

Dehydroepiandrosterone sulfate indicates decreased sulfation capacity and impaired quality of life in patients with primary sclerosing cholangitis

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KEY WORDS

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ABSTRACT

INTRODUCTION Impaired elimination of toxic compounds via inadequate sulfation may contribute to the pathogenesis of primary sclerosing cholangitis (PSC). Dehydroepiandrosterone (DHEA), which is metabolized into its sulfated form (DHEA-S) in the liver, has been linked with health-related quality of life (HRQoL) in various conditions.

OBJECTIVES We aimed to assess the sulfation capacity of the liver in PSC using DHEA-S as a surrogate marker.

PATIENTS AND METHODS We assessed serum levels of DHEA-S in 233 patients with PSC and in 201 patients with other liver conditions serving as controls. We also evaluated the effect of low levels of DHEA-S on the course of PSC and HRQoL assessed using the 36-Item Short Form Health Survey (SF-36) and the PBC-40.

RESULTS The proportion of patients with low DHEA-S in the PSC group was 7-fold higher than in the control group (21% vs 3%; $P < 0.001$). Patients with decreased levels of DHEA-S were younger at the time of PSC diagnosis (median age, 23 vs 29 years; $P = 0.007$) and presented with lower HRQoL scores, particularly regarding the physical domains of the SF-36. Patients with low DHEA-S also complained of more severe fatigue (31 vs 23; $P = 0.006$) assessed with the PBC-40.

CONCLUSIONS Our findings support the role of impaired liver sulfation capacity in the development of PSC. Low levels of DHEA-S are associated with increased fatigue, a devastating symptom significantly affecting HRQoL. Thus, the effects of DHEA administration on chronic fatigue and other measures of HRQoL in patients with PSC warrant further attention.

INTRODUCTION Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease that affects both the small and large bile ducts.¹ Its etiology is most likely multifactorial, with contributing autoimmune, inflammatory, genetic, and possibly infective factors.² Progressive biliary tree damage leads to persistent cholestasis, episodes of cholangitis, and sepsis.³ Frequently, PSC is associated with an increased risk of

cholangiocarcinoma, which may occur in 10% to 12% of patients.^{3,4} Primary sclerosing cholangitis coexists with inflammatory bowel diseases, most frequently with ulcerative colitis, which is present in approximately 70% of patients.⁴ Individuals with PSC-related ulcerative colitis often demonstrate a right-to-left gradient of colonic inflammation, rectal sparing, and backwash ileitis.⁴ This pattern of inflammation

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WHAT'S NEW?

Primary sclerosing cholangitis is a chronic liver disease etiology of which is not fully understood yet. Our results suggest that impaired detoxifying processes, such as sulfation, may contribute to the development of this condition. Patients with primary sclerosing cholangitis and low levels of dehydroepiandrosterone sulfate, a product of sulfation of this steroid hormone precursor in the liver, experience worse quality of life, including chronic fatigue. Thus, treatment with dehydroepiandrosterone sulfate should be considered to improve patient well-being.

is significantly different from that in patients with ulcerative colitis alone.⁵ In particular, pronounced inflammation of the right colon is of interest, and led to the hypothesis that this part of the colon could be more exposed to potential toxins derived from bile, frequently called the “toxic bile hypothesis.”⁶ The accumulation of toxic biliary compounds in the liver results in progressive tissue damage.⁷ In response, several defense mechanisms are induced to counteract liver injury.² These include marked changes in the equilibrium of hepatobiliary transporters, downregulation of uptake systems, and activation of enzymes catalyzing detoxification processes.⁸⁻¹⁰ In our earlier series of experiments, we showed that in patients with PSC, the activation of the pregnane X receptor, a nuclear orphan receptor responsible for orchestrating hepatoprotective mechanisms, is not (as seen in other cholestatic conditions, eg, primary biliary cholangitis [PBC]) associated with downstream upregulation of sulfotransferase 2A1 (SULT2A1), a key enzyme responsible for the sulfation of toxic bile acids, such as lithocholic acid or toxic xenobiotics.^{2,11} We also showed that the concentrations of plasma lithocholic acid sulfate were significantly reduced in patients with PSC compared with those with PBC and healthy controls.¹² SULT2A1 is also a key enzyme responsible for the sulfation of dehydroepiandrosterone (DHEA).¹³ To further investigate our hypothesis on sulfation being impaired in PSC, we analyzed the serum concentrations of DHEA sulfate (DHEA-S) in a large cohort of patients with PSC and controls suffering from other chronic liver conditions such as non-alcoholic fatty liver disease (NAFLD) or chronic hepatitis C virus (HCV) infection. We assumed that if impaired sulfation does indeed contribute to the development of PSC, we would observe a decreased concentration of DHEA-S in the sera of these patients compared with NAFLD/HCV controls. Thus, we used DHEA-S as a surrogate marker of the sulfation capacity of the liver as the liver is a key organ involved in the sulfation of both bile acids and DHEA.¹⁴ DHEA is a precursor of endogenous steroid hormone produced in the adrenal glands that has a variety of biological effects.¹⁵ Its production and serum concentration decrease with age, and its supplementation has been found to be beneficial in preventing osteoporosis, improving various aspects of well-being,

