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Dehydroepiandrosterone sulfate indicates decreased sulfation capacity and impaired quality of life in Primary Sclerosing Cholangitis

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Short title: Dehydroepiandrosterone sulfate in Primary Sclerosing Cholangitis.

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Key words: chronic fatigue, dehydroepiandrosterone, primary sclerosing cholangitis, sulfation
What’s new?

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

Introduction. Impaired elimination of toxic compounds via inadequate sulfation may contribute to the pathogenesis of primary sclerosing cholangitis (PSC).

Dehydroepiandrosterone (DHEA) is metabolized into its sulfated form (DHEA-S) in the liver. DHEA has also been linked with health-related quality of life (HRQoL) in various conditions.

Objectives. We investigated 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 studied 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. We found that proportion of patients with low DHEA-S in the PSC group was 7 times 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 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 PBC-40.

Conclusions. Our findings support the role of impaired liver sulfation capacity in the development of PSC. Low DHEA-S are associated with increased fatigue, a devastating symptom seriously 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 autoimmune, inflammatory, genetic, and possibly infective factors all playing their role [2]. Continual biliary tree damage leads to persistent cholestasis, episodes of cholangitis, and sepsis [3]. PSC is frequently associated with an increased risk of cholangiocarcinoma, which may occur in 10%–12% of patients [3, 4]. PSC co-exists with inflammatory bowel diseases, most frequently with ulcerative colitis (UC), which is present in approximately 70% of patients [4]. Subjects with PSC-related UC often demonstrate a right-to-left gradient of colonic inflammation, rectal sparing, and backwash ileitis [4]. This pattern of inflammation is significantly different from colitis in patients with UC 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 experience more prominent exposure to potential toxins derived from bile, frequently called the “toxic bile hypothesis” [6]. In liver, an accumulation of toxic biliary compounds results in progressive tissue damage [7]. In response, several defense mechanisms are induced to counteract this 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, activation of the pregnane X receptor (PXR), a nuclear orphan receptor responsible for orchestrating hepatoprotective mechanisms, is not (as seen in other cholestatic conditions, e.g., 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 PSC compared to PBC and normal 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 an endogenous steroid hormone precursor 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 non-cirrhotic patients (277 males, median age of 38 years) with chronic liver diseases treated in two medical centers (Warsaw and Szczecin, Poland) were consecutively enrolled. Two hundred and thirty-three patients with PSC (160 males, median age of 32 years) comprised the study group, whereas 201 patients (117 males, median age of 47 years) comprised the control cohort, which included patients with HCV infection (n = 98) and NAFLD (n = 103). We also included 59 healthy volunteers without liver disease (22 males, median age of 53 years) as healthy controls. PSC was diagnosed using the typical findings based on magnetic resonance cholangiography or endoscopic retrograde
cholangiopancreatography and biochemical abnormalities according to the European Association for the Study of Liver Diseases (EASL) guidelines [16]. NAFLD was diagnosed 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 anti-hepatitis C antibodies in the serum and HCV viremia. The included subjects were not diagnosed with primary or secondary adrenal gland insufficiency and were not in receipt of medication that could impair adrenal production of DHEA (including glucocorticosteroids).

**Laboratory Measurements**

The clinical variables and fasting blood samples for 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 (HRQoL)**

To assess the relationship between the levels of DHEAs and HRQoL in patients with PSC two questionnaires—the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and the PBC-40—were applied. The SF-36 is a well-validated, universally used generic questionnaire [18]. It contains 36 items divided into eight domains of physical and mental health. Scores can be obtained for each scale or aggregated into two summary scores, i.e., 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 of the SF-36 v.1 questionnaire in this study (license number QM044529). The PBC-40 was designed for evaluation of the HRQoL in patients with primary biliary cholangitis [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, with higher scores indicating 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’s rank correlation test. Prevalence comparison between groups was performed using either two-tailed Fisher’s exact or chi-squared tests. 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 significantly correlated with the HRQoL domains in the univariable analysis. Calculations and graphs were performed using Statistica 13.0 (Tibco Software Inc. 2017) and GraphPad Prism for Windows (Version 7.0). $P < 0.05$ was considered to indicate statistically significant differences.

**Ethics**

Written informed consent was obtained from the subjects 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

The clinical and demographic characteristics of the study and control groups are presented in Table 1. Forty-eight (21%) of the PSC patients had decreased DHEA-S, compared to 7 (3%) patients in control group and one healthy subject ($P < 0.001$) (Figure 1).

