Editorial

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Endocrine aspects in cystic fibrosis

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Endocrine aspects in cystic fibrosis include all of the following: carbohydrate metabolism, lipid metabolism, pubertal onset and puberty progression, growth, adult height and fertility (Table 1). Cystic fibrosis (CF) occurs with a frequency of 1:3300–1:5800 of all live births in Europe. Prenatal screening using a two tier test involving protein (immunofluorescence) and genetic tests is available in some developed countries. The prevalence of heterozygotes is estimated to be 5%. With these numbers, cystic fibrosis is the most frequently occurring metabolic disease in youths after obesity and diabetes. CF is an autosomal-recessive disorder caused by mutations of the *CFTR* gene (cystic fibrosis transmembrane regulator) on the long arm of human chromosome 7. The *CFTR* gene comprises 27 exons, and six mutations classes leading to disease manifestations have been identified. More than 1500 mutations and variants of the gene have been identified. The most frequent and clinically relevant mutation is the F508del mutation which is detected in approximately 70% of the affected patients. CFTR functions mainly as a cAMP regulated chloride channel and thus changes chloride flux in many tissues and particularly so in endocrine glands and the liver and the gut.

Clinical manifestations can be grouped according to their occurrence during the life span: intrauterine growth retardation (IUGR) and low birth weight are frequent [1]. In the neonatal period meconium ileus, prolaps of the rectum and bowel obstruction can occur. Salt loss is reported especially during the warm seasons and periods of increased sweating. This may lead to salt loss crisis, shock, tachycardia and even death. Later on leading symptoms include dystrophy, failure to thrive and crossing of the percentiles. Finally, coughing, lung disease with infections [2] and progressive respiratory difficulties ensue.

In schoolchildren and adolescents chronic lung disease, pneumonia and frequently recurring bronchitis lead to obstructive-restrictive lung disease, reduced strength and tachydyspnea. Polyposis nasi, chronic sinusitis, cholestasis, biliary cirrhosis, portal hypertension, and gall stones also accompany the progression of the disease. Endocrine sequelae include disturbance of the carbohydrate metabolism, growth and pubertal onset and progression [3]. So far, no cure for CF is available, despite the fact that chloride channel modulators and other new drugs offer promising treatment options. Organ transplantation for respiratory or liver failure and cardiovascular failure are options for some patients and gene therapy and stem cell transplantation may offer hope for a final cure. In this issue of our journal three articles are presented that relate to cystic fibrosis and endocrine and metabolic aspects. These manuscripts are devoted to the patients with CF who manage their lives under difficult conditions and also to the many people who care for patients with chronic diseases such as CF.

Terliesner et al. [4] show that in their cohort of patients with CF, cystic-fibrosis related-diabetes (CFRD) is preceded by and associated with growth failure and deteriorating lung function. It was known that disturbed glucose metabolism and overt CFRD are associated with insufficient weight gain and reduced lung function in children and adolescents with CF. Whether or not imminent CFRD is related to growth failure in children and adolescents was investigated. This report is a retrospective case control study including 32 patients with CF with or without diabetes. Standard deviation scores (SDS) of height, growth, weight, body mass index (BMI), forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) and forced expiratory flow at 75% of expired FVC (FEF75) were recorded during a rather long mean observation period of 13 years per patient. Interestingly and sadly SDS of height and weight were reduced in CF patients with diabetes compared to those without, not only at the point of diagnosis (both $p < 0.05$) but years before the evidence of diabetes. Afterwards there was a significant decline in height ($p < 0.001$) and weight ($p < 0.01$) SDS in CFRD patients and an increasing difference between the height and weight of CF patients with or without diabetes. In contrast, no significant reduction of BMI-SDS was observed in CFRD patients. All analyzed lung function parameters showed a marked decline in CFRD patients starting 1 year prior to the diagnosis of diabetes. In conclusion, growth failure, weight loss and impaired lung function are related to the development

Table 1: List of organ and system manifestations **(endocrine** problems are highlighted in bold letters) in patients with cystic fibrosis.

Skin	**Salt loss**
Lung	Chronic lung disease
Ovary, testis	**Pubertal delay, infertility**
pancreas	Exocrine insufficiency, **CF-related diabetes (CFRD)**
Gut (colon)	Pain, diarrhea, intestinal obstruction syndrome, **weight loss**
Liver, gall bladder	Fibrosis, esophagael varicosis
Heart	Congestion, heart failure
Bone	**Metabolic bone disease**
General health	**Failure to thrive**
Psychosocial	Burden of disease, anxiety, social participation

of CFRD and precede the onset of diabetes several years before the actual diagnosis of diabetes.

Chirita-Emandi and colleagues analyze bone health in 100 patients with cystic fibrosis. In a retrospective analysis, longitudinal changes in bone mineral content was studied. One hundred children (50 females) had dual X-ray absorptiometry (DXA) performed. Of these, 48 and 24 children had two to three scans, respectively, over 10 years of follow-up. DXA data were expressed as lumbar spine bone mineral content standard deviation score (LSBMCSDS) adjusted for age, gender, ethnicity and bone area. Markers of disease, anthropometry and bone biochemistry were collected retrospectively. Seventy-eight percent of the children who had baseline LSBMCSDS >– 0.5, and 35% of the children with poor baseline (LSBMCSDS <– 0.5), showed decreasing values in subsequent assessments. Importantly, lower forced expiratory volume in 1 s percent (FEV1%) low body mass index standard deviation scores (BMI SDS) and vitamin D were associated with reduction in BMC. The authors conclude that mineral content as assessed by DXA was suboptimal and decreased with time in children with CF at one center [5].

The discussion as to when and how to screen for CF-related diabetes is still ongoing. Sensitivity and specificity of cystic fibrosis-related diabetes screening methods were studied by Valérie Boudreau and colleagues [6]. New consensus guidelines will have to follow and will hopefully improve care and prognosis of patients with CF.

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