sexual functioning, and depression.¹⁵ In view of these findings, we also examined the potential effect of DHEA-S on health-related quality of life (HRQoL) in patients with PSC.

PATIENTS AND METHODS **Study groups** A total of 434 noncirrhotic patients (277 men; median age, 38 years) with chronic liver diseases treated in 2 medical centers (Warsaw and Szczecin, Poland) were consecutively enrolled. The study group included 233 patients with PSC (160 men; median age, 32 years), and 201 controls (117 men; median age, 47 years) including patients with HCV infection ($n = 98$) and NAFLD ($n = 103$). We also included 59 healthy volunteers without liver disease (22 men; median age, 53 years) as healthy controls. The diagnosis of PSC was established using the typical findings based on magnetic resonance cholangiography or endoscopic retrograde cholangiopancreatography and biochemical abnormalities according to the guidelines of the European Association for the Study of Liver Diseases.¹⁶ The diagnosis of NAFLD was established in patients with liver steatosis, evaluated using abdomen ultrasound (Aixplorer, SuperSonic Imagine, Aix-en-Provence, France) and confirmed via the controlled attenuation parameter (FibroScan system, Echosens, Paris, France)¹⁷ after excluding other causes of liver disease. Chronic HCV infection was confirmed by the presence of serum anti-hepatitis C antibodies and HCV viremia. The included participants were not diagnosed with primary or secondary adrenal gland insufficiency and were not receiving medications that could impair adrenal production of DHEA (including glucocorticoids).

Laboratory measurements The clinical variables and fasting blood samples for the analysis of liver biochemistry and DHEA-S were obtained from the patients and healthy subjects at the same appointment. The serum DHEA-S concentrations were determined by electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics, Mannheim, Germany). The obtained DHEA-S concentrations were evaluated as normal or decreased according to the manufacturer's instructions after adjustment for the patient's gender and age.

Health-related quality of life We applied 2 questionnaires to assess the relationship between the levels of DHEAs and HRQoL in patients with PSC: the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and the PBC-40.

The SF-36 is a well-validated, universally used generic questionnaire.¹⁸ It contains 36 items divided into 8 domains of physical and mental health. Scores can be obtained for each scale or aggregated into 2 summary scores, that is, a mental component summary score and a physical component summary score. The scale scores ranged between 0 and 100, with a higher score indicating better HRQoL. A license was obtained for the use

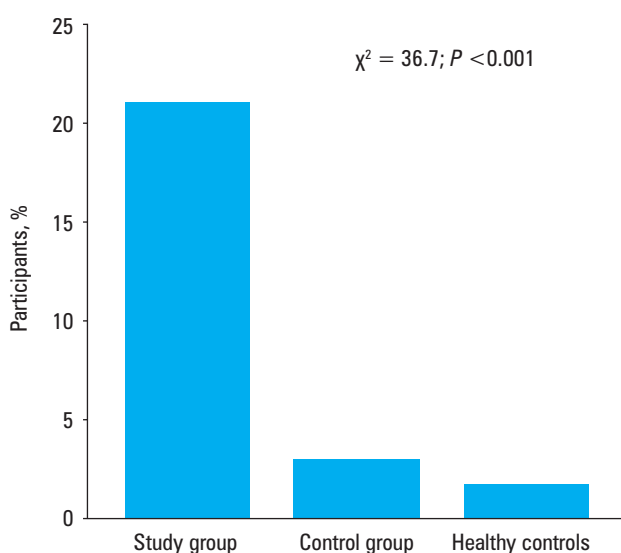
TABLE 1 Clinical and demographic characteristics of the study groups

