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Impaired Health-related Quality of Life in Addison's disease – Impact of Replacement Therapy, Co-morbidities and Socioeconomic Factors

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ABBREVIATIONS

AD: Addison's disease; AI: Adrenal insufficiency;APECED: Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dysplasia; APS-1: Autoimmune Polyendocrine Syndrome type 1; APS-2: Autoimmune Polyendocrine Syndrome type 2; DHEA: Dehydroepiandrosterone; FC: Fludrocortisone; HC: hydrocortisone; HRQoL: Health-related quality of life; NS: Not significant, POF: premature ovarian failure ; SD: Standard deviation; T1D: Type 1 Diabetes Mellitus

SUMMARY

Objective. Patients with Addison's disease (AD) on conventional replacement therapy have impaired health-related quality of life (HRQoL). It is possible that lower hydrocortisone (HC) doses recommended by current guidelines could restore HRQoL. We compared HRQoL in AD patients treated according to current HC recommendations to that of the age- and gender-standardized general population.

Subjects, design and measurement. We assessed HRQoL in a cross-sectional setting with the 15D instrument in a Finnish AD cohort (n=107) and compared the results with those of a large sample of general population (n= 5671).We examined possible predictors of HRQoL in AD. Within the patient group, HRQoL was also assessed by SF-36.

Results Mean HC dose was 22 mg/d, corresponding to 12 ± 4mg/m2. HRQoL was impaired in AD compared to the general population (15D score; 0.853 vs. 0.918, $p<0.001$). Within single 15D dimensions, discomfort and symptoms, vitality and sexual activity were most affected. Stepwise regression analysis demonstrated that Patient's Association membership ($p = 0.02$), female gender ($p<0.01$), presence of other autoimmune or inflammatory co-morbidity

(p <0.02), lower education (p < 0.02), and longer disease duration (p <0.05), independently predicted impaired HRQoL. Replacement regimens, autoimmune-related co-morbidities, total number of co-morbidities or level of healthcare follow-up did not. In AD, HRQoL was impaired also as assessed by SF-36.

Conclusions HRQoL is significantly impaired in AD compared to the general population despite use of recommended HC doses. Patient's Association membership was the most significant predictor of impaired HRQoL. This finding should be explored in more detail in the future.

Introduction

Without life-long replacement therapy, Addison's disease (AD) has devastating consequences, but even when treated AD has been associated with increased mortality (1). Several studies addressing the subjective health status of patients with AD demonstrated a negative impact on health-related quality of life (HRQoL) (2-7). Compared to the general population, the dimensions of vitality/depression, energy/fatigue, general health perceptions and anxiety have been most affected (2,4,8-10).

Standard replacement therapy for primary adrenal insufficiency includes glucocorticoids and mineralocorticoids (11). In addition, the well-being of AD patients may be affected by loss of adrenal dehydroepiandrosterone (DHEA) secretion (9,11). Although standard replacement therapy prevents life-threatening adrenal crisis, it has been estimated that patients with adrenal insufficiency on conventional regimens (approximately 30 mg of hydrocortisone (HC) per day) are over substituted by 6-7 mg /d (12). Bleicken et al. reported that impaired HRQoL in patients with primary and secondary adrenal insufficiency was related to HC doses above 30

mg (5). On the other hand, replacement therapy with any current glucocorticoid regimen does not mimic the circadian physiological cortisol profile and patients on HC replacement therapy spend the early morning hours in a glucocorticoid deficient state (13). During the last years, smaller HC replacement doses have been recommended (11,14) and a recent consensus statement on AD suggests 15-25 mg per day (15). Besides glucocorticoid replacement, demographic factors, duration of the disease, clustering of other autoimmune diseases, socio-economic status and the level of expertise of the health-care follow-up may affect HRQoL.

The aim was to evaluate what replacement doses Finnish AD patients currently use and to investigate HRQoL in Finnish AD patients in a cross-sectional setting with the 15D (16) and SF-36 questionnaires. We analysed whether factors such as replacement therapy regimen, concomitant diseases, level of current follow-up within the health-care system and socioeconomic issues are related to HRQoL in AD. In addition, we compared HRQoL in AD patients to that of a large sample of age- and gender-standardized general population.

