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# NUTRITIONAL STATUS OF CZECH PATIENTS WITH CYSTIC FIBROSIS: IS IT INFLUENCED BY DIABETES MELLITUS AND INSULIN THERAPY?

*ABSTRACT: Cystic fibrosis (CF) is a life-shortening autosomal recessive disease. CF manifests with chronic obstructive lung disease, exocrine pancreatic insufficiency, elevated sweat chloride concentration and in males infertility due to obstructive azoospermia. Monitoring of the nutritional status is very important, because nutritional intervention may slow the decline in pulmonary function. Impaired glucose tolerance and diabetes mellitus are frequent complications. Within the framework of CFRD screening the authors examined oral glucose tolerance test in 144 CF patients older than 10 years. In positive cases insulinopenia was assessed by i. v. GTT as a sum of insulin response in 1. and 3. mins. <1 percentile in healthy controls (<48 mIU/L). Body composition was assessed by anthropological parameters (height, weight, mid-arm circumference-SDS, 4 skinfolds). Controls with normal glucose tolerance were sex / age matched to cases. Insulinopenia was found in 31/144 CF patients. Insulinopenic patients were treated immediately by small dosage of intermediate insulin. Abnormal glucose metabolism appears to have a negative impact upon nutrition of CF patients. Early detection of insulinopenia by i. v. GTT and its early treatment improves nutritional status, stabilizes pulmonary function and improves life expectancy.*

*KEY WORDS: Nutritional status – Cystic fibrosis – Diabetes mellitus – CFRD – Impaired glucose tolerance*

## INTRODUCTION

Cystic fibrosis (CF) is a life-shortening autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. In individuals with CF the defective chloride transport leads to abnormal ion and water transport, which causes dehydratation of secretions and malfunctioning of the obstructed exocrine glands. CF manifests itself with chronic obstructive lung disease, exocrine pancreatic insufficiency and failure to thrive, elevated sweat chloride concentration and in males infertility due to obstructive azoospermia. The survival of CF patients has immensely improved throughout past decades due to new therapeutic processes, like physiotherapy, aggressive antibiotic treatment, pancreatic enzyme replacement and nutritional support (Frederiksen *et al.* 1996, Bronsveld 2000, Vávrová *et al.* 1999). Both lung function and nutritional status deteriorate with age and severity of the disease (Durie, Forstner 1999, Vávrová *et al.* 1995). Relative underweight has been shown to be a major factor adversely affecting lung function, bacterial infection and survival (Corey *et al.* 1988). Our research in Czech patients confirmed as well that nutritional intervention may slow the decline in pulmonary function (Zemková *et al.* 2002). Therefore monitoring of the nutritional status is of great importance and anthropometrics is a suitable, simple non-invasive method.

On the other hand, due to improved treatment and prolonged life expectancy of our CF patients, we observe more CF complications. One the most serious is CF related diabetes mellitus (CFRD). Etiopathogenesis of CFRD is a complex process. The primary cause is the destruction of

the islets through fibrosis of the pancreas and progressive loss of insulin secretion capacity. However, the glucose metabolism is influenced by other factors unique to CF: malabsorption, chronic and acute infection, elevated energy expenditure, liver dysfunction and glucagon deficiency etc. Chronic inflammations lead to dysregulation of immune system and probably to higher incidence of autoimmune diseases. Autoimmune mechanisms could also enforce the pathogenesis of CFRD in some cases (Moran *et al.* 1998). In older patients with CFRD, a reduced life expectancy has been established (Reisman *et al*. 1990, Koch *et al.* 2000). Unfortunately, CFRD is often late diagnosed and treated. Insulinopenia leads to protein catabolism long time before manifestation of DM with typical symptoms and deterioration of clinical status. Our aim was 1. to elaborate screening programme of CF-related diabetes to identify cases with severe insulinopenia prior to the onset of typical symptoms, and 2. to elucidate the influence of severe insulinopenia in asymptomatic CF patients on their body composition, pulmonary function, including monitoring of their changes during treatment by small dosage of intermediate insulin.

## PATIENTS AND METHODS

We currently monitor 222 CF patients aged 0.4–35.9 years (12.3±7.3).

