CORTISOL is an essential stress hormone produced by the adrenal glands and tightly regulated via the hypothalamic-pituitary-adrenal axis. Cortisol deficiency is a rare, but life-threatening condition, requiring immediate diagnosis and treatment. The most common cause of primary adrenal insufficiency (AI) is an autoimmune process [1], but also infections, tissue infiltration, drugs or surgery may lead to insufficient production of glucocorticoids (GC) in the adrenal glands [2]. Secondary and tertiary AI are most often due to a pituitary adenoma or traumatic injury [3].

Regardless of the aetiology, patients with cortisol deficiency need an individual substitution treatment plan, which has to be adjusted in stressful situations. In particular, severe illness and surgery require additional stress hormones, but also milder diseases, such as vomiting and diarrhoea, may trouble AI patients if GC doses are not adjusted [2]. In addition, exhausting physical activity like in sports and mental stress may lead to an increased demand of cortisol, potentially resulting in an adrenal crisis with an incidence of 6.3 per 100 patient years [4].

Detailed information is a cornerstone of patient education and treatment in AI [5]; affected individuals should be empowered to self-treatment and adequate dose adjustment to reduce morbidity and mortality [6]. Accordingly, it has been recommended that every AI patient has an emergency kit [2, 7, 8] as well as an emergency ID [9]. Previous data suggest that physicians are the main source of information for patients with AI [10]. However, even in educated patients with chronic AI, an adrenal crisis occurs in a substantial proportion of cases [11]. A recent European study revealed that common problems in AI patients are non-adherence
to treatment, concerns about potential adverse effects, such as weight gain and osteoporosis, and dissatisfaction with the provided information on the therapeutic approach [12]. Addressing these concerns seems to be very important since chronic over-substitution of GCs may lead to premature mortality due to cardiovascular, infectious and malignant diseases [13]. Presumably, additional information on GC replacement therapy – provided by the treating physicians – has a beneficial effect on drug adherence of AI patients [12]. However, we recently demonstrated that also physicians may lack knowledge on AI, which may result in inadequate treatment of the disorder [14, 15].

So far, there is only sparse data on the patients’ view of their health care situation [6, 10, 12, 16], and hardly any information on AI patients’ knowledge of their disease. Aim of the present study was to assess AI patients’ knowledge and special needs for patient education through a multiple choice question (MCQ)-based survey and to compare the results with physician’s expertise.

Materials and Methods

We conducted a comprehensive anonymous survey in AI patients treated at the Endocrine outpatient clinics of the University Hospital in Kiel and Luebeck, Germany. The questionnaire (see Supplementary material) included a general information section, four questions regarding patient care and supply of information on AI, as well as 25 MCQs on different aspects of various GC preparations, physiological cortisol production, symptoms of GC over- and under-replacement and adjustment strategies in illness and stress. Data were collected in three months during summer 2016; a total of 40 patients were asked to fill out the questionnaire. Nine out of the 25 MCQs had previously been presented to 209 physicians working at various university hospitals and non-academic institutions in Germany (questionnaire see Supplementary material); those results were now used for comparison between patients’ and physicians’ knowledge on GC replacement therapy in AI. The study protocol was approved by the Ethics Committee of the University of Luebeck, Germany, informed consent was obtained (Az:16-090).

All questionnaires were filled out anonymously with data being compiled in an Excel data sheet afterwards, and a descriptive analysis of the patient group was performed. Missing answers regarding epidemiologic data were omitted; in the MCQ-part we considered them as false replies. Chi-quadrat test was used to determine potential differences between the patient and the physician group with a p-value <0.05 considered to be significant. Fisher’s exact test was used when sample size was small.

