

2 **A specific nursing educational program in patients with cushing's**
3 **syndrome**

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10 **Abstract** Cushing's syndrome (CS) is a rare endocrine
11 disease, due to cortisol hypersecretion. CS patients have
12 comorbidities, often still present after biochemical cure.
13 Specific nursing healthcare programs to address this dis-
14 ease and achieve improved health related quality of life
15 (HRQoL) are lacking. Thus, an educational nursing inter-
16 vention, through the development and promotion of
17 specific educational tools, appears to be justified. The
18 objective of this study is to assess the effectiveness of an
19 educational nursing program in CS patients on HRQoL,
20 clinical parameters, level of pain and physical activity,
21 patterns of rest, and use of health resources. A prospective,
22 randomized study was conducted in two reference hospitals

for CS. Sixty-one patients (mean age 47 ± 12.7 years, 23
83.6 % females) were enrolled and divided into 2 groups: 24
an "intervention" group where educational sessions were 25
performed over 9 months and a "control" group, without 26
these sessions. Specific questionnaires were used at the 27
beginning and end of the study. After educational sessions, 28
the intervention group had a better score in the Cush- 29
ingQoL questionnaire ($p < 0.01$), reduced level of pain 30
($p < 0.05$), improved physical activity ($p < 0.01$) and 31
healthy lifestyle ($p < 0.001$) compared to the control 32
group. A correlation between the CushingQoL score and 33
reduced pain ($r = 0.46$, $p < 0.05$), improved physical 34
activity ($r = 0.89$, $p < 0.01$), and sleep ($r = 0.53$, 35
 $p = 0.01$) was observed. This educational nursing program 36
improved physical activity, healthy lifestyle, better sleep 37
patterns, and reduced pain in CS patients, influencing 38
HRQoL and reducing consumption of health resources. 39
Moreover, the brief nature of the program suggests it as a 40
good candidate to be used in CS patients. 42

Keywords Cushing's syndrome · Nursing · Educational 43
program · Health-related quality of life 44

Introduction 45

Patients with cushing's syndrome (CS) suffer from multi- 46
ple comorbidities, mainly cardiovascular (hypertension, 47
atherosclerosis, changes in heart functionality), and meta- 48
bolic (dyslipidemia, central obesity, diabetes), as well as 49
thrombotic disorders, bone disorders, cognitive and neu- 50
ropsychological impairment, and impaired sexual function 51
due to glucocorticoid (GC) excess [1–6]. 52

The assumption that resolution of hypercortisolism 53
normalized comorbidities is currently questioned, since 54

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55 there is evidence that cured CS patients still have increased
56 morbidity and mortality despite endocrine control [7–9].
57 Most patients with CS develop metabolic syndrome, which
58 may persist after remission of hypercortisolism, con-
59 tributing to increased cardiovascular risk and deserve to be
60 treated according to common standard practice [7].
61 Awareness of this persistent increase in cardiovascular risk
62 in CS patients after endocrine cure leads to strict control of
63 improvable factors, including blood pressure, dyslipemia,
64 hyperglycemia, smoking, obesity, and prothrombotic state
65 [10].

66 There is ample evidence on the positive effect of edu-
67 cational nursing interventions in the management of each
68 of the comorbidities described above [11–14]. Educational
69 nursing interventions in chronic diseases like ischemic
70 heart disease, rheumatoid arthritis, osteoporosis, diabetes,
71 hypertension, etc., improve the outcome of these patients.

72 This sort of intervention reduces consumption of drugs,
73 changes dietary habits, and physical activity, favoring a
74 better self-management, increasing self-efficacy and self-
75 care [11, 12]. Health education not only informs the patient
76 and family about the disease but modifies their behavior by
77 adopting new life habits, in order to actively manage their
78 care [13–15]. Many studies confirm the important role of
79 nurses in education of diabetic patients to improve dietary
80 habits, control chronic diseases, and reduce cardiovascular
81 risk [16–23].

82 Health-related quality of life (HRQoL) in patients with
83 CS is also severely affected, especially in active disease
84 [24], and still impaired after cure of hypercortisolism [25,
85 26]; this limits social activity of patients and may increase
86 pain perception [27]. Since we were unaware of any edu-
87 cational program for patients with CS, we aimed to develop
88 a specific nursing educational program, with specific edu-
89 cational tools. We investigated their outcome after fol-
90 lowing the program, in a prospective randomized study.