Material and methods

Design

We included adult patients with autoimmune Addison's disease (AD) that have been diagnosed and treated at the Helsinki University Central Hospital (HUCH) including the Meilahti, Jorvi and Peijas hospitals at some time point from 1997 onwards. In addition, we recruited patients with AD from the national Patients' Organization (APECED ja Addison Ry, http://www.apeced.org). Patient charts with the ICD code for Addison's disease (E27.1, E27.1 or E 27.4) and the questionnaires from subjects recruited via the patients´organization were screened by an endocrinologist (N.M. or C.S.-J.) and only subjects fulfilling the diagnostic criteria for AD were included in the study. Patients with APECED were excluded from this

study. The impact of APECED (or APS-1) on HRQoL has been reported elsewhere (17). The Ethical Committee of HUCH Internal Medicine approved the study and each participant signed an informed consent.

HRQoL in the present cohort was assessed with two self-administered HRQoL questionnaires, the 15D and the SF-36. In addition, we recorded current hormone replacement therapy and dosage (hydrocortisone, HC or prednisone, fludrocortisone (FC), DHEA, social and demographic information, current weight, height, blood pressure, other chronic comorbidities such as hypertension, coronary heart disease, type 2 diabetes, thyroid dysfunction, and other autoimmune diseases, affiliation to the Patients' Association and current level of disease follow-up in the health-care system (University hospital/specialist in endocrinology, general hospital/specialist in internal medicine or local health care center/general practitioner). APS-2 was defined as patients with AD associated with at least one of the following additional autoimmune conditions: hypo- or hyperthyroidism, T1D, ovarian failure, celiac disease, pernicious anemia / atrophic gastritis, vitiligo or alopecia areata. Any other auto-immune or inflammatory diseases were considered separately.

Questionnaires

The questionnaires were mailed along with an explanatory letter, an informed consent form, and a prepaid envelope for return of the questionnaires. In case of no response, patients were sent an additional letter asking for their willingness to participate.

The 15D is a generic, comprehensive, 15-dimensional, standardized, self-administered measure of HRQoL that can be used both as a profile and single index instrument (18). It is a well validated test consisting of 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. Each dimension is divided into five ordinal levels.

The patient or person chooses the level best describing his or her current health status for each dimension. The valuation system of the 15D is based on an application of the multi-attribute utility theory. The single index score (15D score), representing the overall HRQoL, and the dimension level values, reflecting the goodness of the levels relative to no problems on the dimension and to being dead, both on a 0-1 scale, are calculated from the questionnaire by using a set of population-based preference or utility weights. The maximum 15D score is 1 (no problems on any dimension) and minimum score 0 (equivalent to being dead). The minimal clinically important change in the 15D score has been estimated at 0.018 for improvement and -0.045 for deterioration (19). The HRQoL thus measured was compared to that of a sample of age- and gender-standardized general Finnish population (n = 5671). The data for the general population came from the National Health 2000 Health Examination Survey (20).

The SF-36 (also known as RAND-36) is a HRQoL survey that has been widely used in previous studies on HRQoL in AD. It is a self-rated, profile-based HRQL measure and originates from the Medical Outcomes Study 36-item short-form health survey. It comprises 36 items that assess eight health concepts: physical functioning (10 items), physical role limitations (4 items), emotional role limitations (3 items), social functioning (2 items), bodily pain (2 items), general mental health/emotional well-being (5 items), energy/vitality (4 items), and general health perceptions (5 items). We used the Finnish version of the SF-36 as it has good reliability and construct validity in the Finnish general population (20). The SF-36 is scored in two steps. Each item is first scored on a scale from 0 to 100 (a higher score defining a higher HRQoL), and an average value is calculated for each of the eight dimensions. If more than 50% of the items in a dimension are missing, the average value cannot be calculated (21).

Statistical analysis

Statistical analysis was conducted with SPSS Statistics 19 (IBM). Patients' characteristics are presented as means and SDs for continuous variables and as frequencies and proportions for categorical variables. Patients' characteristics were compared using the Chi-square test for categorical variables and Student's independent samples t-tests for continuous ones. Correlations between age, age at diagnosis, duration of the disease, and total 15D scores were analysed by Spearman's rank correlation coefficient. Stepwise regression analysis was used to estimate how gender, duration of the disease, demographic factors, educational level, body mass index, association with APS-2, number of auto-immune diseases associated with APS-2, other auto-immune and inflammatory diseases, hypertension, type 2 diabetes and coronary heart disease, overall number of co-morbidities, affiliation to Patients' Association, place of follow-up (primary health care centre, regional hospital or university hospital), and replacement therapy dosage explained the variance in the 15D scores. The 15D score served as the dependent variable. Additionally, binary logistic regression was used to explain the factors associated with association membership. Statistical significance threshold was set at $p<0.05$.