Variable	Study group (n = 233)	Control group (n = 201)	Healthy controls (n = 59)
Age at survey, y	32 (17–71)	47 (19–83)	53 (28–81)
Age at diagnosis, y	29 (9–70)	47 (19–83)	NA
Gender, n (%)	Male	160 (69)	117 (58)
	Female	73 (31)	84 (42)
ALP, IU/l (reference <120 IU/l)	229 (5–1515)	72 (32–177)	61 (36–122)
GGT, IU/l (reference <42 IU/l)	195 (7–1515)	41 (6–464)	17 (4–264)
Bilirubin, mg/dl (reference <1.0 mg/dl)	0.7 (0.2–28)	0.5 (0.1–11)	0.4 (0.1–1.6)
ALT, IU/l (reference <30 IU/l)	71 (8–973)	35 (6–570)	15 (9–40)
AST, IU/l (reference <30 IU/l)	48 (12–831)	29 (12–178)	18 (12–47)
Albumin, g/dl (reference, 3.8–5.4 g/dl)	4.5 (2.8–5.8)	4.6 (3.8–5.7)	4.8 (4.1–7.6)

Data are presented as median (interquartile range) unless otherwise indicated.

SI conversion factors: to convert ALP, ALT, AST, GGT to $\mu\text{kat/l}$, multiply by 0.0167; bilirubin to $\mu\text{mol/l}$, by 17.104; albumin to g/l, by 10.0.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyltransferase; NA, not applicable

**FIGURE 1** Proportion of decreased dehydroepiandrosterone sulfate in the study groups

of the SF-36 v.1 questionnaire in this study (license number QM044529).

The PBC-40 was designed to evaluate the HRQoL in patients with PBC,¹⁹ but its usefulness has also been confirmed in patients with PSC.²⁰ It contains 40 questions covering the following domains: fatigue, cognitive, social-emotional, itch, and other symptoms. Higher scores indicate poorer HRQoL.

Statistical analysis Descriptive statistical methods were used to analyze all of the variables. The Shapiro–Wilk normality test was used to examine the normal distribution of the quantitative variables. Because the variables showed non-normal distribution, we used nonparametric methods for further statistical analyses. The continuous variables are presented as median and range values, while the categorical data

are described using the number of observations and relative frequencies. The Mann–Whitney test was applied to calculate the differences between the subgroups. Correlation analysis was performed using Spearman rank correlation test. Prevalence comparison between groups was performed using either 2-tailed Fisher exact test or χ^2 test. Multivariable linear regression analysis was applied to analyze the relationship between chosen independent variables and HRQoL measures. In the multivariable analysis, we adjusted for cofounders that correlated significantly with the HRQoL domains in the univariable analysis. Calculations and graphs were performed using Statistica, version 13.0 (Tibco Software Inc, 2017) and GraphPad Prism for Windows, version 7.0. A *P* value of less than 0.05 was considered to indicate statistically significant differences.

Ethics Written informed consent was obtained from the participants included in the study. The study was performed following the principles of good clinical practice and in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The study protocol was approved by the ethics committees of Medical University of Warsaw (KB/58/A/2016) and Pomeranian Medical University, Szczecin, Poland (KB-0012/08/18).

RESULTS Clinical and demographic characteristics of the study and control groups are presented in **TABLE 1**. Forty-eight patients (21%) with PSC had decreased DHEA-S compared with 7 patients (3%) in the control group and one healthy participant (*P* < 0.001) (**FIGURE 1**).