91 Patients and methods

92 Patients

93 Patients with CS of pituitary or adrenal origin followed in 2
94 reference centers [Hospital Sant Pau (HSP) and Hospital
95 Clínic (HC)] were included in this multicenter, prospective,
96 randomized study.

97 Patients who did not attend 100 % of the educational
98 program sessions and those who for cognitive reasons or
99 psychiatric or neurological problems could not continue the
100 education sessions were excluded. All patients signed an
101 informed consent after study approval by the hospitals
102 Ethics Committee.

Of the 137 patients treated in HSP and HC, 37 declined 103
to participate. Of the remaining 100, 39 did not meet the 104
inclusion criteria (30 did not accept to participate, and the 105
remaining 9 patients had functional or psychiatric limita- 106
tions). The final sample included 61 patients, 48 were of 107
pituitary origin and 13 of adrenal origin. 108

Of the final sample, 45 were considered cured (repeat- 109
edly normal 24-h urinary-free cortisol, serum cortisol 110
suppression after overnight 1 mg dexamethasone 111
<50 nmol/L or adrenal insufficiency with hydrocortisone 112
substitution therapy); 24 had undergone radiotherapy and 113
nine suffered hypopituitarism. Sixteen were active, all on 114
medical therapy with ketokonazole and eight also with 115
metyrapone. 116

Remission was re-confirmed in all patients after the 117
9 months of follow up. No patients developed any recur- 118
rence during that period. The two cohorts of patients had 119
similar clinical characteristics, and no differences in 120
duration of remission were present. The patients were 121
followed up long term over the years, and they were not in 122
the early phase of surgical remission. Moreover, eucorti- 123
solemia was confirmed in all patients on medical therapy. 124

Sociodemographic and clinical variables were collected 125
during a clinical interview and included personal data, age, 126
sex, education level, employment status, and social activ- 127
ity. Anthropometric variables included weight, height, 128
body mass index (BMI), waist, and hip circumference, and 129
systolic and diastolic blood pressure. Details related to CS 130
like type of surgery, size of the lesion, symptoms, treat- 131
ments, and recurrence were also collected. Table 1 shows 132
the baseline clinical characteristics of the study partici- 133
pants. Table 2 shows urinary-free cortisol (UFC), ACTH 134
values, and comorbidities at the end of the study. 135

Patients were randomized into two groups: (1) Inter- 136
vention group (31 patients), who followed a specific 137
nursing interventional program and (2) Control group (30 138
patients), who did not undergo the specific nursing inter- 139
ventional program. This randomization was stratified by 140
center, by a computer generation of random numbers. 141

Nursing educational intervention 142

The educational intervention was carried out over 143
9 months in the University School of Nursing, HSP. There 144
were 5 visits: 4 educational sessions and 1 last visit, when 145
questionnaires were repeated and final data were collected. 146

The 4 educational sessions lasted 2 h, with intervals 147
between sessions of 30 to 40 days, with a compulsory 148
attendance for all the sessions. The first educational session 149
was named as “baseline” (visit 1), and the last was named 150
as “final visit” (visit 4). The study finalized (visit 5, “end 151
of study”) 9 months after the baseline session. All educa- 152
tional sessions were conducted by a nurse experienced in 153

Table 1 Baseline clinical characteristics of study participants

		Total	Control group	Intervention group
Demographic data	Number of patients	61	30	31
	Males	10	5	5
	Females	51	25	26
	Age (mean \pm SD)	47.25 \pm 12.6	48.3 \pm 13.2	46.1 \pm 12.2
Educational level	Incomplete primary school	2	2	0
	Primary school	22	8	13
	Secondary school	18	8	10
	University	19	12	8
Previous health education	No	58	29	29
	Yes	3	1	2
Type of Cushing's Sd	Pituitary	48	24	24
	Adrenal	13	6	7
Disease duration (years)	Mean \pm SD	2.5 \pm 1.5	2.7 \pm 1.7	2.3 \pm 1.3
Active/cured	Number of patients	16/45	7/23	9/22
Urinary-free cortisol (UFC) (nmol/24 h)	Mean \pm SD	111.1 \pm 78.2	104.3 \pm 81.88	118.1 \pm 77.52
ACTH (pg/mL)	Mean \pm SD	16.5 \pm 17.0	18.9 \pm 18.1	14.1 \pm 14.9
Pituitary tumor size	Number of patients	48	24	24
	Macro/microadenoma	2/46	1/23	1/23
Duration of remission in cured patients ($n = 45$)	Years (mean \pm SD)	6.67 \pm 5.19	7.37 \pm 5.70	5.88 \pm 4.61
Partial, hypopituitarism	Number of patients	5	4	1
Total, hypopituitarism	Number of patients	4	2	2
Hypertension	Number of patients	23	8	15
Obesity	Number of patients	29	12	17
Hypercholesterolemia	Number of patients	33	16	17
Diabetes	Number of patients	8	3	5
Depression	Number of patients	13	4	9
Osteoporosis	Number of patients	9	3	6