Results

Sociodemographic and clinical data

A total of 138 patients were contacted by mail and 107 returned the questionnaires (response rate 78%). Eighty-four of the respondents were women and 23 men. The patient characteristics are summarized in **Table 1**. Hypothyroidism was the most frequent auto-immune disease associated with AD (56%). There was no significant difference between genders in the prevalence of any autoimmune disease or other chronic co-morbidity. Sixty-four patients (60%) were considered having APS-2. The APS-2 group displayed a female

predominance (p = 0.022). Otherwise, both isolated AD and APS-2 patients displayed similar age, age at diagnosis, duration of the disease and hormone replacement doses (HC, FC, or DHEA, p > 0.05) (*data not shown*). The number of auto-immune disease components of APS-2 ranged from 2 (mainly AD and hypothyroidism) to 5 in one patient. Eight patients (7%, 8/107) suffered from some other autoimmune or inflammatory disease. Three patients had a past history of cancer (prostate cancer or breast cancer in 2 cases). When considering the overall number of diseases in a patient (including any auto-immune or inflammatory disease, other chronic comorbidity and cancer), the mean number of co-morbidities was 2 ± 1.2 (range from 1 to 7).

Hormone replacement therapy

The mean calculated HC dosage in HC equivalents was 22 mg ± 7 (range 5 to 90 mg daily) (**Table 1**). Ninety-five percent of the patients (102/107) used a dosage up to 30 mg/daily. Only one patient took less than 15 mg hydrocortisone daily. The mean HC dosage per body surface area was 12 mg/m2 ± 4 (7-21). Ninety-nine patients (99/107, 92%) were exclusively taking HC as hormone replacement, with a mean dosage of 22 ± 6 mg daily (20-70 mg) (**Table 1**). Eight patients were on prednisolone; four of them took prednisolone combined with a HC dose of 5 to 7.5 mg/d and four of them prednisolone alone (5 to 20 mg/d). Briefly, 19% (20/107) of the patients took less than 20 mg/daily, 37% (40/107) took 20 mg/d, 25% (27/107) between 20 and 30 mg/d and 19% (20/107) took 30 mg or more daily. Among the 5 patients with high dose equivalent of HC (over 30 mg/day), one took 7.5 mg prednisolone daily because of stable auto-immune hepatitis. The highest dose equivalent was 90 mg HC daily (20 mg prednisolone daily and 10 mg HC daily) in a patient with a history of epilepsy.

In most patients, HC was divided into two (49.5%, 53/107) or three daily doses (47%, 50/107), only 4% (4/107) had one daily morning dose. Patient weight and BMI were positively correlated with HC dose ($r = 0.241$, $p = 0.013$ and $r = 0.214$, $p = 0.027$ respectively). HC and FC doses did not differ significantly between female and male patients. Regular local or systemic corticosteroids for other reason than AD were used by 9% (9/105) of the AD patients. The use of FC and DHEA (females only) is given in **Table 1**.

Level of health-care follow-up

The follow-up of the AD patients was equally distributed among the different health care levels: 33.6% (35/104) were followed up by general practitioners at the local primary health care centre, 41.3% (43/104) by a specialist in internal medicine at a general hospital and 32.7% (34/104) by an endocrinologist at a university hospital. Eight patients were followed up jointly by two health care organizations (primary health care center and general hospitals, n = 2; or university hospitals, n = 6). The mean HC dose did not differ significantly between the health care levels: 24 ± 12 mg/d at the local primary health care centre, 23 ± 9 at the general hospital and 22± 6 at the university hospital. The corresponding mean FC doses were 0.7± 0.4 mg/wk, 0.7± 0.3 mg/wk and 0.6± 0.2 mg/wk, respectively.

Health-related quality of life in Addison patients compared to the general population

AD patients had a significantly lower mean 15D score compared to the age-and gender-standardized general population (0.853 ± 0.122 versus 0.918 ± 0.082, $p < 0.001$) (**Figure 1**). In the patients, 15D scores ranged from 0.461 to 1.000. Only 5.6% (6/107) reported full health (i.e., a 15D score of 1).The patients were worse off than the general population on all single dimensions except for “eating” and “seeing” (**Figure 1**). The dimensions of “usual

activities", "excretion", "mental status", "depression", "distress", "vitality" and "sexual activity" were most affected (all $p < 0.001$) (**Figure 1**).