Factors associated with a decreased level of dehydroepiandrosterone sulfate in patients with primary sclerosing cholangitis In the next step of the analysis, we searched for factors associated with decreased

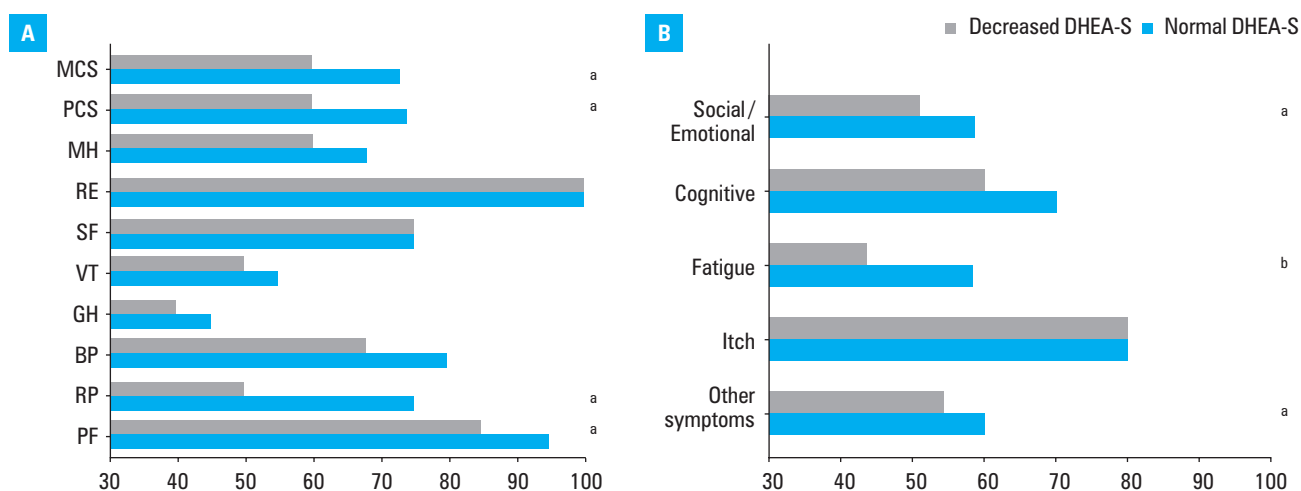


FIGURE 2 A comparison of the Medical Outcomes Study 36-Item Short Form Health Survey (A) and the PBC-40 (B) domains between patients with primary sclerosing cholangitis with normal and decreased dehydroepiandrosterone sulfate (DHEA-S). Data are presented as medians. The Mann–Whitney test was used for comparisons with a *P* value of less than 0.05 indicating significant differences.

a *P* < 0.05

b *P* < 0.01

Abbreviations: BP, bodily pain; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role limitation-emotional; RP, role limitation-physical; SF, social functioning; VT, vitality

DHEA-S in patients with PSC. In comparison to patients with normal DHEA-S concentrations, those with decreased DHEA-S levels were younger, both at the time of diagnosis (median [range], 29 [9–70] years vs 23 [13–66] years; *P* = 0.007) and at the time of the survey (median [range], 34 [17–71] years vs 30 [17–66] years; *P* = 0.03). Moreover, women were more likely to have decreased DHEA-S in comparison with men (28.8% women vs 16.8% men; *P* = 0.049). Regarding the laboratory parameters, participants with decreased DHEAs had lower serum albumin concentrations (median [range], 4.4 [2.8–5.8] g/dl vs 4.5 [3.1–5.4] g/dl; *P* = 0.03), but this remained within the reference range. The results of other liver function tests were comparable in both groups.

Association between decreased dehydroepiandrosterone levels and health-related quality of life

Patients with decreased levels of DHEA-S reported significantly lower HRQoL scores in both the SF-36 (the physical functioning, physical role, and physical component score domains) and the PBC-40 (the other symptoms, fatigue, and social-emotional domains) questionnaires (FIGURE 2). In the multivariable linear regression analysis, decreased DHEA-S came out as independent predictor of lower quality of life scores in all the above HRQoL domains, except for the physical functioning domain of the SF-36 (TABLE 2).