No differences in the clinical characteristics were evidenced between intervention and control groups

154 educational programs for secondary prevention of cardio-
155 vascular risk factors (CG). Schedule and contents of edu-
156 cational sessions are reported in Table 3.

157 There was a progression in the different contents and in
158 the patient's autonomy in the management of the knowl-
159 edge of the disease, as indicated in Table 2. Educational
160 resources with reference material were offered to the
161 patient and family throughout the visits, and all the mate-
162 rials were in Spanish.

163 All questionnaires were administered at baseline (visit
164 1) and end of the study (visit 5), both to the control group
165 and to the intervention group by the nurse who conducted
166 the educational sessions. The time to complete all ques-
167 tionnaires was approximately one hour.

168 The intervention group received the educational pro-
169 gram progressively during 4 sessions; it included
170 knowledge on CS, comorbidities, treatments, general

management, and autonomy in healthy lifestyles 171
(Table 2). By contrast, the control group only attended 172
their usual medical appointments, with the information 173
given by their doctor during scheduled visits, without any 174
specific monitoring program or educational intervention 175
visits ("treatment as usual"). 176

Three sessions were patients group sessions (2nd, 3rd, 177
and 5th), attended only by the patients, and in the other two 178
sessions (1st, 4th), the patients could be accompanied by 179
their families (Table 2). The aim of these latter sessions 180
was that the relatives participated in the learning process 181
and in the promotion of healthier lifestyles. 182

This specific nursing interventional program had four 183
main priorities: 184

1. To identify signs and symptoms of CS and their 185
comorbidities. 186

Table 2 Urinary-free cortisol, ACTH values, and comorbidities at the end of the study

		Total	Control group	Intervention group
Patients included in the study	Number of patients	61	30	31
Active/cured	Number of patients	16/45	7/23	9/22
Urinary-free cortisol (UFC) (nmol/24 h)	Mean \pm SD	113.66 \pm 80.17	103.55 \pm 84.51	121.75 \pm 77.76
ACTH (pg/mL)	Mean \pm SD	16.99 \pm 17.21	19.46 \pm 19.23	14.63 \pm 15.08
Hypertension	Number of patients	23	9	14
Obesity	Number of patients	28	12	16
Hypercholesterolemia	Number of patients	30	14	16
Diabetes	Number of patients	5	3	2
Depression	Number of patients	14	5	9
Osteoporosis	Number of patients	10	3	7

No differences were evidenced between intervention and control groups

- 187 2. To demonstrate and to learn capacity for self-control and monitoring of specific comorbidities of CS. 215
 188
 189 3. To apply the acquired knowledge to improve outcome of those comorbidities that negatively affect their long-term prognosis. 216
 190
 191
 192 4. To give the patients tools to facilitate the learning process and its application. 217
 193

194 Data collection and questionnaires

195 The variables studied, collected in both the control group and intervention group at baseline (visit 1) and at the end of the study (visit 5), were the following:

- 198 – *Health-related quality of life (HRQoL)* It was measured with the CushingQoL questionnaire, specifically designed for patients with CS, and demonstrated to be feasible, reliable, and valid [24, 28]. 218
- 199 – *Level of pain* measured with the Spanish Pain Questionnaire, a standard pain measurement instrument [29–31]. 219
- 200 – *Level of physical activity* measured with the International Physical Activity Questionnaire (IPAQ) [32, 33]; it collects weekly physical activity measured in METs (Metabolic Equivalent of Task). One MET is a physiological measure expressing the energy cost of physical activities. It is defined as the energy cost of sitting quietly and is equivalent to a caloric consumption of 1 kcal/kg/h. There are three levels of physical activity: low, moderate, and high. It is estimated that compared with sitting quietly, a person's caloric consumption is three to six times higher when being moderately active (3–6 METs) and more than 6 times higher when being vigorously active (>6 METs). 220
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- *Level of rest or sleep* measured with the Oviedo Sleep Questionnaire (OSQ) [34, 35] and with two specific questions asking for the number of hours of rest and for the self-reported satisfaction with rest (the answer was “yes” or “no”). 221
- *The use of health resources* the number of hospital admissions during the study period, of unscheduled visits or outpatient visits to their own endocrinologist or other health providers, was included. 222
- *Level of nicotine dependence* measured with the Fagerstrom Test for Nicotine Dependence (FTND) to evaluate smoking [36–39]. 223
- *Erectile dysfunction* measured with the Spanish version of the Index of Erectile Function (IIEF 5) [40]. 224
- *Female sexual function* measured with the Spanish version of the Female Sexual Functioning Inventory (FSFI) and with the Female Sexual Function Questionnaire brief profile (B- PFSF) [41–43]. 225
- *Compliance with nutritional habits* measured with the Lifestyle Associated Questionnaire [44, 45]. 226

