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Apolipoprotein E polymorphism and vitamin K status in cystic fibrosis patients not supplemented with vitamin K

P. KRZYŻANOWSKA-JANKOWSKA[1], D. WALKOWIAK[2], S. DRZYMAŁA-CZYŻ[3], N. ROHOVYK[4], L. BOBER[5], J. WALKOWIAK[1]

[1]Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences, Poznań, Poland
[2]Department of Organization and Management in Health Care, Poznan University of Medical Sciences, Poznań, Poland
[3]Department of Bromatology, Poznan University of Medical Sciences, Poznań, Poland
[4]Department of Pediatrics and Neonatology FPGE, Danylo Halytsky National Medical University, Lviv, Ukraine
[5]Cystic Fibrosis Centre, Western Ukrainian Specialized Children's Medical Centre, Lviv, Ukraine

Abstract. – OBJECTIVE: *ApoE* alleles have been shown to significantly correlate with vitamin K status, however, data concerning this phenomenon in cystic fibrosis (CF) are scarce. This study aimed to investigate the effect of *ApoE* polymorphism on vitamin K status in a unique group of CF patients who had never received vitamin K supplementation.

PATIENTS AND METHODS: The study group consisted of 93 CF patients aged from 3 months to 32 years. Vitamin K status was assessed by the concentration of prothrombin induced by vitamin K absence (PIVKA-II) and the percentage of undercarboxylated osteocalcin (u-OC). The clinical status was evaluated in all patients.

RESULTS: Fifty-four (65.1%) out of 83 patients had a pathological PIVKA-II concentration (≥2 ng/ml) and an abnormal percentage of u-OC (≥20%). There were no differences in the clinical parameters, including PIVKA-II concentration (*p*=0.7752) and u-OC percentage (*p*=0.8395), between patients with genotypes *ApoE2/3*, *ApoE3/3* and *ApoE3/4*. Moreover, the frequency of vitamin K deficiency did not significantly differ in CF patients with *ApoE2/3*, *ApoE3/3* and *ApoE3/4* genotypes (66.7 *vs.* 69.9 *vs.* 80%, *p*=0.8411; 87.5 *vs.* 89.6 *vs.* 100%, *p*=1.000, respectively).

CONCLUSIONS: The presence of the *ApoE4* allele does not influence the vitamin K status in CF patients who have never received vitamin K supplementation.

Key Words:
Prothrombin induced by vitamin K absence-II, Undercarboxylated osteocalcin, Restriction fragments length polymorphism, Gastrointestinal diseases, Child, Adolescent, Adults.

Abbreviations

CF: cystic fibrosis, apoE: apolipoprotein E, PIVKA-II: prothrombin induced by vitamin K absence-II, u-OC: undercarboxylated osteocalcin, c-OC: carboxylated osteocalcin, HBC: hydroxyapatite binding capacity of osteocalcin, Gla: γ-carboxyglutamate proteins, $FEV_{1:}$ forced expiratory volume in 1 second, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, CFTR: cystic fibrosis transmembrane conductance regulator, PI/PS: pancreatic insufficiency/pancreatic sufficiency, DMSO: dimethyl sulfoxide, RFLP: restriction fragments length polymorphism, *Z-score*: standardised value of body weight or height.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease, caused by cystic fibrosis transmembrane conductance regulator *(CFTR)* gene mutations, which lead to disorders in the ion transport of the apical surface of epithelial cells of the respiratory tract, pancreas, intestines, and sweat glands[1]. Consequently, pancreatic exocrine insufficiency occurring in CF patients[2] results in fat malabsorption and leads to fat-soluble vitamin deficiency (including vitamin K)[1,3]. CF patients are at risk of vitamin K deficiency also due to liver disease (causing a reduction of the bile acid pool) and frequent antibiotic therapies which may result in microbiota changes. Moreover, the deficiency often occurs despite supplementation[2-6]. Vitamin K is a cofactor of protein carboxylation, such as

Corresponding Author: Patrycja Krzyżanowska-Jankowska, MD;
e-mail: pkrzyzanowska@ump.edu.pl

prothrombin, osteocalcin, matrix Gla-protein, in which glutamic acid residues are transformed into γ-carboxyglutamic acid residues, having the calcium-binding capacity necessary for the proper function of these proteins[7-9].