Results

Limited patients’ knowledge of their form of adrenal insufficiency

Thirty-three patients (median age 51 years, range 18-85) returned the questionnaire; 181 out of 2,474 answers were missing (7.3%). Patients’ demographics (see Table 1) showed that about a third of the patients (n=12; 36%) suffered from primary AI, whereas more than a third (n=13) was treated for a secondary or tertiary AI. Of note, almost one third of the respondents (n=8; 32%) was not able to name correctly their form of AI leading to substitution therapy. Information on gender of the participants was not available for 2 patients. The average daily dose of hydrocortisone was 25 mg (range 10-50 mg), with patients equally taking their drugs q.d. (n=17) or b.i.d. (n=16).

Table 1 Patients’ demographics

| Patients (n) | 33 |
| Diagnosis (n) |    |
| Primary AI | 12 |
| Secondary/tertiary | 13 |
| Missing | 8 |
| Age (years) |    |
| Median | 51 |
| Range (min-max) | 18-85 |
| Gender (n) |    |
| Female | 19 |
| Male | 11 |
| Missing data | 2 |
| Disease duration (years) |    |
| Median | 16 |
| Range (min-max) | 0.25-43 |
| Hydrocortisone dosage (mg) |    |
| Median | 25 |
| Range (min-max) | 10-50 |
Physicians are the major source of information on AI

The overwhelming majority of AI patients (97.0%) named their treating physician as the main source of education on the disorder. In addition, some patients claimed to have received information on AI by brochures (39.4%) and the internet (24.2%), only two patients indicated to have been instructed by other affected patients. However, almost half of the participants (n=14; 43.8%) reported to be part of an AI support group.

In the previous year, two thirds of the patients increased the substitution dose temporarily (65.5%), one fourth (28.6%) even more than 5-fold, 5 patients did not indicate their answer.

Almost 1/3 of AI patients reported controversies with healthcare professionals regarding GC replacement

To evaluate potential interaction problems between AI patients and medical staff concerning GC replacement therapy, study participants were asked to identify previous situations: Ten participants (30.3%) reported on problems in convincing the medical staff to increase or even continue GC substitution; seven patients (21.1%) with nurses, two patients (6.0%) with general practitioners and three of the study group (9.0%) with other healthcare professionals.

Hydrocortisone was the best-known drug used in replacement therapy

Interviewees were asked on their knowledge regarding various GC formulas and application forms. Among all patients, HC was the best-known drug used for substitution therapy (87.9%), only a few participants were familiar with prednisolone (27.3%), retarded formulations (15.2%) or dexamethasone (9.1%) as potential substitutes (Fig. 1). While dexamethasone due to the pronounced Cushing-like side effects should only be given if no other glucocorticoid is available, it is considered an alternative [9].

Intramuscular injection as one mean to administer GC was hardly known by AI patients (27.3%), whereas knowledge on oral (100%), rectal (63.6%) and intravenous administration (66.7%) was widely spread.

The results for GC substitution therapy are mirrored by those obtained from physicians: The majority of physicians in our previous survey was well aware of hydrocortisone (92.3%), while prednisolone (47.40%) and in particular dexamethasone (22.5%) as well as retard formulations (21.5%) were less familiar to the interviewees.

Seven AI patients (21.2%) answered correctly when asked for the half-time of HC. Similarly, only 19.6% of all physicians were aware of the short-lasting effect of HC.

Patients estimate physiological cortisol production like physicians

To assess knowledge of human physiology with respect to the adrenal glands, patients were asked to identify the average daily production of cortisol in a healthy human being. The correct amount was named by less than half of the patients (n=15; 45.5%);
however, this result was comparable to that of the physicians’ replies: Only 86 out of 209 professional interviewees (41.4%) knew the right answer.

