%) edematous  14/24 (58%) non-edematous |  |  | 71/77 (92%) EPI  59/71 (83%) had severe EPI | EPI prevalent SAM children, especially edematous. Pancreatitis common SAM | Trypsinogen only measured in 39 |
| El-Hodhod et al. 2005 | Marasmus (less than 60% of the expected  weight for age)  Kwashiorkor (KWO): oedema and between 60 and 80% of the expected weight for age.  Marasmus-Kwashiorkor(MKWO): less than 60% of the expected weight for  age but had oedema.  *Weight (kg)*  Control 9.50±1.78 | Weight (kg)  Baseline:  Marasmus-4.99±1.15  KWO-6.00±1.89  MKWO-5.51±1.67  Malnourished population significantly lower than controls:  Marasmus (p<0.001)  KWO (p<0.01)  MKWO (p<0.001)  Significant improvement after nutritional rehabilitation:  Marasmus (p<0.001)  KWO (p<0.001)  MKWO (p<0.001) | Edema mentioned, data not provided | 1. Controls used as reference values  S. amylase (U/dl) 120.28±28.90  S. lipase (U/l) 66.13±17.35  2. Ultrasound (US): Pancreatic head size (cm3) [controls]  5.13±2.33 | Baseline S. amylase:  Marasmus 68.88 ± 28.90  KWO 51.54±16.90  MKWO 56.04±13.02  All groups lower than controls (p<0.001)  Significant improvement after nutritional rehabilitation all groups (p<0.001)  Baseline S. lipase:  Marasmus 38.59±21.08  KWO 34.63±17.58  MKWO 21.67±21.48  Malnourished population lower than controls:  Marasmus (p<0.01)  KWO (p<0.001)  MKWO (p<0.001)  Significant improvement after nutritional rehabilitation.  Marasmus (p<0.001)  KWO (p<0.01)  MKWO (p<0.001) |  |  | Baseline pancreatic head size (cm3):  Marasmus 1.52±0.60  KWO 2.73±0.12  MKWO 3.00±0.54  Malnourished population significantly lower than controls:  Marasmus (p<0.001)  KWO (p<0.01)  MKWO (p<0.05)  Significantly improved after nutritional rehabilitation:  Marasmus (p<0.001)  KWO- t=0.44 (p<0.05)  MKWO- t=1.36 (p<0.05) | Not reported | Pancreatic head size and exocrine function used to evaluate PEM and used as prognostic parameter |  |
| Briars et al. 1998 | HZ, WZ. WHO reference values  Children categorized WZ  -2= severely malnutrition, -1 to -2= moderate malnutrition, above -1= no malnutrition. | 165/659 (25.0%) normally nourished  205/659 (31.1%) moderately malnourished  289/659 (43.9%) severely malnourished |  | IRT compared among study population  No reference value | IRT value (95% CI)  Mount Isa study:  Mean: 10.56 μg/L (9.56-11.67)  normally nourished: 9.59 μg/L (8.49-10.82)  moderately malnourished: 10.92 μg/L (8.64-13.8)  severely malnourished: 13.62 μg/L (10.89-17.02)  IRT correlation with HZ, WZ (ns)  Alice Springs study:  Mean: 27.38 μg/L (22.91-32.74)  normally nourished: 30.21 μg/L (24.86-36.7)  moderately malnourished: 32.6 μg/L (28.36-37.52)  severely malnourished: 29.22 μg/L (25.16-33.93)  IRT correlation with HZ, WZ (ns) |  |  |  | Not reported | High IRT in low WZ confounding effect of gastroenteritis, may result subclinical pancreatic disease in gastroenteritis | WZ interpreted as WAZ |
| Cleghorn et al. 1991 | WAZ:  Normal: weight >-1, moderate: -1 to -2, severely underweight <-2. | Mean WAZ -1.6 (range -3.5 to 1.5)  57/198 (29%) normal,  78 /198 (39%) underweight,  63/198 (32%) severely underweight |  | Serum immunoreactive trypsinogen, (IRT) normal values obtained from population group, (upper normal = 89.1 μg/L | Serum cationic trypsinogen:  Normal; 0/57 (0%) elevated levels.  Moderately Underweight; 11/78 (14%) elevated levels.  Severely Underweight; 6/63 (10%) elevated levels  Significant correlation WAZ vs. IRT (p=0.0014)  IRT significantly higher severely underweight vs. normal (p<0.05) |  |  |  | 17/198 (9%)  elevated IRT = EPI | Pancreatic dysfunction may be common and overlooked to ongoing malnutrition and disease in Australian Aboriginal children | Only 198/ 398 had IRT analyzed, subsequent comparisons only of 198 |