SF-36 mean scores were as follows: physical functioning 79±22, role limitations due to physical health 57±45, role limitations due to emotional problems 68±40, energy/fatigue 56±24, emotional well- being 73±19, social functionning 73±26, bodily pain 69±26 and general health 51±25. There was a significant positive correlation between the 15D score and SF-36 on every scale (*Spearman correlation $p < 0.001$, data not shown*).

Predictors of impaired HRQoL in Addison patients

Possible determinants of HRQoL within the patient group were assessed by stepwise regression analysis (**Table 2**). Regression analysis revealed that gender, i.e. female sex, Patients' Association membership, longer disease duration, lower educational level and presence of an inflammatory or a systemic autoimmune disease not belonging to APS-2 predicted impaired HRQoL. By contrast, replacement therapy, timing of HC, APS-2, number of APS-2 autoimmune disorders, overall number of co-morbidities, or level of health-care follow-up did not predict HRQoL. The 15D results according to Patients' Association membership are given in **Figure 2**.

Health-related quality of life in Addison patients belonging to the Patients' Association

Twenty-seven patients (25.2%) were members of the Patients' Association, 81.5% of them being females. The response rate among subjects belonging to the Patients' Association was high (96.4%, 27/28). The mean 15D score was significantly lower among members compared to non-members, 0.802 ± 0.122 vs. 0.870 ± 0.117, $p = 0.003$; **Figure 2).** Of the individ-

ual dimensions, “excretion”, “usual activities”, “depression”, “distress” and “vitality” were significantly more affected in this group ($p < 0.05$).

Discussion

Previous studies in patients with primary or secondary adrenal insufficiency, demonstrate that impaired HRQoL correlates with the HC dose and patients with a total dose above 30 mg have impaired HRQoL compared to those with a lower daily dose (4,5). We here report that the mean calculated daily HC dose in our Finnish AD cohort was 22.4 ± 7.3 mg, indicating that the patients are treated according to current recommendations of smaller daily HC doses in the range of 15-25 mg (11,15). Despite this, Finnish AD patients have significantly impaired overall HRQoL in comparison to a large sample of general population. With regards to the single dimensions, excretion, usual activities, depression, distress, vitality and sexual activity were most impaired (all $p< 0.001$ compared to the general population). In the present study, the HC dose was mostly divided into two (49.5%) or three (46.7%) daily doses but this dosage regimen did not correlate with HRQoL. Although three daily doses seem more physiological, our results are in line with Bleicken et al., who did not report superior HRQoL in patients taking HC thrice daily compared to patients taking HC twice daily (5). Our finding that smaller HC dose does not restore impaired HRQoL may reflect the fact that it is impossible to fully mimic physiological cortisol kinetics with HC replacement therapy. The physiological cortisol profile varies according to diurnal rhythm and daily stress signals, which may have important implications for our well-being (13). During replacement therapy, low HC concentrations appear during early morning hours and before dosing. Furthermore, replacement therapy induces peak and area under the curve blood and salivary cortisol concentrations that are not physiological and may create false stress signals (23,24).

Data from Germany (4) and other Scandinavian countries, namely Norway (2) and Sweden (25), previously reported impaired HRQoL in AD. Our cohort was quite similar to other European series regarding number of patients included (107 in the present study, 50 to 200 patients in other series) (2,24), female predominance (78.5% in the present study compared to 63.6 to 80% (24)) as well as prevalence of autoimmune co-morbidities (thyroid disease 57.9% (44.6 to 62.5%), type 1 diabetes 8.4% (3.8 to 12%)) and other rare manifestations (ovarian and testicular failure, pernicious anemia, atrophic gastritis, alopecia areata; 15.8% compared to 13.4 to 30.6%) (24).

In addition to the 15D, our cohort was also studied with the SF-36 questionnaire, to enable an indirect comparison with some of the previous studies. In the present study, there was a significant positive correlation between the 15D score and all SF-36 items. Using SF-36, role limitations due to physical health (57), general health (51) as well as energy and fatigue (56) were most affected. Although direct comparison is not possible, our findings are in agreement with those of Løvås *et al.* in their Norwegian cohort (2) as well as those of Hahner et al. in Germany (4), who found similar dimensions to be most affected, with scores of 60, 56, 51 (2) and 66, 56, 51 (4) respectively.

