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Poor quality of life, depressed mood, and memory impairment may be mediated by sleep disruption in patients with Addison's disease

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HIGHLIGHTS

- In latent variable models, Addison's disease directly affected quality of life.
- The indirect effect of sleep on quality of life was significantly greater, however.
- AD had no direct effect on memory, but the indirect effect of sleep did.
- Disrupted sleep may underlie behavioral, cognitive, and affective complaints in AD.

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ABSTRACT

Standard replacement therapy for Addison's disease (AD) does not restore a normal circadian rhythm. In fact, hydrocortisone replacement in AD patients likely induces disrupted sleep. Given that healthy sleep plays an important role in improving quality of life, optimizing cognition, and ensuring affect regulation, the aim of this study was to investigate whether poor quality of life, mood alterations, and memory complaints reported by AD patients are associated with their disrupted sleep patterns. Sixty patients with AD and 60 matched healthy controls completed a battery of self-report questionnaires assessing perceived physical and mental health (Short-Form 36), mood (Beck Depression Inventory—II), sleep quality (Pittsburgh Sleep Quality Index), and cognition (Cognitive Failures Questionnaire). A latent variable model revealed that although AD had a significant direct effect on quality of life, the indirect effect of sleep was significantly greater. Furthermore, although AD had no direct effect on cognitive functioning, the indirect effect of sleep was significant. The overall model showed a good fit (comparative fit index = 0.91, root mean square of approximation = 0.09, and standardized root mean square residual = 0.05). Our findings suggest that disrupted sleep, and not the disease per se, may induce poor quality of life, memory impairment, and affect dysregulation in patients with AD. We think that improving sleep architecture may improve cognitive, affective, and physical functioning.

1. Introduction

Addison's disease (AD) results from destruction of the adrenal cortex, with subsequent decreased production of glucocorticoids and mineralocorticoids. If left untreated, the disease can be life-threatening. The typical medication regime consists of oral hydrocortisone or alternative preparations to replace cortisol, and mineralocorticoid (fludrocortisone) to control sodium and potassium balance [1,2].

Despite current replacement therapy, patients with AD report relatively poor quality of life, with reduced general health perception (both emotional and physical), decreased vitality, memory impairment, increased prevalence of affective disorders, sleep disturbances, and fatigue [3–7]. Despite known and independent relationships between sleep and (a) general health, (b) memory, and (c) mood, no studies in AD patients have explored contemporaneous associations between these four variables. We postulate that poor sleep in AD patients is a biological mechanism underlying self-reported disturbances in quality of life, mood, and cognition.

Lovas, Loge, and Husebye [3] suggest that fatigue is a feature of adrenal failure, that it persists despite replacement therapy, and that it is a major contributor to self-reported impaired health in AD. Patients with AD also demonstrate increased daytime fatigue, which may be a consequence of poor quality of sleep [8]. Although few studies report on sleep impairments in AD, patients appear to experience disrupted sleep that is of poor quality [5,8,9]. Lovas, Husebye, Holsten, and Bjorvatn [5] found that 34% of their sample of patients with AD reported frequent sleep disturbances, including difficulty falling asleep and repeated and early morning awakenings.

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Sleep plays important roles in memory consolidation and affect regulation [10]. Rapid eye movement (REM) sleep and non-REM sleep provide optimal conditions for consolidation of different forms of memory [11]. Furthermore, REM sleep has a mood regulatory function [12], with research demonstrating that patients with mood disorders have, relative to healthy individuals, altered REM intensity and integrity [13]. Because cortisol plays a key role in initiating and maintaining these different sleep stages, it has an important influence on the memory consolidation and affect regulation that take place during normal, healthy sleep [14].

Regarding cognitive functioning in AD, a small number of studies report that, even when on replacement therapy, declarative memory is worse in patients than in healthy controls [15]. Increased levels of anxiety and depression have also been reported in AD populations [6]. None of these studies, however, explored disrupted sleep as a possible mechanism underlying the observed deficits.

No studies in AD patients have explored the relationship between sleep and general health, mood, and memory. Our objectives were therefore to characterize self-reported quality of life in a sample of South African AD patients, and to investigate whether sleep disturbances correlate with poor quality of life, cognitive impairment, and affective dysregulation. We hypothesize that AD patients will report poor quality of life (marked by impaired cognition and mood alterations), and that this may be explained by sleep disturbances. Our hypothesis is based on literature showing that (a) cortisol plays a key role in sleep maintenance and integrity, (b) sleep plays an important role in cognitive functioning and affect regulation, and (c) hydrocortisone replacement medication used by AD patients does not restore the natural circadian rhythm and has direct effects on sleep architecture.

2. Patients and methods

2.1. Research and ethics

The research ethics committees from the Department of Psychology and Faculty of Health Sciences at University of Cape Town, both of which adhere to the Declaration of Helsinki, approved the study procedures. All participants gave informed consent.