| Sauniere et al. 1988 | Malnutrition defined on clinical and anthropometric symptoms of PEM: decreased weight and height, diarrhea, loss of appetite, edema |  | 28/28 (100%) PEM. | SST: Reference values for amylase, lipase, trypsin, CMT not given. Instead values compared to controls in same setting, and controls in France.  Dakar control: U/ml  amylase 49.8±18  lipase 24.6±4.5  phospholipase 1.2±0.2  trypsin 2.0±0.4  CMT 12.6±3.6  Abidjan control: U/ml  amylase 54.2±10.3  lipase 164.4±44.6  phospholipase 4.8±1.0  trypsin 6.2±1.3  CMT 27.8±6.6 | Dakar PEM vs. Dakar control ns  PI not improved after 28 days  Abidjan PEM significantly lower phospholipase, lipase, trypsin, CMT activity vs. Abidjan controls (p<0.05)  Abidjan: placebo-lipase, trypsin, CMT, amylase, phospholipase significantly improved (p<0.05)  Amylase and lipase significantly improved treatment group vs. placebo (p<0.05) |  |  |  | Can’t determine | West Africa, latent PI involving water, electrolytes, and enzymes. PI neither aggravated by kwashiorkor nor corrected by feeding | Authors compared enzyme measurements with both controls in same area and French controls  Dakar controls significantly lower vs. French controls |
| Sauniere et al. 1986 | KWO- clinical and biological abnormalities: weight loss (not quantified by authors), edema, diarrhea, dehydration, skin discoloration, low serum protein concentration, anemia |  | 28/28 (100%) KWO clinical symptoms  (25 first admittance, 3 readmitted KWO) | SST: Pancreatic enzymes(Units/ml in 15min)  Lipase  Amylase  Phospholipase  CMT  Trypsin  Cases compared with African controls, Parisian controls, and African controls + recovered kwashiorkor | Absolute numbers not reported  Lipase, amylase, and CMT significantly higher normal Africans vs. KWO Africans  Amylase, lipase, phospholipase, CMT significantly lower KWO Africans vs. normal and recovered KWO  No significant differences normal Africans and healed KWO children |  |  |  | Not reported | PI in KWO reversible, trypsin more resistant, no relationship KWO and tropical pancreatitis | Amylase not analyzed French controls |
| Durie et al. 1985 | Patients sub-classified according degree malnutrition: ideal weight/length/age  ‘severe’: weight < 75%  ‘moderate’: 75% to 85%  ‘mild’: 85% to 95%  ‘normal’ >90% | Severely malnourished: 25/50 (50%)  moderately malnourished: 23/50 (46%)  mildly malnourished: 2/50 (4%) |  | 1. IRT values based on controls:  32.3±10.4 ng/ml  2. 3-5 day fat balance studies. Fat malabsorption if fat losses >7% in those 6 months or older, >15% in those younger than 6 months | IRT:  severe malnutrition (compared to controls): 77.4±42.0 ng/ml  (p<0.001)  moderately malnutrition: 54.2±16.1 ng/ml (p<0.02)  mild malnutrition: control levels (ns) |  | Fat malabsorption 17/43 (40%) |  | 36/50 (72%) | IRT in malnourished may be pancreatic acinar cell damage or obstructed pancreatic ducts.  IRT normal after improvement nutritional status | 13/17 (76%) steatorrhea due to non-pancreatic cause |