237 Statistical analysis

238
239
240 Statistical analysis was performed using SAS version 9.3 software program (SAS Institute, USA). The normality assumption was tested using the Kolmogorov -Smirnov 241
242

Table 3 Schedule and contents of educational sessions

Educational session	Type of session	Content
Visit 1 baseline	Patients + family, group sessions	Data Collection and baseline Questionnaires Pathophysiological basis of Cushing's syndrome Cause, effect, and origin of hypercortisolism Difference between cured and active disease Description and management of comorbidities that occur in Cushing's syndrome Basis of self-care in Cushing's syndrome.
Visit 2 (1.5 months after baseline)	Patients group sessions	Effects, dosage, and side effects of treatments Risk factors and health care Type of comorbidities associated with the disease Difficulties and limitations of self-care Perception of patient experiences. Healthstyle instructions: diet, exercise, physical activity, smoke Specific recommendations for physical activity
Visit 3 (2 months after baseline)	Patients group sessions	Banned or restricted food consumption Role of salt, phosphorus, calcium, magnesium, and fats Foods allowed and prohibited for each risk factor Practice on balanced diets Practical calculation of caloric content Basic rules for an optimal level of relaxation Problems and limitation of sexual activity Strengthen physical activity recommendations
Visit 4 Final visit (2.5 months after baseline)	Patients + family, group sessions	Proper diet, food groups (carbohydrates, protein, saturated and unsaturated fats, vitamins, water, trace elements, foods rich in calcium, phosphorus, and magnesium, fiber) Workshop on preparation of balanced diets
Visit 5 End of the study (9 months after baseline)	Patients group sessions	Final data Collection and final Questionnaires

Visit 1 information on themes related to the knowledge of the pathology and comorbidities

Visit 2 information on themes related to the treatment, difficulties in the management of the disease and patient perceptions

Visit 3 information on themes related to the correct management of the disease and healthy living habits

Visit 4 information on nutrition and healthcare habits

243 test. Categorical variables are indicated as percentages.
244 Quantitative variables are expressed as mean \pm standard
245 deviation (SD). Student *t* test was used for quantitative
246 variables. Chi-square test or a Fisher test (when appropriate)
247 was used for categorical variables.

248 Two types of analyses were done for all variables: one
249 compared the differences between control group and
250 intervention group, firstly at baseline and secondly at the
251 end of the study. The other type of analysis compared the
252 changes within each group (on one hand control group and
253 on the other hand intervention group) in all the variables,
254 throughout the study. Both analyses used Student *t* tests.

255 Pearson test was used to find correlations between
256 variables. A statistically significant level of <0.05 was
257 considered.

Results

258
259 Of the 61 patients enrolled (30 in the control group without
260 educational intervention and 31 in the intervention group
261 with educational intervention), 57 (93.4 %) completed the
262 study as planned in the protocol; 4 patients ended prema-
263 turely for various reasons (illness or moving to another city).

264 No significant differences in terms of baseline clinical
265 characteristics were detected between control and inter-
266 vention group (Table 1).

