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Fecal Calprotectin in Cystic Fibrosis patients during respiratory exacerbation

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Cystic Fibrosis

- The most common, life-shortening, recessive disease in Caucasians.
- Average life expectancy of 40 years. Usually due to respiratory failure.
- The CF transmembrane conductance regulator (CFTR) protein functions as a cyclic AMP-dependent chloride and a bicarbonate channel.
- Absent or defective CFTR leads to viscous luminal secretions several organs: lungs, intestines, and pancreas.
- Dysfunction in the CFTR protein in GI tract: loss of transepithelial bicarbonate secretion, resulting in thick mucus and an acidic intestinal environment.

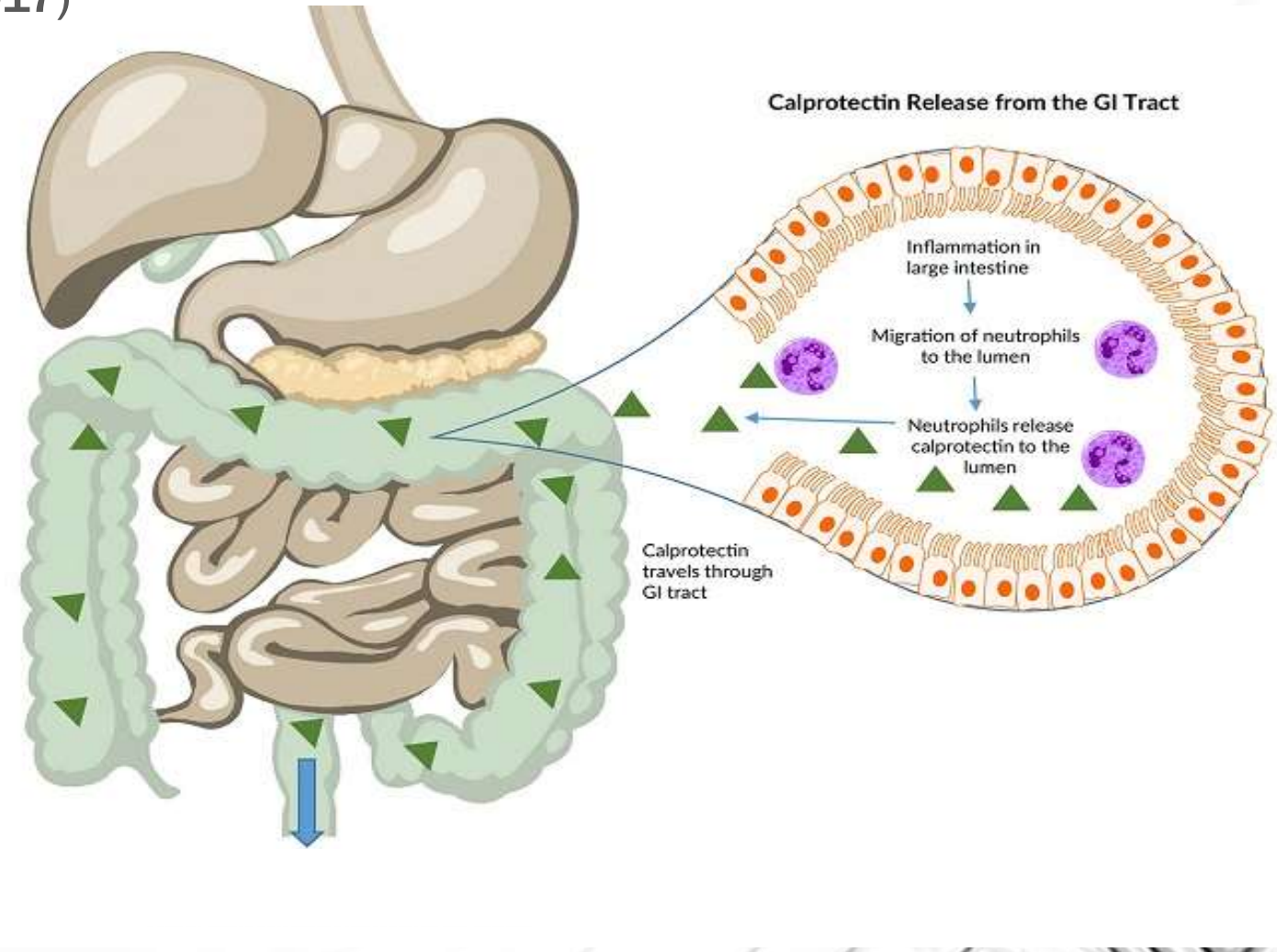
Cystic Fibrosis

- An increased risk of inflammation within the GI tract is observed.
- The patho-mechanism is not entirely understood:
  - Changes to the contents of the intestinal flora.
  - Bacterial overgrowth of the small intestine.
  - Chronic antibiotic therapy.
  - Low pH of the intestinal contents.
  - Intestinal motility disorders.
- Increased inflammatory proteins (α1-antitrypsyn, IgA, M, G, IL-8, IL-1β) in colon rinsed liquid. (Wiecek et al. 2017)