Glucose tolerance was screened by oral glucose tolerance test in 144 patients older than 10 years without acute exacerbation and/or clinical symptoms of diabetes mellitus. In subjects with a pathological oGTT subsequently the intravenous glucose tolerance test was made to assess stimulated insulin secretion (FPIR, sum of insulin levels in the 1st and 3rd minute after i. v. glucose bolus). 1st percentile of FPIR in healthy population is 48 mIU/l. Our criterion of severe insulinopenia was FPIR≤20 mIU/l or glycaemia in 60. minute>7.8 mmol/L.

Insulinopenic patients were treated immediately by small dosage of intermediate insulin (1 daily). Self-monitoring by glucometer and diet with minimal restriction of carbohydrate were recommended.

Body composition was assessed by anthropological parameters (height, weight, mid-arm circumference, 2 skinfolds). Values were compared with the healthy population norms (Bláha *et al.* 1993) and expressed in SD score and percentiles. Pulmonary function tests are expressed in % of predicted values after Zapletal (Zapletal *et al.* 1984). $FEV_1$ (forced expiratory volume in 1st second) was selected to analysis. Controls with normal glucose tolerance (NGT) were sex/age matched to cases. Two tailed pair t-test was used for statistical analysis.

## RESULTS

Mean body height of our patients is –0.7±1 SD, body weight –0.7±0.9, mid-arm circumference –0.6±1 SD and weight/height 37.5±26 percentiles. Mean value of $FEV_1$ was 75.1±22,9 % p. v., median 77%. Nutritional status deteriorates with age (weight/height r=–0.14 p=0.03) and the severity of the disease and correlates with lung function (weight/height r=0.39 p<0.01) as shown in *Figure 1*.

Results of our screening of glucose tolerance are summarized in *Table 1*. Insulinopenia was found in 31/144 CF patients (11.1–28.5; med–16.5 years). CF in insulinopenic patients was diagnosed significantly earlier than in NGT controls (1.8±3.2 vs 3.6±3.6; p=0.04) likely due to the higher prevalence of "severe" (Class I–III) mutations (p=0.04). In controls pancreatic insufficiency appeared later. We did not find any differences in sweat chloride concentrations, occurrence of meconium ileus and chronic bacterial infection. As shown in *Table 2*, body height and weight did not differ in both groups. Mid-arm circumference in insulinopenic CF cases was significantly lower (–1.2±0.9 SD vs NGT –0.7±0.9 SD; p=0.01) and

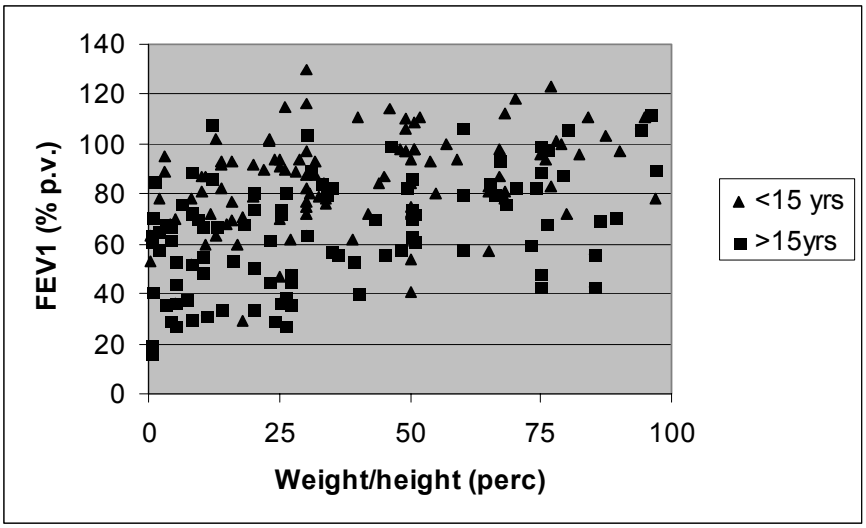


FIGURE 1. Correlation between nutritional status and lung function in Czech CF patients. Correlation coefficient r=0.39; p<0.01.