**Severe knowledge deficits of patients were found in glucocorticoid adjustment**

To determine AI patients’ competence on GC replacement therapy, individuals were interviewed regarding personal behaviour and experience with GC dose adjustments (Table 2). While 25 patients (86.2%) knew that in severe illness the dose can reach the 5-fold of normal substitution therapy, none of the interviewed patients identified the need for adjustment in all given situations (severe illness, fever, exhausting sport, psychical stress, headache) correctly. Of note, only 72.7% of patients would correctly double the GC dose in fever (correct physicians’ answers: 94.3%; \(p<0.001\)). Only 12 patients (36.4%) were aware that the GC dose should be increased in intensive sportive activity (physicians: n=85, 40.7%; not significant). Although there is no consensus for a dose adjustment before prolonged physical activity [9] previous data showed that strenuous physical activity is an important factor for adrenal crisis in 7-8% of the cases [3]. Even less patients (n=9; 27.3%) would increase the substitution in severe psychological stress situations, while significant more physicians (n=101; 48.3%) would adjust the dose in this circumstance (\(p<0.05\)). However, the majority in both groups correctly denied dose adjustment in headache. An emergency treatment was considered to be essential by 19 patients (57.5%), significant less compared to the physicians’ opinion (83.7%; \(p<0.001\)). Of interest, none of the patients and only 20 out of 209 physicians (\(p=0.086\)) correctly identified all situations requiring adjustment of therapy.

**Insufficient preparedness of AI patients for emergency situations**

To identify possible problems for AI patients in emergency situations, interviewees were asked on an emergency ID for AI and an emergency kit. The majority of AI patients (n=29; 87.9%) were holder of an emergency ID. Almost 2/3 of the patients (n=20; 64.5%) possess an emergency kit – 2 did not indicate an answer –, but only 12 out of the 20 patients (60%) felt secure about using it. Four patients with an emergency kit (20%) even claimed not to have received any instructions for correct handling.

**Lack of knowledge on symptoms of GC over- and under-replacement**

Everyday symptoms of over- or under-replacement (e.g. weight gain 81.8% or nausea 66.7%) were properly recognized by the majority of patients (Fig. 2A, B). Symptoms only detectable with medical assistance (e.g. hyperglycaemia, hypertension) were less known; only 1/5 of patients were aware of hyperglycaemia as a symptom of over-substitution. Six patients (18.2%) recognized all symptoms of GC over-replacement, whereas seven study participants (21.2%) could name all asked symptoms of under-replacement.

In contrast to these results, there was a significant difference in knowledge on under- and over-substitution among physicians in our previous survey: 148 physicians (71.5%) correctly identified all symptoms of over-replacement. However, only 51 physicians (24.4%) were aware of all symptoms in questions of GC under-replacement in AI. Hence, physicians were by far more aware of potential adverse effects of over-substitution when compared to AI patients (\(p<0.001\)), while both groups scored poorly regarding symptoms of GC under-replacement (\(p=0.249\)).