It has been suggested that the vitamin K status may depend on the apolipoprotein E genotype (*ApoE*) in haemodialysis patients[10]. *ApoE* plays an important role in lipid metabolism, and its different forms were suggested to significantly correlate with serum vitamin K concentrations[10]. *ApoE* constitutes three alleles: *ApoE*2 (rs7412-T, rs429358-T), *ApoE*3 (rs7412-C, rs429358-T) and *ApoE*4 (rs7412-C, rs429358-C), differing in the amino acid composition at positions 112 and 158, which result in structural and functional differences with physiological consequences. The *ApoE4* allele was suggested to be associated with a higher rate of triglycerides and vitamin K clearance, thus, could potentially predispose to vitamin K deficiency in overall healthy subjects[11]. However, there are only two studies concerning this phenomenon in CF patients. The study published by Mosler et al[12] comprised a relatively small group of patients (n=47) and showed no significant differences in vitamin K between CF patients with genotypes *ApoE*2/3, *ApoE*3/3, *ApoE*3/4, and *ApoE*4/4. Previously, we reported that CF patients receiving vitamin K supplementation and carrying the *ApoE*4 allele had better body resources compared to those without *ApoE*4 allele[13].

The present study aimed to investigate the effect of *ApoE* polymorphism on vitamin K status in a unique group of CF patients who had never received vitamin K supplementation.

Patients and Methods

Patients

The study group consisted of 93 CF patients aged from 3 months to 32 years, 40 (43.0%) females and 53 (57.0%) males, not receiving vitamin K. Eighty-eight CF patients came from a centre in West Ukraine (Lviv) and the remaining subjects were from Poland (Rabka, Poznań). The inclusion criteria comprised CF diagnosed according to European Guidelines[14]. The exclusion criteria were defined as serious medical conditions concerning poor nutritional status according to ESPEN-ESPGHAN-ECFS Guidelines[15] and the end-stage pulmonary disease and FEV_1<20%.

Nutritional status (standardized body height and weight) and clinical expression of disease (lung function: spirometry, exocrine pancreatic function), faecal elastase-1[16,17] and biochemical markers of liver function (ALT, AST, GGT), *Pseudomonas aeruginosa* colonization were assessed in all CF patients. *P. aeruginosa* colonization was referred to as an isolation of the bacteria from the sputum at least once within six months before the study. Additionally, information about coexisting diseases (diabetes, liver cirrhosis) were collected. Biochemical parameters were measured at the time of blood sample collection. The clinical characteristics of the study subjects are shown in Table I.

Eighty-five (91.4%) participants were pancreatic insufficient. *P. aeruginosa* colonization was found in 72 (77.4%) CF patients, with liver cirrhosis and diabetes in 6 (6.5%) and 1 (1.1%) CF subjects, respectively.

The *CFTR* genotypes in CF participants were as follows: F508del/F508del (n=31), F508del/- (n=13), F508del/2184insA (n=11), F508del/N1303K (n=7), F508del/G542X (n=4), F508del/1898+1G>A (n=4), F508del/3849+10kbC>T (n=3), F508del/CFTRdele2,3(21kb) (n=3), F508del/W1282X (n=2), F508del/185+1G>T (n=1), F508del/2143delT (n=1), F508del/621-1G>T (n=1), F508del/R347H (n=1), F508del/R553X (n=1), G542x/N1303K (n=1), N1303K/2183AA-G (n=1), R347P/R347P (n=1), 2184insA/2184insA (n=1), 2184insA/3849+10kbC>T (n=1), 2184insA/N1303K (n=1), 3272-11A>G/3272-11A>G (n=1), 621-1G>T/3849+10kbC>T (n=1), 2184insA/-(n=2).

Table I. Clinical characteristics of CF patients.

Clinical parameters	Median (1st-3rd quartile)
Age [years]	8.3 (5.1-13.5)
Body weight (*Z-score*)	-1.12 (-1.59-0.74)
Body height (*Z-score*)	-1.01 (-1.85-0.29)
FEV_1 [%][1]	77.0 (59.0-90.0)
GGT [U/L]	14.9 (13.0-17.0)
AST [U/L]	32.0 (24.0-40.0)
ALT [U/L]	23.0 (18.0-35.0)

Clinical parameters were assessed for all CF patients (n=93). *Z-score*: standardised value of body weight or height, FEV_1: forced expiratory volume in 1 second, GGT: gamma-glutamyl transferase, AST: aspartate aminotransferase, ALT: alanine aminotransferase. [1]FEV_1 was assessed in 69 patients. The age of the participants (below six years old) determined the possibility of performing the test.