267 The majority were women (83.6 %), with a mean age of
268 47 ± 12.7 years. A mean of 2.5 years had elapsed from the
269 onset of symptoms to diagnosis (range 0–8 years). The
270 mean time from diagnosis to the study was 10.5 years; only
271 4.9 % of patients reported having received health

272	education, despite the long period since diagnosis. There	control group. Moreover, no changes were seen between	317
273	were no differences in waist, waist hip ratio, weight, or	baseline and the end of the study in either group.	318
274	blood pressure between groups at the end of the study or	However, there was a significant improvement in self-	319
275	changes within groups throughout the study.	reported quantity (= number or hours, 7.53 ± 1.10 vs.	320
276	No differences in the questionnaires' scores were evidenced	6.39 ± 1.34 , $p < 0.05$) and quality of rest (measured as the	321
277	between intervention group and control group at baseline.	percentage of patients that referred satisfaction with the	322
278	Quality of life	rest, 64 vs. 89 %, $p < 0.05$) throughout the study, in the	323
279	The intervention group had a better CushingQoL score	intervention group.	324
280	compared to control group, at the end of the study	Finally, there was a positive correlation between the	325
281	(56.47 ± 19.18 vs. 48.49 ± 20.02 , $p < 0.01$).	quantity of rest and the improvement in HRQoL ($r = 0.53$,	326
282	No changes in the CushingQoL score were evidenced	$p = 0.01$).	327
283	within the intervention group. By contrast, the control	Healthy lifestyle	328
284	group decreased their CushingQoL score from baseline to	There was more adherence to educational instructions on	329
285	the end of the study (59.27 ± 19.79 vs. 48.49 ± 20.02 ,	healthy lifestyle in the intervention group compared to	330
286	$p < 0.01$), indicating a worsening in HRQoL, (Fig. 1).	control group at the end of the study (4.00 ± 0.38 vs.	331
287	Finally, the subgroup of patients of the intervention group	2.76 ± 0.29 , $p < 0.001$).	332
288	with worse HRQoL at baseline showed an improvement in	Moreover, an improvement in the adherence to educa-	333
289	the CushingQoL score at the end of the study ($p < 0.01$).	tional instructions on healthy lifestyle was seen in the	334
290	Pain	intervention group at the end of the study compared to	335
291	Pain intensity was less in the intervention group than in the	baseline (3.19 ± 0.32 vs. 4.00 ± 0.38 , $p < 0.05$). By con-	336
292	control group, at the end of the study (5.00 ± 4.06 vs.	trast, adherence worsened in the control group throughout	337
293	5.97 ± 4.72 , $p < 0.05$).	the study period (3.00 ± 0.37 vs. 1.66 ± 0.29 $p < 0.05$).	338
294	Moreover, the final pain intensity fell in the intervention	Use of health resources	339
295	group compared to its baseline scores (7.21 ± 4.36 vs.	The intervention group has lower number of unscheduled	340
296	5.00 ± 4.06 , $p < 0.01$). By the contrast, no differences in	visits (0.11 ± 0.57 vs. 2.38 ± 1.12 $p < 0.01$) and admis-	341
297	pain intensity have been evidenced in the control group	sions to the emergency services (0.04 ± 0.09 vs.	342
298	compared to its baseline scores (Fig. 2).	1.55 ± 0.50 $p < 0.05$) compared to control group at the	343
299	Finally, there was a positive correlation between	end of the study.	344
300	reduced level of pain and improvement in HRQoL	Moreover, there was a reduction in unscheduled visits	345
301	($r = 0.46$, $p < 0.05$).	(2.15 ± 1.40 vs. 0.11 ± 0.57 $p < 0.01$) and in admissions	346
302	Physical activity	to the emergency services (0.55 ± 0.80 vs. 0.04 ± 0.09 ,	347
303	The percentage of high physical activity level was higher in	$p < 0.05$) in the intervention group throughout the study	348
304	the intervention group compared to control group, at the	period. By contrast, the number of unscheduled visits	349
305	end of the study (46.4 vs. 10.3 %, $p < 0.01$).	increased throughout the study period in the control group	350
306	Moreover, an increase in the percentage of patients with	(1.30 ± 1.40 vs. 2.38 ± 1.12 , $p < 0.01$), without changes	351
307	high physical activity level (from 17.9 to 46.4 %,	in admissions to the emergency services.	352
308	$p < 0.001$) was observed in the intervention group. By the	Smoking	353
309	contrast, physical activity did not vary from baseline to the	No differences between groups for nicotine dependence	354
310	end of the study in the control group.	were observed at baseline or throughout the study; however,	355
311	Finally, there was a positive correlation between high	the number of daily smoked cigarettes tended to be lower in	356
312	physical activity level and the improvement in HRQoL	the intervention group at the end of the study ($p = 0.06$).	357
313	($r = 0.89$, $p < 0.01$).	Sexual function	358
314	Rest	Forty percent of males with CS showed erectile dysfunc-	359
315	The OSQ indicated insomnia and hypersomnia in CS patients	tion and 50 % of women had a Hypoactive Sexual Desire	360
316	at baseline, without differences between intervention and		