DISCUSSION Primary sclerosing cholangitis is one of the most fascinating and challenging conditions in contemporary hepatology.³ Its etiology remains a mystery, and although underlying immunological mechanisms play an important role, PSC cannot be called a typical autoimmune condition for numerous reasons, summarized

by Karlsen et al.¹ Chronic cholestasis leads to hepatic retention of bile acids, which has a potent detergent property.⁶ This pathological situation activates numerous adaptive mechanisms aimed at the hepatoprotection and amelioration of this effect.² These include, among others, activation of the pregnane X receptor.² This is a ligand-activated member of the nuclear receptor superfamily of transcription factors and is highly expressed in the liver.² It plays the role of xenobiotic sensor, inducing phase I (hydroxylation) and phase II (glucuronidation and sulfation) metabolism of many endogenous and exogenous compounds.¹¹ We previously showed that mechanisms responsible for elimination of endo- and exotoxins may be specifically impaired in PSC.¹¹ In particular, sulfation, a potent hepatoprotective mechanism catalyzed by SULT2A1, responsible for, for example, the elimination of toxic lithocholic acid, was shown to be impaired in PSC,¹¹ with the subsequent reduction of sulfated metabolites in the sera of patients with PSC.¹²

The present study demonstrated that a noticeable proportion of patients with PSC present with low serum levels of DHEA-S. We examined DHEA-S as this endogenous steroid hormone precursor is sulfated by SULT2A1, mostly in the liver. Thus, it could be considered a surrogate marker for the sulfation capacity of the liver. As advanced liver fibrosis/cirrhosis in itself may affect the sulfation efficiency of the liver, leading to decreased levels of DHEA-S,^{21,22} we only included noncirrhotic patients in this study, both in the PSC and control disease groups (NAFLD and HCV patients). We found that the proportion of PSC patients with low DHEA-S was 7-fold higher than in the disease control group, and

TABLE 2 Multivariable linear regression analysis of independent variables impacting health-related quality of life measures in patients with primary sclerosing cholangitis

HRQoL domain	Variable	B	B SE	β	t test	P value	95% CI for B
PBC-40							
Other symptoms	Decreased DHEA-S	1.12	0.42	0.17	2.66	0.008	0.29–1.94
	Gender (female)	1.29	0.37	0.24	3.55	<0.001	0.58–2.01
	Age at survey (per 1 year)	0.09	0.03	0.19	2.79	0.02	0.03–0.15
Fatigue	Decreased DHEA-S	2.72	0.87	0.21	3.14	0.002	1.01–4.44
	Gender (female)	2.48	0.77	0.21	3.21	0.002	0.96–3.99
	Age at diagnosis (per 1 year)	0.14	0.06	0.15	2.22	0.03	0.02–0.27
Social and emotional	Decreased DHEA-S	2.45	0.92	0.18	2.66	0.008	0.63–4.27
	Gender (female)	3.03	0.81	0.25	3.76	<0.001	1.44–4.62
SF-36							
Physical functioning	Age at survey (per 1 year)	–0.49	0.11	–0.30	–4.51	<0.001	–0.70 to –0.27
	Gender (female)	–4.74	1.28	–0.24	–3.71	<0.001	–7.26 to –2.22
Role limitation—physical	Decreased DHEA-S	–9.64	3.39	–0.19	–2.84	0.005	–16.3 to –2.95
	Age at diagnosis (per 1 year)	–0.71	0.24	–0.20	–3.02	0.003	–1.17 to –0.25
Physical component score	Decreased DHEA-S	–3.70	1.75	–0.14	–2.12	0.04	–7.15 to –0.25
	Gender (female)	–5.05	1.53	–0.22	–3.30	0.001	–8.06 to –2.03
	Age at diagnosis (per 1 year)	–0.41	0.12	–0.23	–3.35	0.001	0.65 to –0.17

Abbreviations: DHEA-S, dehydroepiandrosterone sulfate; HRQoL, health-related quality of life; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey

this difference was highly significant. This finding suggests that impaired sulfation in PSC may indeed contribute to the development of this condition and, potentially, to its natural course. This notion may be supported by the fact that patients with PSC and low DHEA-S were diagnosed at a significantly younger age; thus, impaired sulfation may play a role precipitating the presentation of the disease.