Vitamin K Status

Vitamin K status was assessed by prothrombin induced by vitamin K absence-II (PIVKA-II) concentration and percentage of undercarboxylated osteocalcin (u-OC) (percentage u-OC was calculated based on u-OC and c-OC concentrations) as described in detail previously[5,6,18]. PIVKA-II levels were estimated in 93 patients and the u-OC percentage in 83 subjects.

Apolipoprotein E Genotyping

DNA was isolated from whole blood (Blood Mini A&A Biotechnology, Gdynia, Poland). All subsequent reactions were performed with ~100 ng of genomic DNA and 1 unit of Taq DNA Polymerase (Biotools, Madrid, Spain) in a volume of 25 µl in a MasterMix containing: 1×Taq DNA Polymerase Buffer, 0.1 mM dNTPs, 1×$MgCl_2$ buffer, 10% dimethyl sulfoxide (DMSO) and 0.1 mM of each primer (forward primer 5′-TAAGCTTGGCACGGCT GTCCAAGGA-3′ and reverse primer 5′-ACAGAATTCGCCCCG-GCCTGGTACAC-3′). The validated PCR cycling conditions were as follows: initial denaturation at 94°C for 3 min, followed by 40 cycles of 94°C for 30 s, 72°C for 30 s (decreasing 0.4°C in each cycle) and 72°C for 90 s, with a final extension at 72°C for 7 min. Amplification was performed on a CFX96 Real Time-PCR Detection System (Bio-Rad, Hercules, CA, USA). The PCR product of 244 bp was subjected to a restriction fragments length polymorphism (RFLP) procedure using the Hha1 restriction enzyme incubated at 37°C overnight. RFLP products were electrophoresed at 110 V on a 3.5% agarose gel stained with ethidium bromide in 1×TBE buffer and visualised using a UV transilluminator.

Statistical Analysis

PIVKA-II concentrations and u-OC percentages were presented as medians and interquartile ranges. For the purpose of the present study, CF patients with *ApoE*3/3, *ApoE*3/4, and *ApoE*2/3 genotypes were included in the analysis, with differences in PIVKA-II concentrations and u-OC percentages between genotypes assessed using the Kruskal Wallis test. The scarce frequency of vitamin K deficiency according to the various genotypes was compared using the Fisher-Freeman-Halton test. Statistical analysis was performed separately for CF patients who had only PIVKA-II concentration (n=83) assessed and for those with PIVKA-II levels and u-OC percentages (n=74).

The level of significance was set at $p<0.05$. Statistical analyses were performed using StatSoft Inc (2014) STATISTICA (Data Analysis Software System, version 12, Tulsa, OK, USA).

Ethical Considerations

The study was conducted in accordance with the revised Declaration of Helsinki. Informed written consent was obtained from adult patients, patients who were 16 years or over, or the patients' parents for those younger than 16. The study was approved by the Bioethical Committee at Poznań University of Medical Sciences (decision No. 535/2014).

Results

Median concentrations of prothrombin induced by vitamin K absence-II (PIVKA-II) and percentages of undercarboxylated osteocalcin (u-OC) in CF patients were 3.4 ng/ml (1^{st}-3^{rd} quartile: 1.8-7.0 ng/ml) and 76.7% (1^{st}-3^{rd} quartile: 54.9-84.1%), respectively. The pathological PIVKA-II concentration (≥2 ng/ml) and abnormal u-OC percentage (≥20%) were found in 54 (65.1%) from 83 patients.

Regarding *ApoE* genotype, there were 73 (78.5%), 10 (10.8%), 9 (9.7%) and 1 (1.1%) CF patients with *ApoE*3/3, *ApoE*3/4, *ApoE*2/3 and *ApoE*4/4 genotypes, respectively, with no *ApoE*2/2 and *ApoE*2/4 genotypes. There were no differences in the clinical parameters, including PIVKA-II concentrations (p=0.7752) and u-OC percentages (p=0.8395), between CF patients with genotypes *ApoE*2/3, *ApoE*3/3 and *ApoE*3/4. Moreover, the frequency of vitamin K deficiency did not significantly differ in CF patients with *ApoE*2/3, *ApoE*3/3 and *ApoE*3/4 genotypes (66.7 *vs.* 69.9 *vs.* 80%, p=0.8411; 87.5 *vs.* 89.6 *vs.* 100%, p=1.000, respectively) (Table II and III).