Fig. 1 CushingQoL questionnaire scores in control and in intervention groups at baseline and at the end of the study. No differences in the CushingQoL score were evidenced at baseline between the groups. The intervention group had a better CushingQoL score than control group, at the end of the study ($p < 0.01$). No changes in the CushingQoL score were evidenced in the intervention group throughout the study period. The control group decreased CushingQoL score throughout the study period ($p < 0.01$)

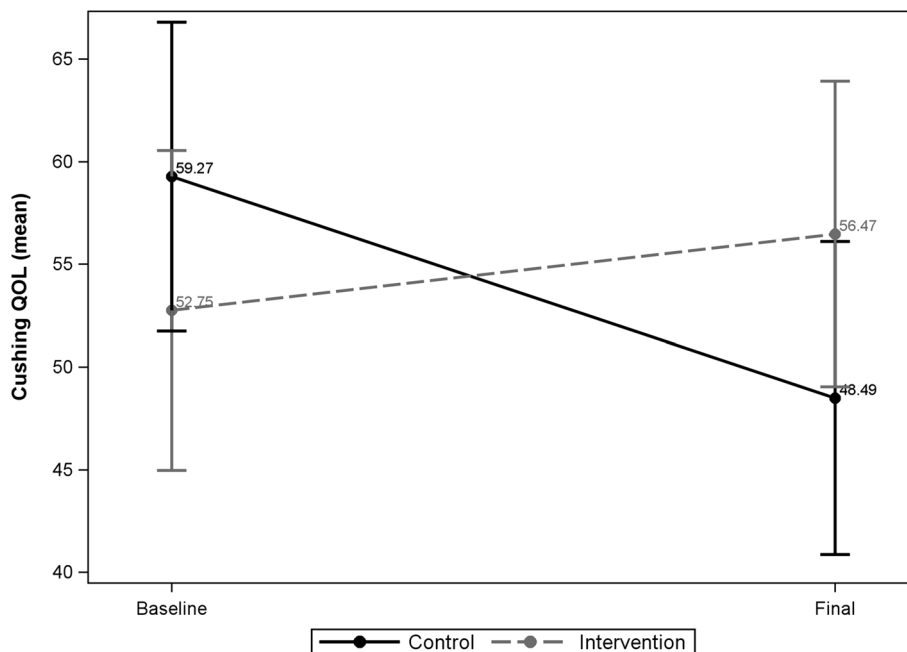
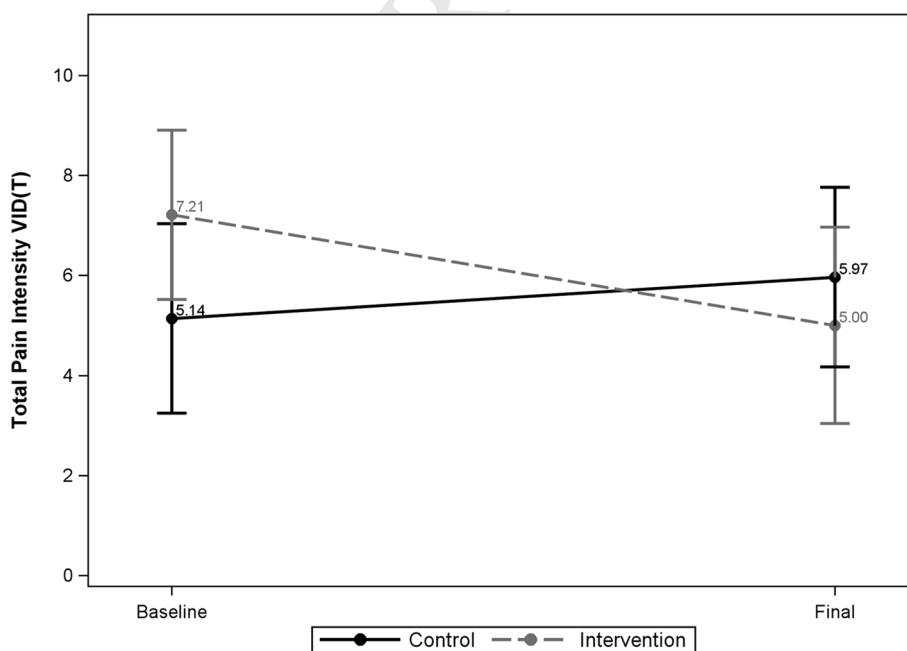