**Table 2** Percentage of correct answers with respect to GC adjustment

<table>
<thead>
<tr>
<th>Situation requiring adjustment of GC dose</th>
<th>Patients (n=33)</th>
<th>Physicians (n=209)</th>
<th>Significance ((p)-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt; 38°C</td>
<td>72.7%</td>
<td>94.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sportive activity (&gt; 30 min.)</td>
<td>36.4%</td>
<td>40.7%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Psychological stress</td>
<td>27.3%</td>
<td>48.3%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Headache, body aches, no fever</td>
<td>81.8%</td>
<td>85.2%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Acute serious illness</td>
<td>69.7%</td>
<td>87.6%</td>
<td>n.s.</td>
</tr>
<tr>
<td>All correct</td>
<td>0%</td>
<td>9.6%</td>
<td>0.086</td>
</tr>
</tbody>
</table>
Adequate GC replacement therapy is an essential part in treating AI to completely restore patients’ well-being, and delayed delivery of GC in situations of increased cortisol demand can be fatal. The impact of AI on affected patients is high and impairment of quality of life is a frequent observation [17-19]. Our data confirm that physicians are still the main source of information for AI patients [10], despite the widespread availability of professional and semi-professional sources in the internet era. This may be due to the age of participants, with most of them being middle-aged or older, but may change in the following years when younger patients being more familiar with modern communications technologies will form the majority of AI patients. So far, professional education seems to remain essential for best practice and self-management of AI. In contrast to recently published data [12], the vast majority of AI patients (90.0%) was satisfied with the information regarding the disease and given by their physicians. However, this answer might be biased, as the treating physicians distributed the questionnaires. On the other hand, despite this “high-level” specialist-driven care, AI patients still showed major knowledge gaps on the disease and its treatment modalities; e.g. 8 out of 33 individuals (24%) did not know if they had primary or secondary AI. This notion troubles, since therapeutic modalities and outcome differ in some ways, like substitution of the
mineralocorticoid function or additional central hormone deficits. The lack of knowledge regarding the underlying disorder in affected AI patients clearly demonstrates that additional efforts should be made by the treating physicians to inform in detail and a comprehensible way on the disease. Of note, we previously also revealed significant knowledge gaps in physicians of different hospitals and specialties with respect to therapy of AI [14, 15]. While these results probably cannot be generalized to endocrinologists working at Endocrine outpatient clinics, our data rather emphasis that treatment of AI patients is of concern to all physicians, as inconsistent information given by physicians may confuse patient and therefore making it difficult for them to gain or maintain the skills they need to prevent or treat acute AI. Moreover, in real-life, endocrinologists are often not routinely consulted or even available when AI patients are admitted for various reasons. It clearly needs to be addressed that the vast majority of physicians did not recognize all situations that require GC dose adjustment. Accordingly, many patients appear not to know how and when to adjust the GC dose. Similarly, only two thirds of AI patients stated to have an emergency kit, a fact that reflects the inadequate information and education provided by the prescribing physician.

The present data show that patients have in parts similar knowledge about GC replacement therapy as physicians or are sometimes even better informed. Support groups may contribute to an equal or better performance of patients. Recently, Repping-Wuts et al. demonstrated that participation in a glucocorticoid education group meeting resulted in a significant increase of correct answers about proper use of stress-related glucocorticoid dose adjustment and in the use of self-management tools [20].

In our study, common symptoms of over- and under-replacement were more frequently recognized, presumably due to the fact that symptoms like weight gain or osteoporosis are health problems self-experienced or known by the patients. Various studies have shown that 55-80% of affected patients were concerned about long-term side effects of therapy [12, 16, 21], thereby highlighting probable long-term side-effects as osteoporosis, fatigue and obesity. However, almost 80% of patients could neither correctly identify all given symptoms of GC over-replacement nor under-replacement, pointing to a strong need for additional education.

It seems to be a challenge that many patients still have to argue with the attending physician or emergency department staff to receive adequate emergency treatment. This highlights the urgent need for improved information and education of healthcare professionals to overcome this endangering behaviour. This is in accordance to previous data [22-24].

Conclusions

In conclusion, we showed that: (i) AI patients have some knowledge gaps on modalities and adequacy of GC replacement therapy; (ii) long-term management of patients with adrenal insufficiency remains a challenge requiring an experienced specialist; and (iii) further education of physicians as primary source of information is necessary. Additional education by trained physicians who are familiar with all aspects of AI may help patients to empower them to adequate self-management and to facilitate adherence to GC therapy.

Acknowledgments

We thank the participating patients at the Endocrine outpatient Departments of the University Hospitals in Luebeck and Kiel as well as the AI support groups in Luebeck and Kiel for their valuable contributions. In addition, we thank Prof Hendrik Lehnert for reading through the manuscript and his advice in English grammar and wording.

Disclosure

Declaration of funding: There was no funding.
Declaration of financial/other relationships: Nothing to declare.

Conflicting Interests

Nothing to declare.

Author Contributions

BH, DK and CSH designed the study, distributed the questionnaire, performed the statistics, analysed and interpreted the data, wrote and corrected the manuscript. HM contributed to the study idea and gave intellectual input into the manuscript.
References