2.2. Patients and healthy controls

Sixty adult patients with a diagnosis of AD (recruited from the South African Addison's disease (SAAD) database [16]) completed the self-administered survey described below. The diagnosis of AD was made on the basis of the suggestive clinical presentation, low basal cortisol level and simultaneously elevated ACTH concentration, or, where indicated, a peak cortisol level following 250 μg ACTH stimulation, of less than 550 nmol/L associated with a basal raised plasma ACTH level, exceeding 10.1 pmol/L. There was confirmed etiology for 49 of the 60 AD patients: autoimmune (82%; $n = 40$), idiopathic (12%; $n = 6$), tuberculosis (4%; $n = 2$), and X-linked adrenal hypoplasia (2%; $n = 1$). For all AD patients, clinical and demographic data were extracted by interview and from patient folders.

Sixty healthy controls, recruited using advertisements placed at the University of Cape Town and in large corporations in the Cape Town metropolitan area, also completed the survey.

We used a case–control design, matching groups by age, sex, ethnicity, and household income. We restricted enrolment to individuals between the ages of 18 and 75 years.

2.3. Procedure

A member of the research team systematically inspected the SAAD database and then contacted AD patients telephonically to invite them to participate. Healthy control participants were enrolled in the study after they responded to advertisements by contacting the research team.

All potential participants received a consent form and the study questionnaire in the post, and were asked to return the completed consent form and questionnaires by way of return post. Fig. 1 presents the flow of participants through the recruitment and study processes.

2.4. Measures

A *sociodemographic and medical questionnaire* elicited data about (a) demographic variables (e.g., age, race, and household income), (b) medical history, and (c) type and dosage of current medication, and length of time since diagnosis (AD patients only).

The *Medical Outcomes Study 36-Item Short-Form Health Survey* (SF-36) [17] assesses eight health-related concepts: a) physical functioning; b) role limitations due to physical health; c) pain; d) general health; e) role limitations due to emotional problems; f) energy/fatigue; g) emotional well-being; and h) social functioning. On each of these concepts, the range of scores is 0–100, with higher scores representing better QoL. Four of these concepts (a–d, listed above) are averaged to produce a global Physical QoL score, and the other four (e–h, listed above) are averaged to produce a global Mental QoL score.

The *Beck Depression Inventory—Second Edition* (BDI-II) [18] is a 21-item instrument that measures intensity, severity, and depth of depression in respondents. Possible scores range from 0 to 63, with higher scores representing more depressive symptomatology.

The *Pittsburgh Sleep Quality Index* (PSQI) [19] assesses sleep quality and disturbances over the previous 1 month. It comprises 19 items that relate to seven components: sleep quality, sleep latency, sleep duration, sleep disturbances, habitual sleep efficiency, the use of sleeping medication, and daytime dysfunction due to disrupted sleep. The score on each component ranges from 0 to 3; hence, the total PSQI score ranges from 0 to 21, with higher scores representing more disrupted sleep.

The *Cognitive Failures Questionnaire* (CFQ) [20] is a frequently used 12-item measure of cognitive lapses and slips, over the previous 6 months. Each of the 12 items loads onto one of three factors: *Clumsiness*

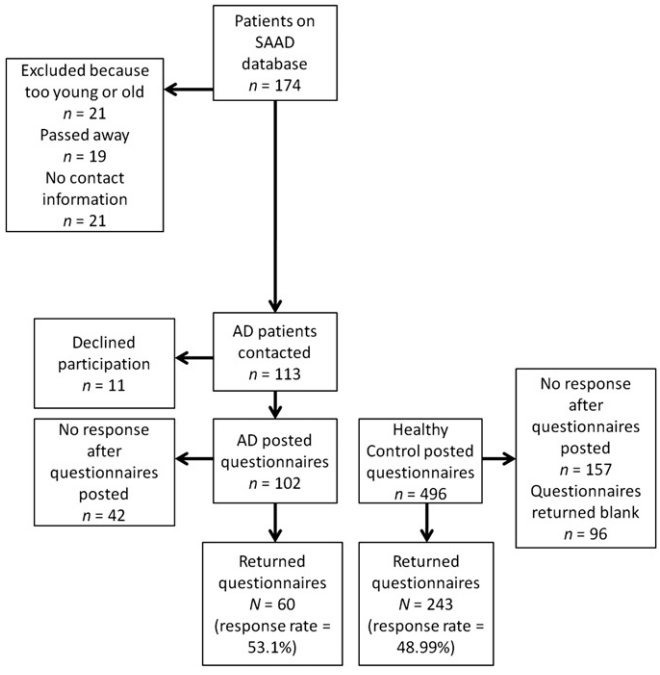

Fig. 1. Flow of participants through the recruitment and study processes. To facilitate a case–control design, we selected, based on age, sex, race, and household income, 60 participants from the pool of 243 possible healthy controls. SAAD—South African Addison's disease database and AD—Addison's disease.