TABLE 1. Results of glucose tolerance screening in Czech CF patients older than 10 years. NGT – normal glucose tolerance according to WHO criteria IGT; impaired glucose tolerance; DM - diabetes mellitus.

| | n=144 | Prevalence % |
|---|---|---|
| NGT | 105 | 72.9 |
| IGT without insulinopenia | 8 | 5.6 |
| IGT with insulinopenia | 11 | 7.6 |
| DM | 20 | 13.9 |
| Insulinopenia (DM + IGT) | 31 | 21.5 |

TABLE 2. Comparison between insulinopenic CF patients and age/sex matched controls. I – at detection of insulinopenia (IP) II – one year after detection of IP; III – last examination after 1.1–7.9 years after detection of IP (med. 2.4 yr); Difference in comparison with values at detection significance * <0.05; ** <0.01.

| | | Insulinopenia | | Controls | | IP vs C |
|---|---|---|---|---|---|---|
| | **Parameter** | **mean** | **SD** | **mean** | **SD** | **p** |
| I | Body height (SDS) | –0.6 | 1.1 | –0.8 | 0.9 | |
| n=31 | Body weight (SDS) | –1.1 | 0.8 | –1.0 | 0.7 | |
| | MAC (SDS) | –1.2 | 0.9 | –0.7 | 0.9 | 0.01 |
| | dMAC (SDS) | –0.15 | 0.4 | 0.07 | 0.3 | 0.03 |
| | Weight/height (perc.) | 24.5 | 22.8 | 29.9 | 22.7 | |
| | $FEV_1$ (%pv) | 73.8 | 22.2 | 72.8 | 18.7 | |
| II | Body height (SDS) | –0.5 | 1.0 | –0.8 | 0.9 | |
| n=21 | Body weight (SDS) | –0.9 | 0.8 ** | –1.0 | 0.8 | |
| | MAC (SDS) | –0.9 | 1.1 ** | –0.6 | 1.0 | |
| | Weight/height (perc.) | 27.9 | 24.7 * | 33.3 | 23.0 | |
| | FEV1 (%pv) | 71.8 | 19.4 | 67.9 | 19.0 ** | |
| III | Body height (SDS) | –0.5 | 0.9 * | –0.7 | 1.0 | |
| n=23 | Body weight (SDS) | –0.9 | 0.6 ** | –1.0 | 0.8 | |
| | MAC (SDS) | –0.9 | 0.9 ** | –0.7 | 0.9 | |
| | Weight/height (perc.) | 27.2 | 23.4 | 30.0 | 23.5 | |
| | FEV1 (%pv) | 65.8 | 23.0 | 60.6 | 19.3 ** | |

worsening of the mid-arm circumference 1 year prior to the diagnosis of insulinopenia (p=0.03) was observed. During the first year of insulin treatment nutritional status has improved (p<0.01) and pulmonary function tests became stable ($FEV_1$ 73.8±22.2 vs 71.8±19.4). However, in controls the nutritional status did not change, but pulmonary function tests deteriorated (72.8±18.7 vs 67.9±18.9; p=0.005). Looking closer at body composition, skinfold thickness is reduced in most patients with CF. In both groups the median is between 10 and 25‰. The sum of 2 skinfolds (triceps, scapula) at the detection of insulinopenia was 13.8±5.7 mm vs 16.8±6.8 mm. This difference is of borderline significance (p=0.044). After insulin treatment we observed insignificant improvement in insulinopenic patients (p=0.11). Further there were no significant differences between insulinopenic and control group. During the follow-up in both groups one patient died.

## DISCUSSION

Anthropometry in clinical practice enables objective assessment of nutritional status of the patients and evaluation of the progress in therapy. Moreover, it contributes to elaboration and specification of screening and treatment procedures.

Due to improvement of therapeutic possibilities and intensification of the treatment, the nutritional and clinical status of our CF patients has been continuously improving. Comparing with the results from 1998 (Vávrová *et al.* 1999), SD score of body weight, weight to height and mid-arm circumference has significantly increased (p<0.01). Improvement of lung function makes a slower progress. The difference ($FEV_1$ 70.8±25.2 vs. 75.1±22.9) does not reach the significance level (p=0.09). CF-related diabetes mellitus (CFRD) and glucose intolerance are common CF complications in older patients, which can have an adverse

effect on further course of the disease. Our research shows that insulinopenia has an unfavourable impact on the nutritional status and body composition of CF patients even before marked clinical symptoms. Due to protein catabolism (Hardin *et al.* 1998) the deterioration concerns primarily lean body mass, in a lesser degree the fat mass.