Discussion

This is the first study assessing the influence of *ApoE* genotypes on vitamin K status in a unique group of CF patients who had never received vitamin K supplementation and is a continuation of a previous analysis of CF patients supplemented with vitamin K. Individuals carrying *ApoE*3/4 and receiving the same dose of vitamin K had significantly lower PIVKA-II concentrations and less frequently, vitamin K deficiency than those

Table II. Clinical parameters in CF patients with *ApoE2/3*, *ApoE3/3* and *ApoE3/4* genotypes.

Clinical parameters median (1st-3rd quartile)		*ApoE2/3* (n = 9)	*ApoE3/3* (n = 73)	*ApoE3/4* (n = 10)	*p*
Gender	F	1 (11.1)	31 (42.5)	8 (80.0)	0.0095
	M	8 (88.9)	42 (57.5)	2 (20.0)	
Pancreatic insufficiency	Yes	8 (88.9)	66 (90.4)	10 (100.0)	0.6604
	No	1 (11.1)	7 (9.6)	0 (0)	
Age [years]		7.37 (1.15-11.44)	8.85 (5.58-13.69)	7.40 (4.43-11.31)	0.4386
Body weight (*Z-score*)		-1.31 (-1.62-0.29)	-1.11 (-1.54-0.68)	-1.26 (-1.64-1.03)	0.3473
Body height (*Z-score*)		-0.80 (-1.64-1.00)	-0.95 (-1.78-0.17)	-1.40 (-1.71-1.12)	0.3323
FEV_1 [%]		53.3 (46.6-75.3)	77.0 (60.2-91.3)	75.2 (71.0-84.5)	0.3726
ALT [U/l]		28 (19-65)	23 (18-32)	31 (20-45)	0.3090
AST [U/l]		40 (25-57)	32 (24-37)	31 (25-55)	0.4810
GGT [U/l]		15 (13-15)	15 (13-17)	15 (13-18)	0.7953
PIVKA-II [ng/ml]		2.7 (1.6-3.8)	3.4 (1.8-7.3)	3.50 (2.10-6.75)	0.7752
PIVKA-II	< 2	3 (33.3)	22 (30.1)	2 (20.0)	0.8411
	≥ 2	6 (66.7)	51 (69.9)	8 (80.0)	

Z-score: standardised value of body weight or height, FEV_1: forced expiratory volume in 1 second, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, PIVKA-II: prothrombin induced by vitamin K absence-II.

with *ApoE*3/3[13]. In the present study, PIVKA-II concentrations and u-OC percentages did not significantly differ in CF patients with *ApoE*2/3, *ApoE*3/3 and *ApoE*3/4 genotypes. Moreover, vitamin K deficiency occurred with a similar frequency in CF patients with *ApoE*2/3, *ApoE*3/3 and *ApoE*3/4 genotypes.

There are varied opinions regarding the potential influence of the particular *ApoE* genotype on vitamin K status in different populations[19-22], with a lack of reliable information regarding this phenomenon in CF patients[12]. Yan et al[19] assessed the influence of *ApoE* genotypes on vitamin K status in healthy subjects aged 60-83 years, reporting higher vitamin K1 concentrations (p=0.02) and lower u-OC percentages (p=0.01) in subjects with *ApoE*3/4 and *ApoE*4/4 genotypes compared to those with *ApoE*2/3 or *ApoE*3/3, similar to that observed in CF patients in our recent study. Individuals carrying *ApoE*3/4 and receiving the

Table III. Clinical parameters in CF patients with *ApoE2/3*, *ApoE3/3* and *Apo3/4* genotypes.

Clinical parameters median (1st-3rd quartile)		*ApoE2/3* (n = 8)	*ApoE3/3* (n = 67)	*ApoE3/4* (n = 7)	*p*
Gender	F	1 (12.5)	29 (43.3)	6 (85.7)	0.0148
	M	7 (87.5)	38 (56.7)	1(14.3)	
Pancreatic insufficiency	Yes	7 (87.5)	61 (91.0)	7 (100.0)	0.7712
	No	1 (12.5)	6 (9.0)	0 (0)	
Age [years]		7.84 (4.04-12.20)	9.04 (5.86-13.61)	7.24 (4.65-11.92)	0.7145
Body weight (*Z-score*)		-1.44 (-1.70-0.72)	-1.08 (-1.45-0.64)	-1.08 (-1.54-0.96)	0.5395
Body height (*Z-score*)		-1.14 (-1.89-0.44)	-0.92 (-1.81-0.17)	-1.53 (-1.70-1.19)	0.4559
FEV1 [%]		53.3 (46.6-75.3)	77.0 (59.3-90.3)	77.0 (68.5-79.5)	0.4232
ALT [U/l]		25 (19-50)	23 (18-33)	21 (19-36)	0.9135
AST [U/l]		36 (24-47)	33 (24-38)	26 (24-31)	0.5001
GGT [U/l]		14 (13-16)	15 (13-18)	14 (13-15)	0.7493
PIVKA-II [ng/ml]		3.15 (1.55-4.60)	3.70 (1.80-7.75)	3.50 (1.65-4.75)	0.5713
PIVKA-II	< 2	3 (37.5)	20 (29.9)	2 (28.6)	0.8991
	≥ 2	5 (62.5)	47 (70.1)	5 (71.4)	
u-OC [%]		65.0 (51.8-79.4)	76.7 (53.9-84.1)	80.3 (67.6-81.9)	0.8395
u-OC	< 20%	1 (12.5)	7 (10.4)	0 (0)	1.0000
	≥ 20%	7 (87.5)	60 (89.6)	7 (100.0)	