DHEA-S itself has been widely advertised as an over-the-counter supplement that can improve various symptoms related to different conditions, including depression and mood disorders, osteoporosis, adrenal insufficiency, and rheumatoid arthritis.¹⁵ Data in support of these claims remain controversial, with numerous meta-analyses producing inconclusive results.^{23–26} Supplementation with DHEA had a positive effect on the HRQoL in small groups of patients with systemic lupus erythematosus and hypopituitarism.^{27,28} A positive association between the DHEA-S level and global cognitive function was initially reported in a large cohort of 1034 elderly patients,²⁹ a finding subsequently confirmed in a meta-analysis including 25 publications.³⁰ In terms of cholestasis, animal studies in bile duct ligated rats have shown that supplementation of DHEA-S has an ameliorating effect on fatigue.³¹ Data on DHEA-S in the context of chronic cholestatic/autoimmune liver conditions remain scarce. To the best of our knowledge, there is only one study assessing serum DHEA-S in patients with cholestatic condition, namely, PBC. In their study, Ahboucha et al³² measured the DHEA-S levels in 15 patients with chronic fatigue and 10 without fatigue. They found significantly lower levels of DHEA-S in fatigued patients, measured using

the fatigue impact score. Of interest, they also assessed serum levels of DHEA and pregnenolone, which were comparable in both groups, possibly suggesting that the deficiency of DHEA-S could be responsible for fatigue. These authors postulated that supplementation with DHEA or DHEA-S could be of potential benefit for addressing chronic fatigue in these patients.

Our study is the first analysis of DHEA-S in patients with PSC. After showing that a significant proportion of patients indeed had low levels of DHEA-S, we then assessed the potential effect of these low levels on HRQoL. We applied 2 questionnaires, the generic SF-36 and the disease-specific PBC-40. The latter was developed for the assessment of various aspects of HRQoL in patients with PBC. As patients with PBC and PSC both share clinical symptoms affecting HRQoL, including pruritus and chronic fatigue, PBC-40 has been found to be a useful tool for assessing HRQoL in PSC as well.²⁰ Of importance, PBC-40 also assesses cognitive dysfunction, previously found to be impaired in patients with various conditions and low DHEA-S.²⁵ Our study clearly showed an association between decreased DHEA-S and low HRQoL. In terms of the SF-36 questionnaire, patients with decreased DHEA-S scored significantly worse in 4 out of the 10 domains of this test, including the physical functioning, physical role, mental health, and physical component scores. The differences in mental component score reached borderline significance. Regarding PBC-40, patients with low DHEA-S presented with significantly more pronounced fatigue and impaired social-emotional and other symptoms domains. However, no difference was

observed in the cognitive domain. These findings were strengthened with multivariable linear regression analysis of risk factors for worse HRQoL, which showed a striking and highly significant association between decreased DHEA-S and several domains of the SF-36 and PBC-40 questionnaires.

Thus, our data show that low DHEA-S levels are associated with significantly worse HRQoL in patients with PSC. Of particular note is the significant difference seen in fatigue levels, a devastating symptom observed across the spectrum of autoimmune conditions.³³ In many patients, it prevents normal functioning, greatly impacting their everyday activities and leading to long-term sickness absence.³⁴ Patients with multiple sclerosis describe chronic fatigue as being a more debilitating symptom than urinary incontinence.³⁵ In view of our strongly limited ability in managing this symptom,³⁶ our findings are of importance, and a study designed to examine the effects of DHEA-S supplementation in patients with PSC deserves further attention.

We acknowledge some limitations of our study. First, this is a clinical continuation of our previous studies and did not allow us to gain insights into the molecular background underlying the observed reduction in DHEA-S levels, that is, the role of SULT2A1 activity in liver tissue. Thus, further in vitro and in vivo studies are needed to explore our hypothesis. Moreover, a controlled randomized trial on the impact of DHEA-S supplementation on symptom-specific, patient-reported outcome measures is needed to investigate the relationship between the various aspects of patients' well-being and DHEA-S in detail.