Many other factors than HC replacement could explain the impaired HRQoL observed in AD, including increased patient age, delay in diagnosis, female gender and autoimmune co-morbidities (2, 26). In accordance with previous studies, female gender was associated with impaired HRQoL also in the present study (2, 26). In contrast to Meyer et al. (26), we did not observe a link between auto-immune APS-2 co-morbidities and impaired HRQoL. According to stepwise regression analysis, the APS-2 related co-morbidities did not influence the HRQoL in our cohort. In contrast, we found that non APS-2 related inflammatory and autoimmune diseases such as inflammatory bowel disease, rheuma-

toid arthritis or Sjögren's syndrome had a significant impact on HRQoL. This is not surprising as patients suffering from these diseases have impaired HRQoL (26, 27).

Stepwise regression analysis did not demonstrate that the level of follow-up within the health-care system had an impact on HRQoL in AD in Finland. As demonstrated previously (4, 29, 30), DHEA supplementation was not associated with improved HRQoL in female AD patients. However, in the present study, this subgroup was fairly small with only 20 patients.

Higher educational level (high school graduation and over) was associated with better 15D scores in the present study. This is in line with a previous report on socio-economic background and HRQoL (31). We did not specifically investigate the possible effect of annual personal and familial income or current work activity of the patient.

Lastly, we wanted to know whether affiliation to the Patients' Association was associated with HRQoL. Without surprise, the members were more eager to participate in the study. However, a novel finding of the present study was that this patient group disclosed a more impaired subjective HRQoL compared to non-members (**Figure 2**). The result may seem surprising, as a general belief perhaps is that Patients' Associations are able to provide a strong supportive environment resulting in a better HRQoL. Binary logistic regression using a backward stepwise method with Association membership as the dependent variable showed that only the 15D total score ($p = 0.003$) and the duration of the disease ($p = 0.05$) were significantly associated with membership affiliation in the present study. The association of impaired HRQoL and Patients' Association affiliation could reflect a recruiting bias, as patients seeking membership may be more seriously affected and therefore have the most impaired HRQoL. Another possibility is that sharing and changing information on the disease and the burden of it, could impact HRQoL negatively. Finally, it is possible that members of the Pa-

tient's Association, consciously or not, lower their HRQoL when answering our study questionnaire in hope of obtaining better recognition or other benefits. Previously, van Haastregt et al. showed that patients who benefited from a Patients' Association where the ones who were relatively ill (32). Furthermore, nothing indicated that receiving information would lead to better well-being in these patients suffering from neuromuscular disorders (31). In a cohort of 258 patients with inflammatory bowel diseases, Selinger et al. observed that better disease knowledge was associated with a higher anxiety level in the patients (33). Our results demonstrate an association between membership and HRQoL impairment, but does not prove causality. Further studies are needed to explore this issue.

The main limitation of our study is the relatively small sample size. The cross-sectional design of the study does not allow a comparison of HRQoL in the time period before vs. after introduction of smaller HC doses in Finland. We chose to use the 15D instrument for studying HRQoL as it is well validated, serves both as a single index score as well as a profile instrument on multiple dimensions, and because it allowed us to compare the data with that of a large sample of general population, as in previous publications (34). Of note, a recently published disease-specific HRQoL questionnaire for AD is not yet available in Finnish and could therefore not be used (25,35). Although direct comparison is not possible, our patients also filled in the SF-36 questionnaire and the results of the present study were very similar to European data (2,4,9). General health, vitality, physical and emotional role limitations are most affected in all populations (2,4,9).

Taken together, we here demonstrate that current HC doses in Finnish Addison's disease patients are close to those currently recommended. Despite this, HRQoL is severely impaired in AD compared to the general population ($p< 0.001$) with excretion, usual activities, depression, vitality and sexual activity being the most severely affected dimensions. Patient's Asso-

ciation membership, female gender, presence of other autoimmune or inflammatory co-morbidity, lower education and longer disease duration predicted impaired HRQoL.

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Legends of the figures

Figure 1. The 15D score and profiles of AD patients (n = 107) and population controls standardized for age and gender (n =5 671)

Figure 2. The 15D score and profiles of AD patients according to Patients' Association membership

Table 1. Sociodemographic and clinical data, including hormone replacement dosages in Finnish Addison's disease patients