Factors Associated with Decreased DHEA-S in Patients with PSC

In the next step of the analysis, we searched for factors associated with decreased DHEA-S in PSC. In comparison to patients with normal DHEA-S concentrations, subjects with decreased DHEA-S levels were younger, both at the time of diagnosis (29 (9–70) vs. 23 (13–66) years; $P = 0.007$) and at the time of the survey (34 (17–71) vs. 30 (17–66) years; $P = 0.03$). Moreover, females were more likely to have decreased DHEA-S in comparison to males (28.8% females vs. 16.8% males; $P = 0.049$). Regarding the laboratory parameters, subjects with decreased DHEAs had lower serum albumin concentrations (4.4 (2.8–5.8) vs. 4.5 (3.1–5.4); $P = 0.03$), but this remained within a normal range. The other liver function tests were comparable in both groups.

The Association between Decreased DHEAs and HRQoL

Patients with decreased 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 mentioned HRQoL domains, except for the physical functioning domain of the SF-36 (Table 2).
DISCUSSION

PSC 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 in [1]. Chronic cholestasis leads to hepatic retention of bile, which has a potent detergent property [6]. This pathological situation activates numerous adaptative mechanisms aimed at the hepatoprotection and amelioration of this effect [2]. These include, among others, activation of the pregnane X receptor (PXR) [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 found that the 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, e.g., for 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 non-cirrhotic 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 times higher than in the disease control group, and this difference was highly statistically 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 on 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, Abouchach et al. measured the DHEA-S levels in 15 patients with chronic fatigue and 10 without fatigue [32]. 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 finding that a significant proportion indeed had low levels of DHEA-S, we then looked at the potential effect of these low levels on HRQoL. We applied two 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 on the 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, 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, our study is a clinical continuation of our previous works and did not allow us to gain insights into the molecular background underlying the observed reduction in DHEA-S levels, i.e., the role of SULT1A2 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.

**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 analysed the data; KMW, EW and PM wrote the paper. PM - Guarantor of article

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REFERENCES


Table 1. Clinical and demographic characteristics of analysed subjects.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Study group (n=233)</th>
<th>Control group (n=201)</th>
<th>Healthy controls (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at survey, years</td>
<td>32 (17-71)</td>
<td>47 (19-83)</td>
<td>53 (28-81)</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>29 (9-70)</td>
<td>47 (19-83)</td>
<td>N/A</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>160 (69%) /73 (31%)</td>
<td>117 (58%) /84 (42%)</td>
<td>22 (37%) /37 (63%)</td>
</tr>
<tr>
<td>ALP, IU/l; normal:&lt;120</td>
<td>229 (5-1515)</td>
<td>72 (32-177)</td>
<td>61 (36-122)</td>
</tr>
<tr>
<td>GGT, IU/l; normal:&lt;42</td>
<td>195 (7-1515)</td>
<td>41 (6-464)</td>
<td>17 (4-264)</td>
</tr>
<tr>
<td>Bilirubin, mg/dl; normal:&lt;1.0</td>
<td>0.7 (0.2-28)</td>
<td>0.5 (0.1-11)</td>
<td>0.4 (0.1-1.6)</td>
</tr>
<tr>
<td>ALT, IU/l; normal:&lt;30</td>
<td>71 (8-973)</td>
<td>35 (6-570)</td>
<td>15 (9-40)</td>
</tr>
<tr>
<td>AST, IU/l; normal:&lt;30</td>
<td>48 (12-831)</td>
<td>29 (12-178)</td>
<td>18 (12-47)</td>
</tr>
<tr>
<td>Albumin, g/dl; normal:3.8-5.4</td>
<td>4.5 (2.8-5.8)</td>
<td>4.6 (3.8-5.7)</td>
<td>4.8 (4.1-7.6)</td>
</tr>
</tbody>
</table>

Abbreviations: alanine aminotransferase, ALT; alkaline phosphatase, ALP; aspartate aminotransferase, AST; gamma glutamyltransferase, GGT. Data presented as number (percent) or median (range). N/A – not applicable
Table 2. Multivariable linear regression analysis of independent variables impacting HRQoL measures in patients with PSC.

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

*Abbreviations:* Health-related quality of life, HRQoL; dehydroepiandrostone sulfate, DHEA-S.
Figure 1. Proportion of decreased dehydroepiandrosterone sulfate (DHEA-S) in the study groups.
Figure 2. A comparison of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (A) and the PBC-40 (B) domains between primary sclerosing cholangitis (PSC) patients with normal and decreased DHEA-S. Data presented as median. Mann–Whitney test; with $P < 0.05$ indicating statistically significant differences, * $P < 0.05$, ** $P < 0.01$; Bodily Pain, BP; General Health, GH; Mental Component Summary, MCS; Mental health, MH; Physical Component Summary, PCS; Physical Functioning, PF; Role Limitation-Emotional, RE; Role Limitation-Physical, RP; Social Functioning, SF; Vitality, VT.