Clinical Nutrition 33 (2014) 150–155

Contents lists available at SciVerse ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Loss of fat-free mass over four years in adult cystic fibrosis is associated with high serum interleukin-6 levels but not tumour necrosis factor-alpha☆

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ARTICLE INFO

Article history:
Received 12 November 2012
Accepted 9 April 2013

Keywords:
Body composition
Cystic fibrosis
Fat-free mass
Nutritional status
Interleukin-6

SUMMARY

Background & aims: Malnutrition is associated with poorer outcome in cystic fibrosis (CF). This follow-up study aimed to document nutritional status changes, including fat-free mass (FFM), in adults with CF; and to identify predictors of FFM loss.

Methods: Fifty-eight non-transplanted CF adults (mean ± SD forced expiratory volume in one second (FEV_1) 63.7 ± 21.4%predicted; mean ± SD age 30.3 ± 7.7years at baseline) were studied at baseline and 3.6 ± 0.4 years later. Body composition was measured using dual-energy X-ray absorptiometry. At follow-up, blood was analysed for interleukin-6 and tumour necrosis factor-α (TNF-α) on three occasions over six months and averaged for each participant. Associations with annual percentage change in FFM (ann%ΔFFM), including cytokines, CF genotype and annual change in FEV_1%predicted (annΔFEV_1%), were determined.

Results: Mean FFM was 49.5 ± 8.8 kg at baseline and 49.6 ± 8.9 kg at follow-up ($p = 0.66$). Ann%ΔFFM ranged from −2.0 to +3.6%. FEV_1%predicted declined by 1.2 ± 2.4% per year. Forty percent of participants had elevated average interleukin-6 levels. Ann%ΔFFM was negatively correlated with interleukin-6 levels (rho −0.34, $p = 0.008$), but not TNF-α or annΔFEV_1%. F508DEL homozygote or heterozygote participants had greater FFM loss than those carrying no F508DEL allele ($p = 0.01$).

Conclusion: Higher serum interleukin-6 and presence of the F508DEL mutation, but not TNF-α, were associated with FFM loss in adults with CF.

1. Introduction

Lifetime, centre-based care for CF patients and high energy unrestricted fat diets have been associated historically with improved nutritional outcomes.[1] However, body composition alterations including depletion of fat-free mass (FFM) are prevalent; and these deficits are associated with more severe lung disease.[2–4] The question of whether FFM depletion is associated with greater mortality in CF has not been examined, but this has been documented in other respiratory conditions such as chronic obstructive pulmonary disease (COPD), in which FFM depletion is a better predictor of survival than body mass index (BMI) alone.[5] In previous cross-sectional studies in CF, low FFM stores were associated with high levels of systemic inflammation.[3,4] In a large baseline

☆ Conference presentations: 1. ESPEN Congress, Brussels, Belgium, 2005. King SJ, Wilson JW, Kotsimbos T, Nyulasi IB. Nutritional status and body composition are preserved in an adult cystic fibrosis population receiving specialised multidisciplinary care. *Clin Nutr* 2005: 24(4): 551. 2. North American Cystic Fibrosis Conference, Baltimore, USA, 2005. King SJ, Nyulasi IB, Kotsimbos T, Wilson JW. Predictors of loss of fat-free mass in an adult cystic fibrosis population. *Pediatr Pulmonol* 2005; Supplement 28: 347.

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http://dx.doi.org/10.1016/j.clnu.2013.04.012

List of non-standard abbreviations

Ann%ΔFFM	annual percentage change in fat-free mass
AnnΔFEV_1%	annual rate of change in FEV_1%predicted
CF	cystic fibrosis
CFRD	cystic fibrosis-related diabetes mellitus
EER	estimated energy requirements
F508DEL	delta F508 mutation for cystic fibrosis
FEV_1%predicted	forced expiratory volume in one second as a percentage of predicted
IL-6sR	interleukin-6 soluble receptor
IVAB	intravenous antibiotics
RDI	recommended daily intake
sTNF-R1	soluble TNF receptor 1
sTNF-R2	soluble TNF receptor 1

cross-sectional study of an adult CF population we identified that FFM depletion was associated with male gender and poorer pulmonary function, but low BMI had a low sensitivity for detecting FFM depletion.[6] It has been hypothesised that chronic pulmonary infection and accompanying inflammation may contribute to the development of nutritional abnormalities in CF.[3] To our knowledge, there are no published long-term studies documenting the body composition changes in an adult CF population, nor longitudinal studies examining any relationships between changes in body composition and clinical parameters.

Identification of the factors influencing the evolution of malnutrition and depleted FFM in CF is important for predicting which patients are most at risk of nutritional decline, and for developing treatment strategies. We report here the results of a follow-up to our baseline cross-sectional study in adults with CF.[6] The specific aims of the study were to document the changes in nutritional status, including FFM, over a 3–4-year period in an adult CF population; and to identify factors associated with FFM loss.