Despite its limitations, some important conclusions could be drawn from our study. We found that a significant proportion of patients with PSC express low serum levels of DHEA-S, strengthening our previous findings on liver sulfation capacity being impaired in PSC as sulfation in liver is an effective mechanism for the elimination of toxic metabolites. Low DHEA-S remains very strongly associated with worse quality of life, suggesting that DHEA-S supplementation may have clinically important significance in improving the HRQoL in patients with PSC and in ameliorating troublesome symptoms such as chronic fatigue.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT EW and PM designed the study. KMW, EW, BK, MW, and PM performed the research. KMW, EW, BK, and KKP collected the data. EW and PM analyzed the data. KMW, EW, and PM wrote the paper. PM supervised writing of the manuscript.

CONFLICT OF INTEREST None declared.

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REFERENCES

- Karlsen TH, Folseraas T, Thorburn D, Vesterhus M. Primary sclerosing cholangitis – a comprehensive review. *J Hepatol.* 2017; 67: 1298-1323. [↗](#)
- Milkiewicz M, Klak M, Kempinska-Podhorodecka A, et al. Impaired hepatic adaptation to chronic cholestasis induced by primary sclerosing cholangitis. *Sci Rep.* 2016; 6: 39573. [↗](#)
- Milkiewicz P, Wunsch E. Primary sclerosing cholangitis. *Recent Results Cancer Res.* 2011; 185: 117-133. [↗](#)
- Weismüller TJ, Trivedi PJ, Bergquist A, et al. Patient age, sex, and inflammatory bowel disease phenotype associate with course of primary sclerosing cholangitis. *Gastroenterology.* 2017; 152: 1975-1984.
- Weismüller TJ, Wedemeyer J, Kubicka S, et al. The challenges in primary sclerosing cholangitis-aetiopathogenesis, autoimmunity, management and malignancy. *J Hepatol.* 2008; 48 (suppl. 1): S38-S57. [↗](#)
- Trauner M, Fickert P, Halilbasic E, Moustafa T. Lessons from the toxic bile concept for the pathogenesis and treatment of cholestatic liver diseases. *Wien Med Wochenschr.* 2008; 158: 542-548. [↗](#)
- Trauner M, Meier PJ, Boyer JL. Molecular pathogenesis of cholestasis. *N Engl J Med.* 1998; 339: 1217-1227. [↗](#)
- Zollner G, Fickert P, Fuchsichler A, et al. Role of nuclear bile acid receptor, FXR, in adaptive ABC transporter regulation by cholic and ursodeoxycholic acid in mouse liver, kidney and intestine. *J Hepatol.* 2003; 39: 480-488. [↗](#)
- Zollner G, Fickert P, Zenz R, et al. Hepatobiliary transporter expression in percutaneous liver biopsies of patients with cholestatic liver diseases. *Hepatology.* 2001; 33: 633-646. [↗](#)
- Zollner G, Wagner M, Fickert P, et al. Expression of bile acid synthesis and detoxification enzymes and the alternative bile acid efflux pump MRP4 in patients with primary biliary cirrhosis. *Liver Int.* 2007; 27: 920-929. [↗](#)
- Wunsch E, Klak M, Wasik U, et al. Liver expression of sulphotransferase 2A1 enzyme is impaired in patients with primary sclerosing cholangitis: lack of the response to enhanced expression of PXR. *J Immunol Res.* 2015; 2015: 571353. [↗](#)
- Trottier J, Bialek A, Caron P, et al. Metabolomic profiling of 17 bile acids in serum from patients with primary biliary cirrhosis and primary sclerosing cholangitis: a pilot study. *Dig Liver Dis.* 2012; 44: 303-310. [↗](#)
- Elekima OT, Mills CO, Ahmad A, et al. Reduced hepatic content of dehydroepiandrosterone sulphotransferase in chronic liver diseases. *Liver.* 2000; 20: 45-50. [↗](#)
- Mueller JW, Gilligan LC, Ildkowiak J, et al. The regulation of steroid action by sulfation and desulfation. *Endocr Rev.* 2015; 36: 526-563. [↗](#)
- Kroboth PD, Salek FS, Pittenger AL, et al. DHEA and DHEA-S: a review. *J Clin Pharmacol.* 1999; 39: 327-348. [↗](#)
- EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol.* 2009; 51: 237-267. [↗](#)
- Karlas T, Petroff D, Garnov N, et al. Non-invasive assessment of hepatic steatosis in patients with NAFLD using controlled attenuation parameter and 1H-MR spectroscopy. *PLoS One.* 2014; 9: e91987. [↗](#)
- Ware JE, Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992; 30: 473-483. [↗](#)
- Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. *Gut.* 2005; 54: 1622-1629. [↗](#)
- Raszeja-Wyszomirska J, Wunsch E, Krawczyk M, et al. Prospective evaluation of PBC-specific health-related quality of life questionnaires in patients with primary sclerosing cholangitis. *Liver Int.* 2015; 35: 1764-1771. [↗](#)
- de Araujo Neto JM, Coelho HSM, Chindamo MC, et al. Lower levels of dehydroepiandrosterone sulfate are associated with more advanced liver fibrosis in chronic hepatitis C. *J Viral Hepat.* 2018; 25: 254-261. [↗](#)
- Charlton M, Angulo P, Chalasani N, et al. Low circulating levels of dehydroepiandrosterone in histologically advanced nonalcoholic fatty liver disease. *Hepatology.* 2008; 47: 484-492. [↗](#)
- Sandoughi M, Kaykhaei MA, Langarizadeh E, Dashipour A. Effects of dehydroepiandrosterone on quality of life in premenopausal women with rheumatoid arthritis: a preliminary randomized clinical trial. *Int J Rheum Dis.* 2020; 23: 1692-1697. [↗](#)
- Alkatib AA, Cosma M, Elamin MB, et al. A systematic review and meta-analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency. *J Clin Endocrinol Metab.* 2009; 94: 3676-3681. [↗](#)
- Peixoto C, Jose Grande A, Gomes Carrilho C, et al. Dehydroepiandrosterone for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. *J Neurosci Res.* 2020; 98: 2510-2528. [↗](#)
- Strac DS, Konjevod M, Perkovic MN, et al. Dehydroepiandrosterone (DHEA) and its Sulphate (DHEAS) in Alzheimer's Disease. *Curr Alzheimer Res.* 2020; 17: 141-157. [↗](#)