It is still a matter of controversy whether oral antidiabetic drugs are an alternative initial treatment of CFRD. In our opinion, our results confirm the necessity of the differential treatment of impaired glucose tolerance and CFRD according to insulin levels. In patients with high insulin levels (5.6% of our patients older than 10 years) it is possible to influence the glucose tolerance by peroral anti-diabetic agents. On the other hand in patients with insulinopenia (21.5% of our patients older than 10 years) the treatment with peroral anti-diabetic agents is inappropriate. Insulin treatment leads to improvement of protein metabolism, improvement of nutritional status and stabilization of pulmonary function (Lanng *et al.* 1994). We assume that appropriately treated CFRD should not adversely affect the survival of CF patients.

## CONCLUSION

Due to improvement of therapeutic options and intensification of the treatment, the nutritional status and survival of our CF patients has improved. Abnormal glucose metabolism appears to have a negative impact upon nutrition of CF patients. Early detection of insulinopenia by i. v. GTT and its early treatment by small dosage of intermediate insulin improves nutritional status, stabilizes pulmonary function and improves life expectancy.

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## REFERENCES

BLÁHA P., LHOTSKÁ L., VIGNEROVÁ J., BOŠKOVÁ R., 1993: V. celostátní výzkum dětí a mládeže v roce 1991 (České země) – vybrané antropometrické charakteristiky. *Cs. pediatr*. 48: 621–630.

BRONSVELD I., 2000: *Modifying Factors of Cystic Fibrosis Disease*. CIP-data Koninklijke Bibliotheek, Den Haag. 224 pp.

COREY M., McLAUGHLIN F. J., WILLIAMS M., LEVISON H., 1988: A comparison of survival, growth and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J. Clin. Epidemiol*. 41: 583–591.

DURIE P. R., FORSTNER G. G., 1999: The exocrine pancreas. In: J. R.Yankaskas, M. R. Knowles (Eds.): *Cysic Fibrosis in Adults.* Pp. 261–287. Lippincott-Raven Publishers, Philadelphia.

FREDERIKSEN B., LANNG S., KOCH C., HOIBY N., 1996: Improved survival in the Danish center-treated cystic fibrosis patients: results of aggressive treatment. *Pediatr. Pulmonol*. 21: 153–158.

HARDIN D. S., LEBLANC A., LUKENBAUGH S., PARA L., SEILHEIMER D., 1998: Proteolysis associated with insulin resistance in cystic fibrosis. *Pediatrics* 101:433–437.

KOCH C., RAINISIO M., MADESANI U., HARMS H. K., HODSON M. E., MASTELLA G., MCKENZIE S., NAVARRO J., STRANDVIK B., 2000: Impact of diabetes mellitus on lung function and nutritional status in patients with cystic fibrosis. *Symposium ERCF Stockholm, June 2000, Abstract book*. Hoffmann-La Roche, Basel. Pp.10–12.

LANNG S., THORSTEINSSON B., NERUP J., KOCH C., 1994: Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. *Acta Paediatr.* 83: 849–853.

MORAN A., DOHERTY L., WANG X., THOMAS W., 1998: Abnormal glucose metabolism in cystic fibrosis. *J. Pediatr*. 133: 10–17.

REISMAN J., COREY M., CANNY G., LEVISON H., 1990: Diabetes mellitus in patients with cystic fibrosis: effect on survival. *Pediatrics* 86: 374–377.

VÁVROVÁ V., ZEMKOVÁ D., KRÁSNIČANOVÁ H. *et al.*, 1995: Factors influencing the course of cystic fibrosis in Czech patients: experience of the Prague clinic. *Pädiatrie und Pädologie*. Springer Verlag 30: 19–24.

VÁVROVÁ V., ZEMKOVÁ D., BARTOŠOVÁ J., MACEK M. Jr., 1999: Cystická fibróza. *Postgraduální medicína* 1: 24–32.

ZAPLETAL A., ŠAMÁNEK M., PAUL T., 1984: *Funkce dýchacího ústrojí u dětí a mladistvých. Metody, referenční hodnoty, indikace.* Osvěta, Martin. 456 pp.

ZEMKOVÁ D., HLADÍKOVÁ M., BARTOŠOVÁ J., ZAPLETAL A., MACEK M. Jr., VÁVROVÁ V., 2002: Factors influencing the course of cystic fibrosis in Czech patients. Abstracts of 25th European CF Conference, 20–23 June 2002 Genova, Italy. *J. of Cystic Fibrosis* 1, Suppl. 1: 154.

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