Fig. 2 Pain intensity in the control group and in the intervention group at baseline and at the end of the study, evaluated with the SPQ (Spanish Pain Questionnaire). No differences in the SPQ score were evidenced at baseline between the groups. Pain intensity was less in the intervention group than in the control group at the end of the study ($p < 0.05$). The final pain intensity fell in the intervention group throughout the study period ($p < 0.01$). No differences in pain intensity were evidenced in the control group throughout the study period



361 Disorder. However, no differences between groups or
 362 within each group in the IIEF 5, FSFI, and B- PFSF scores
 363 were evidenced between baseline and the end of the study.

364 **Discussion**

365 A specific nursing interventional program for patients
 366 with CS has been applied in this study, demonstrating
 367 an improvement in physical activity, healthy lifestyle

habits, adherence to therapy, sleep patterns, and a 368
 a reduction in pain level and in use of health resources. 369
 Furthermore, patients who participated in the educa- 370
 tional sessions had better HRQoL than patients who did 371
 not participate, at the end of the study. In particular, 372
 patients with worse HRQoL at the baseline showed a 373
 greater improvement at the end of the study, indicating 374
 that those patients with severe impairment in their 375
 HRQoL benefit more from the educational intervention 376
 than the rest. 377

378 CS patients complained that the complex and specific
379 characteristics of their disease and the absence of specific
380 health education made it difficult for them to cope and to
381 carry out their everyday activities. In fact, only 4.9 % of
382 our patients reported any health education over the years,
383 without a clear specificity on CS comorbidities. Thus, the
384 intervention group had a strong motivation which favored
385 following all the education sessions and to improve their
386 healthstyle.

387 This nursing educational intervention prevented deteri-
388 oration of HRQoL in the intervention group, improving
389 indicators of social life, confidence, relaxation, and pain
390 measured by the CushingQoL questionnaire. This ques-
391 tionnaire indicated improvements in different health indi-
392 cators, such as rest and physical activity, suggesting that an
393 appropriate educational intervention in each of them has an
394 additive effect on the final end point, in this case HRQoL.

395 This improvement was particularly evident in older, less
396 educated, unemployed patients, or housewives; interest-
397 ingly, the educational sessions were particularly useful in
398 this group of patients, referred to as the most vulnerable in
399 the literature, and therefore less likely to acquire healthy
400 habits [14, 15, 17, 18, 46].

401 Educational programs are used in a range of chronic
402 illnesses to enable patients to gain personal control and
403 self-efficacy. Studies indicate that educated patients man-
404 age their symptoms more effectively, leading to a better
405 HRQoL, with an enhanced sense of wellbeing and a
406 reduction in healthcare costs [47]. In other words, patient
407 education plays an essential role in promoting safe self-
408 management practice. When developing and applying a
409 competency-based patient education program, patients
410 learn how to manage the disease and its consequent
411 comorbidities; this leads to a better psychological status
412 that also improves their physical status [16, 48]. The
413 worsening in HRQoL in the control group is an intriguing
414 point, and we do not have a clear explanation. It may be
415 related to the lack of a specific education. The educational
416 intervention focused on multiple dimensions that all to-
417 gether helped to improve HRQoL; by contrast, routine medical
418 approach could only deal with the medical dimension.

419 The results obtained in terms of HRQoL suggest new
420 research fields, such as the relationship between the edu-
421 cational programs and the different bio-psycho-social
422 characteristics of patients; they also suggest the need to use
423 different health resources as nursing programs.

424 The reduction in perceived pain intensity in the inter-
425 vention group after the educational sessions of our study
426 may be related to different causes, approached during the
427 sessions; these include a greater adherence to analgesic
428 treatment, learning healthy posture patterns and increased
429 daily physical activity. In addition, this reduction of pain
430 generated a positive impact on other areas of health and

HRQoL, such as rest, fatigue, and physical activity, as 431
confirmed by the patients and as evidenced in similar studies 432
in the literature [49, 50]. It is known that specific exercise 433
protocols and walking programs have a positive effect on the 434
HRQoL of elderly individuals with osteoarthritis [51, 52]. 435

436 Insomnia is another problem in CS patients, creating a
437 state of fatigue and anxiety that limits their HRQoL. The
438 significant improvement in self-reported quantity (number
439 of hours) and quality of rest (satisfaction) throughout the
440 study in the intervention group clearly improved HRQoL.
441 Apart from the intervention on sleep habits, the reduction
442 of pain and the increased physical activity may also have
443 positively influenced the sleep quality and quantity. Our
444 study found a significant increase in the percentage of
445 patients with a high physical activity level in the inter-
446 vention group; due to the motivation, they had during the
447 educational sessions. Data are emerging regarding the
448 positive effect of physical activity level on rest in chronic
449 diseases; moreover, the relationship between sleep quality
450 and physical activity is bidirectional [53, 54].