| Barbezat and Hansen 1968 | 1. Malnutrition  KWO: edema, skin lesions, growth retardation, and hypoalbuminemia  Marasmus and Chronic malnourished: growth retardation, absence of edema and skin lesions, wasted little or no subcutaneous fat, slight hypoalbuminemia (chronic previous KWO patients)  2. Percent expected weight (50th Boston percentilecontrol values): 94.04% SD 5.09  3. Serum albumin concentration: mean control value 3.72 gm/100ml SD 0.40 | Mean value of percent expected weight  KWO 68.40% SD 11.07  Marasmus 52.61% SD 7.32  Chronically malnourished 67.99% SD 12.71 | KWO: 14  Marasmus: 7  Chronic malnutrition: 10  Serum Albumin  KWO: 1.67 gm/100ml SD 0.47  Marasmus: 2.15 gm/100ml SD 0.40  Chronic malnutrition: 3.39 gm/100ml SD 0.43 | SST:  Analyzed enzymes amylase, lipase, trypsin, and CMT.  Values compared to controls and malnourished subgroups | No absolute values:  Amylase: lower in KWO and marasmus (p<0.01).  KWO group significantly improved after treatment (p<0.01)  Lipase: KWO significantly lower lipase levels (p< 0.01)  Trypsin: KWO lower vs. controls and recovered (p<0.02)  CMT: KWO, marasmus patients lower (p<0.01) (most affected enzyme)  Chronically malnourished less CMT than recovered KWO(p<0.02) |  |  |  | Not reported | Pancreatic enzyme output grossly deficient in KWO and marasmus. Complete restoration pancreatic function after dietary therapy |  |
| Thompson et al. 1952 | Established KWO defined as pitting edema, without obvious renal or cardiac cause, changes in hair, and subnormal weight. Other noted features were hyperpigmentation of skin, raw weeping areas, diarrhea and wasting |  | 59/59 (100%) children fulfilled the criteria for kwashiorkor  Diarrhea present in 85% | 1. Pancreatic stimulation test (PST): lipase and amylase extracted. Reference values based on control values  Amylase units/ml;  mean: 2.92 SD: 1.62  Lipase units per 0.1 ml; mean: 3.84 SD: 1.04  2. Necropsy performed on children who died: histopathology of pancreas noted | Group 1= followed up (n=40)  group 2= not followed up (n=10)  group 3= died (n=8)  group 4=not treated (n=1)  Amylase at admission  group 1: 0.40 units/ml; group 2: 0.50 units/ml; group 3: 0.53 units/ml; group 4: 0.05 units/ml  Discharge  group 1: 4.33 units/ml; group 4: 0.1 units/ml  Lipase at admission group 1: 1.0 units/0.1ml; group 2: 1.3 units/0.1ml; group 3: 0.81 units/0.1ml; group 4: 1.0 units/0.1ml  Discharge:  group 1: 3.88 units/ml; group 4: 0.9 units/0.1ml  On admission amylase and lipase significantly lower in KWO (p<0.001). Fully recovered after nutritional rehabilitation (p<0.01) |  |  | Histopathology:  2 children that died: loss of cytoplasm in acinar cells, collapse of acinar structure, and increase in fibrous tissue.  2 children who died from intercurrent infection histologically normal | 100% (58/58) | KWO children well below normal amylase and lipase, reversible with treatment | 40 /59 (68%) children who were re-evaluated after treatment |

%CoA, percent fecal fat absorption; AHAZ, adujsted height for age Z-score; CDC, Centers for Disease Control; CMT, chymotrypsin; ERCP, endoscopic retrograde cholangiopancreatography; FE, fecal elastase [FE-1 = fecal elastase-1]; EPI, exocrine pancreatic insufficiency; HZ, height Z-score; HAZ, height for age Z score; IRT, human immunoreactive trypsinogen; KWO, kwashiorkor; MKW0, marasmus kwashiorkor; MUAC, mid upper arm circumference; NO-FE, no pancreatic activity; NS, not significant; PEM, protein energy malnutrition; PI, pancreatic insufficiency/pancreatic insufficient; PS, pancreatic sufficiency; PST, pancreatic stimulation test; R-FE, residual pancreatic activity; S., serum; SAM, severe acute malnutrition; SD, standard deviation; SST, secretin stimulation test; US, ultrasound; W/H, weight/height; WZ, weight Z-score; WAZ, weight for age Z score; WHZ, weight for height Z score