2. Methods

This study was a prospective follow-up study of nutritional indices and clinical factors hypothesised to be associated with loss of FFM in adults with CF. Eighty-six non-lung-transplanted adults with CF who were attending the Alfred Hospital Adult CF Service had participated in a baseline cross-sectional study of nutritional status, bone density, body composition and clinical factors.[6,7] A second evaluation was conducted in this population after a 3–4-year interval. We report here the results of the cohort studied at follow-up ($n = 58$) in terms of change since baseline. Inclusion and exclusion criteria for the baseline study were reported previously.[6] Baseline participants were eligible for follow-up if they were able to attend the Alfred Hospital Adult CF Service. They were excluded if they had undergone lung transplantation since baseline, were pregnant or were unable to complete the study requirements. Eligible patients were identified from attendance records and approached when attending the Service. The study was approved by the Alfred Hospital Institutional Ethics Committee. Written informed consent was obtained from each participant prior to testing.

Height was measured using a wall-mounted stadiometer with the participant dressed in light clothing without shoes. Participants underwent whole body dual-energy X-ray absorptiometry (DXA) scanning (DPX-IQ, Lunar Radiation Corporation, Madison, Wisconsin, USA, version 4.7e), as previously described.[6] All DXA scans were analysed using the manufacturer's software in "extended research analysis" mode by a single radiographer. FFM was calculated using the sum of lean tissue mass (LTM) and bone mineral content (BMC) for each participant. Body weight was calculated as the sum of LTM, BMC and fat mass. Fat-free mass index (FFMI), fat mass index (FMI) and body mass index (BMI) were calculated by dividing FFM, fat mass and weight respectively, by the square of height. *In vivo* precision measured separately in fifteen adults with CF and healthy volunteers, each scanned three times using the same scanner and procedures, showed that DXA estimations had coefficients of variation of 0.8%, 3.2% and 0.3% for FFM, fat mass and weight respectively. Change in FFM between baseline and follow-up testing was calculated, then standardised as annual percentage change in FFM (ann%ΔFFM) by dividing absolute change by the follow-up interval; then dividing by baseline FFM and multiplying by 100.

The following data were collected from medical records and at interview at each timepoint: age, pancreatic status; CF genotype; diagnosis of cystic fibrosis-related diabetes mellitus (CFRD) or liver disease, all as described previously[7] and serum albumin level (Hitachi 747 and 917 analysers; Roche Diagnostics, Mannheim, Germany). Pulmonary function (forced expiratory volume in one second as a percentage of predicted (FEV_1%)) was assessed as described previously.[7] Days of intravenous antibiotic therapy (IVAB) in the twelve months prior to follow-up testing were collected from the medical record. FEV_1% data were collected from medical records for the period between baseline and follow-up testing. The highest FEV_1% in the three months prior to each timepoint was recorded. In addition, the annual rate of change of FEV_1% between baseline and follow-up testing for each participant was calculated using a linear regression of all available test results.[8]

Physical activity was assessed at baseline and follow-up, using the Baecke Physical Activity Questionnaire,[9] as described previously.[7] Dietary intake was assessed at baseline and follow-up, using a four-day, prospective household measures food record. Average daily protein and energy intakes were estimated by a dietitian using a dietary analysis program (Foodworks, v2.10, Xyris Software Australia Pty Ltd, Brisbane, Australia). Protein intake was expressed as a percentage of the recommended daily intake for adult Australians (%RDI).[10] Energy intake was expressed as a percentage of the estimated daily energy requirements (%EER).[6]

Serum was sampled at follow-up on three occasions over a six-month period which included the follow-up DXA scan, and when clinically stable. Samples were analysed for the cytokines interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and their soluble receptors (IL-6sR, sTNF-R1 and sTNF-R2) (IL-6 and TNF-α: Quantikine High Sensitivity assays; IL-6sR, sTNF-R1 and sTNF-R2: Quantikine assays, R&D Systems, Minneapolis, MN, USA). Intra- and inter-assay coefficients of variation were 3.5–7.4% and 4.1–13.4% respectively. The average of the three timepoints for each participant for each cytokine was calculated. Median levels for the group were determined from each participant's average level. Reference ranges for each cytokine were established using data from a sample of 24 healthy adult volunteers of similar age range, whose serum was analysed concurrently. The upper limit of the reference range was taken as the 95th percentile values from the healthy volunteers' results.

Statistical analyses were performed using Stata Statistical Software (v7.0, Stata Corporation, College Station, TX, USA). Data were analysed for normality, and expressed as mean ± SD, median (interquartile range (IQR)) or proportions as appropriate. Paired *t*-tests, Wilcoxon matched-pairs sign-rank tests and McNemar's tests for paired proportions were used to compare parameters at baseline and follow-up. Unpaired *t*-tests, Mann–Whitney tests, Chi-squared and Fisher's exact tests were used for comparisons between participants. Univariate analysis using Mann–Whitney tests, Kruskal–Wallis tests, and Spearman rank correlations were used to identify clinical correlates of ann%ΔFFM, which was non-normally