Calprotectin

- a 35kD protein composed of two monomers, S100A8 and S100A9.
- Has a regulatory role in inflammatory processes.
- Antibacterial and pro-apoptotic properties, probably by binding the ions of calcium and zinc.
- It inhibits bacterial enzymes, stimulates neutrophils and the production of IL-8.
- In the intestine, calprotectin is mainly derived from neutrophils and eosinophils.

- In inflammations of the gastrointestinal tract, the mucous permeability increases and there is an increase in the secretion of calprotectin. (Więcek et al. 2017)



Calprotectin in CF

- Fecal calprotectin in healthy children is typically elevated in infancy and early childhood. (Garg et al. 2017, Roca et al. 2017)
- An increased level is observed in IBD, food allergies, celiac disease, and infectious diseases of the gastrointestinal tract, especially of bacterial etiology.
- Fecal calprotectin levels were higher in CF patients than in healthy controls. (18 years<, PI, underweight, *P. Aeruginosa,* CFRD). (parisi et al. 2016)
- Capsule endoscopy: GI tissue inflammation mucosal ulceration, erythema, mucosal breaks as correlated with elevated fecal calprotectin levels in PI CF patients. (Werlin et al. 2010)
- Fecal calprotectin levels correlated with quality of life questionnaire scores in CF. (Campo et al.2014)

Calprotectin in CF

- Calprotectin can be measured in body fluids but is six times more concentrated in feces than in blood. (Rumman et al. 2014)
- Sputum and plasma calprotectin has been described as a biomarker of CF lung disease. (Reid et al. 2015)
- Sputum calprotectin levels has shown to decrease during treatment of an exacerbation with antibiotic. (Gray et al. 2010)
- Serum C reactive protein (CRP), amyloid A (SAA) and calprotectin levels has shown to decrease during azithromycin treatment in a CF interventional trial. (Ratjen et al. 2012)

Pilot study: Fecal Calprotectin in Cystic Fibrosis patients during respiratory exacerbation

Rational

- Inflammation exists in GI tract of CF patients.
- Antibiotic Treatment aimed at pulmonary complaints may improve inflammatory GI tract status.

Aim

- Assessing CF patients' gastrointestinal inflammatory burden (f-calprotectin) during a pulmonary exacerbation.

Method

Prospective study: evaluation of f-calprotectin levels before and after systemic antibiotic treatment during respiratory exacerbation.

Pilot study: Fecal Calprotectin in Cystic Fibrosis patients during respiratory exacerbation

- **Primary Endpoint:**
- Fecal calprotectin levels at the beginning and end of hospitalization during an acute pulmonary exacerbation.
- **Secondary Endpoints:**
- Absolute and relative change in percent predicted forced expiratory volume in 1 second (FEV1) from baseline at time of hospitalization (and relation to f-calprotectin decline).

Pilot study: Fecal Calprotectin in Cystic Fibrosis patients during respiratory exacerbation

- **Inclusion criteria**:
  CF diagnosis.
  1 year<
  Systemic antibiotic treatment due to respiratory exacerbation.
- **Exclusion criteria**:
  IBD diagnosis
  Previous antibiotic therapy 1 month prior to current treatment.
  Any GI problems 1 month prior to current treatment. (DIOS)