Z-score: standardised value of body weight or height, FEV_1: forced expiratory volume in 1 second, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, PIVKA-II: prothrombin induced by vitamin K absence-II, u-OC: undercarboxylated osteocalcin.

same dose of vitamin K had significantly lower PIVKA-II concentrations and less frequently, vitamin K deficiency than those with *ApoE*3/3[13]. By contrast, Holden et al[21] suggested that higher PIVKA-II concentrations were associated with the *ApoE*4 allele (r=0.23, p=0.021) in patients with 3 to 5 stage chronic kidney disease and moderate malnutrition. However, they did not find a significant relationship between u-OC percentage and *ApoE*4 allele in their study group[21]. Pilkey et al[20] reported that the *ApoE*4 allele was associated with poorer vitamin K status in 142 non-CF patients with chronic kidney disease, as evidenced by a significantly higher percentage of u-OC (60.1±29.4% *vs*. 47.8±24.4%, p=0.035), while Crăciun et al[22] described *ApoE*2 but not *ApoE*4 allele as a risk factor for developing vitamin K deficiency in healthy newborns, children (aged 4-48 months) and young adults (aged 20-23 years). The authors documented that the *ApoE* genotype was a major determinant of unusual metabolic products of γ-carboxyglutamate proteins (Gla) excreted in urine[22], finding that individuals with *ApoE*2 alleles (*ApoE*2/2, *ApoE*2/3, *ApoE*2/4 genotypes) had significantly lower urinary Gla extraction, thus poorer vitamin K status (median, min-max Gla/creatinine: 10.5, 8.3-21.4 mg/g *vs.* 19.6, 13.3-29.2 mg/g, p<0.001).

As mentioned earlier, data concerning the impact of different *ApoE* genotypes on vitamin K status in CF subjects is very scarce, limited to a small group of patients studied by Mosler et al[12] and to our recent study[13]. Mosler et al[12] assessed the potential impact of *ApoE* genotypes on vitamin K status measured by the hydroxyapatite binding capacity of osteocalcin (HBC) in CF patients (n=32) and healthy controls (n=18) not receiving vitamin K. They did not find significant differences between individuals with the genotypes *ApoE*2/3, *ApoE*3/3, *ApoE*3/4 and *ApoE*4/4[12], but the small sample size was a confounding factor. However, we documented that in CF patients with one *ApoE*4 allele receiving vitamin K supplementation, vitamin K status assessed by PIVKA-II concentration, not the u-OC percentage, was better, and vitamin K deficiency was less frequent. Our findings suggested that CF subjects with the genotype *ApoE*3/4 better responded to vitamin K supplementation than those with *ApoE*3/3[13]. In the present study, we did not find any difference in vitamin K status in CF patients without vitamin K supplementation. However, the ten and nine subjects with *ApoE*3/4 and *ApoE*2/3 genotype respectively qualified for the present study do not constitute a sufficiently comparative group to those with genotype *ApoE*3/3. Although we included a significantly larger number of patients than Mosler et al[12], the sample size is still a major limitation. It would be also warranted to include direct assessment of vitamin K status and future investigations comprising larger cohorts which would help to assess the effects of rare variants.

Conclusions

The presence of the *ApoE*4 allele does not influence the vitamin K status in CF patients who have never received vitamin K supplementation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

PKJ designed the study, performed apolipoprotein E genotyping and the statistical analysis, analysed and interpreted data, and drafted the manuscript. DW, SDC, NR, LB provided the data and revised the manuscript. JW designed the study, coordinated data acquisition, analysed and interpreted data, drafted and revised the manuscript. All authors read and approved the final manuscript.

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