- 27 Nordmark G, Bengtsson C, Larsson A, et al. Effects of dehydroepiandrosterone supplement on health-related quality of life in glucocorticoid treated female patients with systemic lupus erythematosus. *Autoimmunity*. 2005; 38: 531-540. [↗](#)
- 28 Brooke AM, Kalingag LA, Miraki-Moud F, et al. Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. *J Clin Endocrinol Metab*. 2006; 91: 3773-3779. [↗](#)
- 29 Valenti G, Ferrucci L, Lauretani F, et al. Dehydroepiandrosterone sulfate and cognitive function in the elderly: The InCHIANTI Study. *J Endocrinol Invest*. 2009; 32: 766-772. [↗](#)
- 30 de Menezes KJ, Peixoto C, Nardi AE, et al. Dehydroepiandrosterone, its sulfate and cognitive functions. *Clin Pract Epidemiol Ment Health*. 2016; 12: 24-37. [↗](#)
- 31 Butterworth RF, Lalonde R, Power C, et al. Dehydroepiandrosterone sulphate improves cholestasis-associated fatigue in bile duct ligated rats. *Neurogastroenterol Motil*. 2009; 21: 1319-1325. [↗](#)
- 32 Ahboucha S, Pomier-Layrargues G, Vincent C, et al. Reduced plasma dehydroepiandrosterone sulfate levels are significantly correlated with fatigue severity in patients with primary biliary cirrhosis. *Neurochem Int*. 2008; 52: 569-574. [↗](#)
- 33 Milkiewicz P, Heathcote EJ. Fatigue in chronic cholestasis. *Gut*. 2004; 53: 475-477. [↗](#)
- 34 Janssen N, Kant IJ, Swaen GM, et al. Fatigue as a predictor of sickness absence: results from the Maastricht cohort study on fatigue at work. *Occup Environ Med*. 2003; 60 (suppl. 1): i71-i76. [↗](#)
- 35 Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Mult Scler*. 2003; 9: 219-227. [↗](#)
- 36 Wunsch E, Kruk B, Snarski E, et al. Plasmapheresis in the treatment of chronic fatigue in patients with primary biliary cholangitis. *Pol Arch Intern Med*. 2021; 131: 205-207. [↗](#)