	Total **(n = 107)**	**Male** **(21.5%, n = 23)**	**Female** **(78.5%, n = 84)**
mean age (yr)	49.8 +/- 12.5 (range 20 - 72)	45.5 +/- 13.0 (range 23-74)	51 +/- 12.2 (range 24 – 76)
mean age at diagnosis (yr)	35.3 +/- 12.6 (range 4 - 65)	27.7 +/- 12.5 (range 4 - 55)	31.2 +/- 11.9 (range 13 - 65)
mean disease duration at time of survey **(yr)**	14.7 years +/- 11.6 (range 0 – 54)	18.1 +7- 14.5 (range 2 – 54)	13.8 +/- 10.6 (range 0 – 54)
Marital status			
Single	9% (10/107)	17% (4/23)	7% (6/84)
In a relationship	70% (75/107)	78% (17/23)	69% (58/84)
Divorced	17% (18/107)	4% (1/23)	20% (17/84)
Widowed	3.7% (4/107)	0% (0)	5% (4/84)
Educational status			
High school or less	62% (66/107)	48% (11/23)	65.5% (55/84)
Above high school	38% (41/107)	52% (12/23)	34.5% (29/84)
Structure of fol-			

low-up (n)			
Health care center	34% (35/104)*	32% (7/22)*	35% (28/82)*
Regional hospital	41% (43/104)*	32% (7/22)*	44% (36/82)*
University hospital	33% (34/104)*	41% (9/22)*	30% (25/82)*
Patients' Association Membership	25% (27/107)	22% (5/23)	26% (22/84)
APS-2	60% (64/107)	39% (9/23)	65% (55/84)
T1D	8 % (9/107)	17 % (4/23)	6 % (5/84)
Hypothyroidism	56 % (60/107)	39 % (9/23)	60 % (51/84)
Hyperthyroidism	2 % (2/107)	0 %	2 % (2/84)
Celiac disease	6 %(7/107)	4 % (1/23)	7 % (6/84)
POF	5% (5/107)	-	6% (5/84)
Testicular failure	2% (2/107)	8% (2/23)	-
Atrophic gastritis	0.1% (1/107)	0.00 %	1% (1/84)
Pernicious anemia	0.1% (1/107)	0.00 %	1% (1/84)
Alopecia areata	0.1% (1/107)	0.00 %	1% (1/84)
Vitiligo	0.1% (1/107)	0.00 %	1% (1/84)
Other autoimmune and inflammatory diseases			
IBD	2.8% (3/107)	0 %	4% (3/84)
Psoriasis	0.1% (1/107)	4 % (1/23)	0%
Morphea	0.1% (1/107)	4 % (1/23)	0%
AH	0.1% (1/107)	4 % (1/23)	0%
RA	0.1% (1/107)	0 %	1% (1/84)
Sjögren syndrome	0.1% (1/107)	0 %	1% (1/84)
Other chronic comorbidity			
T2D	6 % (7/107)	0%	8 %(7/84)
Hypertension			

Coronary heart disease Other	15 % (16/107) 2 % (2/107) 2% (2/107)	17% (4/23) 0% 0%	14% (12/84) 2 % (2/84) 2 % (2/84)
Adrenal hormone replacement therapy			
Hydrocortisone mg/day	22 +/- 7 (5 - 90)	23 +/- 6	23 +/- 11
Fludrocortisone mg/wk.	0.65 +/- 0.30	0.63 +/- 0.32 (n = 20)	0.65 +/- 0.298 (n = 68)
DHEA mg/d	24 +/- 20	0	24 +/- 20 (n = 20)

AH: Autoimmune hepatitis; IBD: inflammatory bowel disease; NA: Not applicable; NS: Not significant ($p > 0.05$); POF: premature ovarian failure; RA: Rheumatoid arthritis; T1D: type 1 diabetes; T2D: type 2 diabetes. Morphea denotes localized scleroderma.

*Not available for three subjects. Eight patients are followed-up both at the health care center and at a General hospital (n = 2) or University hospital (n = 6). Percentage does not sum up to 100.

Table 2. Stepwise regression* using the 15D total score as dependant variable in patient with AD

	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	t	Sig.
(Constant)	.959	.036		26.392	.000
Patient's association membership	-.078	.024	-.287	-3.222	.002
Gender (female versus male)	-.083	.028	-.275	-2.995	.004
Presence of other autoimmune or inflammatory diseases	-.103	.042	-.217	-2.430	.017
Education status (highschool or over level versus under highschool)	.055	.023	.222	2.408	.018
Duration of the disease	-.002	.001	-.205	-2.193	.031

* The following variables were not significantly associated with 15D total score: age, BMI, marital status, level of health-care follow-up, number of co-morbidities, number of autoimmune disease, diagnosis of APS-2, other chronic comorbidities, hormonal dosage regimen including hydrocortisone, fludrocortisone and DHEA