451 Regarding nutritional habits, the intervention group
452 learned specific diet recommendations and correct eating
453 habits during the sessions, which included a workshop on
454 preparation of balanced diets. Moreover, the active par-
455 ticipation of the family in the group sessions favored
456 patient's engagement in changing eating behaviors. The
457 intervention group significantly improved compliance to
458 healthy lifestyle food habits at the end of the study; by
459 contrast, the control group worsened during the study
460 period. This is in line with literature data on educational
461 processes in chronic diseases leading to changes in eating
462 habits [55–57].

463 Regarding sexuality, even if there was not improvement
464 after the educational program it is important to mention
465 that a significant percentage of patients (both men and
466 women) reported alterations, mainly erectile dysfunction
467 and low sexual desire. As far as we know, this is the first
468 study to address this issue with validated instruments. Our
469 results indicate the convenience of evaluating these prob-
470 lems in clinical practice and of performing further inter-
471 ventions to improve sexual function in patients with CS.

472 Finally, our study evidenced a decrease in the number of
473 admissions and unscheduled visits in the intervention group
474 during the educational program, with the consequent
475 decrease in consumed health resources.

476 Nine patients had hypopituitarism (5 partial and 4 total),
477 equally distributed in the control and the intervention
478 group, all were on stable replacement therapy started at
479 least 2 years before the study. Therefore, hypopituitarism
480 would not appear to influence the results of this educational
481 program.

482 There were no differences in the type and severity of
483 comorbidities between the control and intervention group,

484 neither at baseline nor at the end of the study, suggesting
485 that they did not affect the investigated variables. However,
486 one might have expected that the number of comorbidities,
487 especially cardiometabolic, would have decreased in the
488 educational group, although this cannot be excluded in the
489 long term.

490 Limitations of our study included a limited time of the
491 educational sessions; a longer educational program might
492 have helped the patients in reducing their cardiometabolic
493 comorbidities (reducing BMI and weight) and to improve
494 further their HRQoL. Indeed the important role of the
495 nursing management in education is well known, in par-
496 ticular that a structural evaluation of cardiovascular risk
497 factors and an integrated nurse-led approach can success-
498 fully reduce risk in cardiovascular patients [58].

499 The number of daily smoked cigarettes only tended to
500 be lower in the intervention group; possibly a longer time
501 of educational sessions might have helped to stop smoking.

502 All active patients were on medical therapy, and
503 eucortisolemia was confirmed in all patients. In “naïve”
504 patients, the educational sessions would probably have
505 been more effective. However, on one hand, it is not ethic
506 to maintain naïve of treatment a CS patient for 9 months,
507 and on the other hand, controlling this condition during the
508 study would influence the results of the program.

509 Regression analysis could have been done; however, we
510 preferred to do t tests because regression analysis would
511 evaluate the change along the time and not the values at
512 baseline or at the end of the study.

513 Finally, the number of patients studied is relatively
514 small despite including patients from two 2 reference
515 centers, a problem which is practically unavoidable in rare
516 diseases, especially if followed up long-term over the
517 years.

518 Conclusions

519 A specific nursing educational program, addressed to CS
520 patients, obtained a positive modification of different living
521 habits, achieving an improvement of physical activity,
522 healthy lifestyle habits, sleep patterns, and reduction in
523 pain level. Even if the program only included 4 educational
524 sessions, it considerably influenced patient’s HRQoL. In
525 particular, patients with worse HRQoL at baseline showed a
526 greater improvement at the end of the study. Moreover, the
527 educational sessions allowed not only clinical improve-
528 ment, but also a reduction of hospital admissions and
529 unscheduled visits. Finally, the brief nature of the program
530 makes it as a good candidate to be used in clinical man-
531 agement of patients with CS.

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Compliance with ethical standards

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