Results

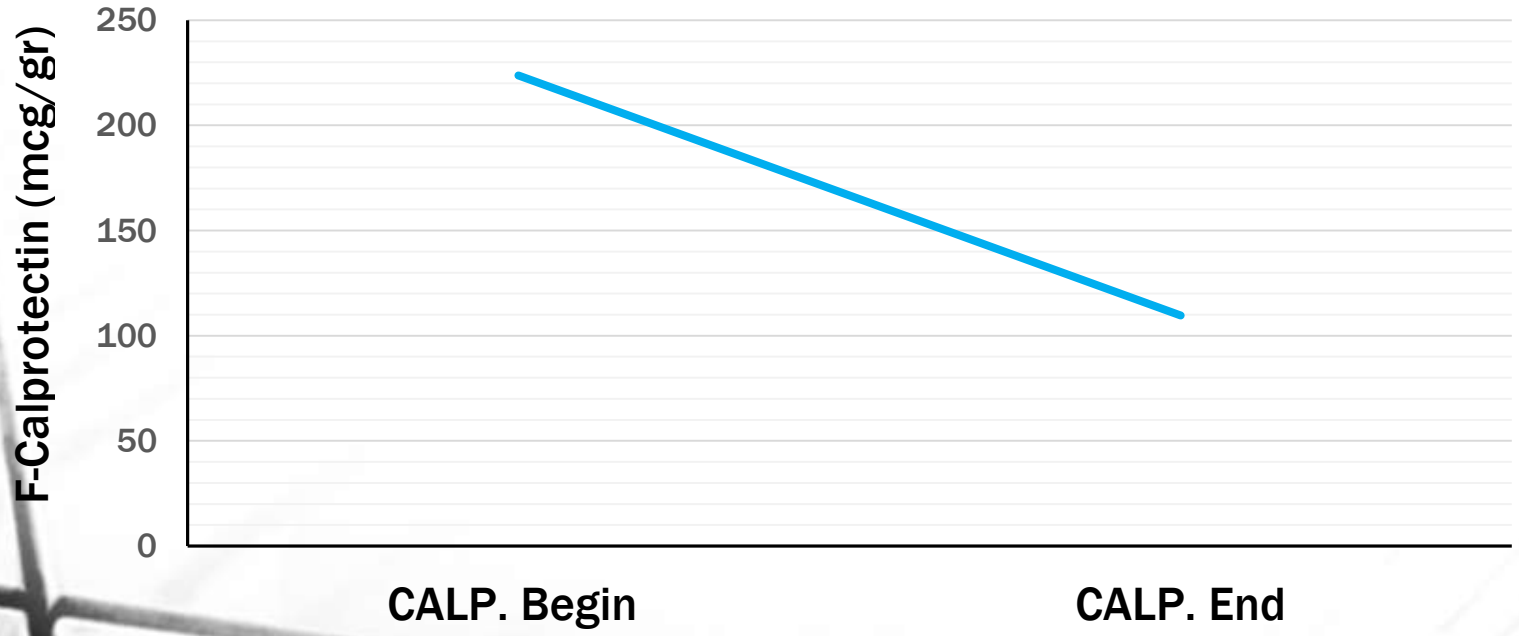
No. patients	11
age	
Mean	28.09
Minimum	6
Maximum	44

Mutation type	No. of patients	%
ΔF508/ΔF508	5	45.5
N1303K/1717+1G>A	1	9.1
N1303K/4010delTATT	1	9.1
N1303K/N1303K	1	9.1
R1158X/G85E	1	9.1
W1282X/W1282X	1	9.1
W1282X/ G542X	1	9.1
Total	11	100.0

Results

	CALP. Begin (mcg/gr)	CALP. End (mcg/gr)
Mean	223.73	109.55
Minimum	28	7
Maximum	748	486

CALP. Diff. %	
Mean	38.1



p=0.045 :Wilcoxon rank test

Results

	FEV 1 % Begin	FEV 1 % End
Mean	52.282	60.336
Minimum	22.0	24.3
Maximum	89.8	109.0

p=0.007 :Wilcoxon rank test

- No correlation was found: change in FEV1 and change in Calprotectin.

To Sum things up…

- CF is a multi organ disease.
- Inflammation of GI tissue correlates with elevated fecal calprotectin levels in CF patients.
- Systemic antibiotic treatment has shown to improve various systemic inflammatory markers. (serum and sputum calprotectin).
- Fecal calprotectin levels may be reduced as a result of systemic antibiotic treatment.

Limitations

- Small group of patients.
- Different genotype of patients. (similar phenotype).
- Different antibiotic therapy.
- Microbiome (?)

- Further work is need to be done.

Thanks

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Fecal Calprotectin and Eosinophil-derived Neurotoxin in Healthy Children Between 0 and 12 Years.

Roca M, Rodriguez Varela A, Donat E, Cano F, Hervas D, Armisen A, Vaya MJ, Sjölander A, Ribes-Koninckx C

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