We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,600
Open access books available

177,000
International authors and editors

195M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Chapter

Prevalence and Predictive Factors of Low-Bone Mineral Density in Patients with Addison Disease on Long-Term Corticosteroid Replacement Therapy

Dhouha Ben Salah and Khouloud Boujelben

Abstract

Addison disease (AD) is associated with high risk of decreased bone mineral density (BMD) and osteoporosis. Causes are complex, including lifelong glucocorticoid replacement therapy. The aim of our study was to assess the influence of glucocorticoid replacement therapy on BMD among patients with AD and determine predictive factors of low BMD. A descriptive and analytical cross-sectional study was conducted at the department of endocrinology-diabetology at HediChaker Hospital, including 50 patients with AD for at least 5 years. Serum levels of bone turnover markers were measured and BMD was determined. The mean age of patients was 49.5 ± 13.9 years. Received average daily dose of hydrocortisone (HC) was 27.4 ± 6.7 mg. Mean cumulative HC dose was 374.636 ± 283.821 mg. Mean T-score at lumbar spine and femoral neck was –0.61 ± 1.06 (range, –4.2 –1.1) and –1.18 ± 1.33 (range, –2.9 –1.3), respectively. Low BMD was observed in 48% of patients. No fracture was observed. Patients who developed osteoporosis were significantly older than those with normal BMD (p = 0.018). Menopause was a significant predictor of incident osteoporosis (p = 0.006). Furthermore, osteoporosis was significantly more prevalent among females (p = 0.046). Daily and cumulative HC dose were higher in patients with osteoporosis than those with normal osteodensitometry. Glucocorticoid replacement therapy in AD may induce bone loss. Thus, glucocorticoid therapy must be adjusted to the lowest tolerable dose.

Keywords: Addison disease, glucocorticoid replacement therapy, bone mineral density, osteoporosis, bone health

1. Introduction

Patients with AD lack sufficient endogenous secretion of glucocorticoids [1]. The treatment of AD usually involves lifelong glucocorticoid replacement therapy, most usually oral hydrocortisone (HC). Nevertheless, glucocorticoid replacement therapy...
usually produces cortisol levels higher than the normal physiological endogenous secretion [2].

In spite of the fact that prolonged substitution with glucocorticoids carries a significant risk of bone loss by a proapoptotic action on osteoblasts, promoting osteoclastic activity [3], and decreasing intestinal calcium absorption [4], BMD assessment is not indicated in regular follow-up of patients with PAI. To date, few researches have focused on skeletal health in patients with AD. The majority of studies included relatively small series of patients and reported variable results between BMD, glucocorticoid dose, duration disease (duration therapy), glucocorticoid regimens, and cumulative dose [5–9]. Several studies reported normal BMD [8], while others showed reduced density in all or some bone sites [6]. Thus, the aim of our study was to assess the impact of glucocorticoid replacement therapy on bone density in patients with AD and determine predictive factors of low BMD in this population.

2. Materials and methods

2.1 Study design, area, and period

A cross-sectional study was carried out at the department of Endocrinology-Diabetology of Hedi Chaker Academic Hospital -Sfax –Tunisia, from March 2020 to July 2021. In addition, the study comprised retrospective collection of clinical data from patients’ medical records.

Inclusion criteria were patients with AD and disease duration of at least 5 years. Patients under the age of 18 years, presenting conditions that may affect bone homeostasis (hypogonadism except physiological menopause, primary hyperparathyroidism, hyperthyroidism, rheumatoid arthritis, chronic renal failure, hepatocellular dysfunction, hemochromatosis, chronic pancreatitis, gastrointestinal diseases that cause malabsorption syndrome and prolonged immobilization), taking drugs that may interfere with bone metabolism (heparin, vitamin K antagonist, thiazide diuretics, calcitonin, bisphosphonates, anticonvulsant drugs and hormone therapy for menopause) were excluded.

Patients meeting the inclusion criteria were recruited. All patients gave their written informed consent before being assessed.

A total of 80 patients with AD were contacted, 37.5% of the patients did not respond or declined to be assessed. Lastly, 50 patients with AD were recruited in the present study.

The data of patients including age, gender, age at diagnosis, disease duration, physical activity, Body Mass Index (BMI), and menopausal status for female patients were assessed.

2.2 Glucocorticoid treatment

All patients were treated with HC.

The average daily HC doses were assessed (mg and mg/kg) and were adjusted for body surface area (mg/m²).

As well, cumulative glucocorticoid dose, defined as the cumulative amount of glucocorticoid intake since the time of diagnosis to the date of BMD measurement, was estimated by summing partial cumulative doses for each time period during which the dose remained constant.
To determine partial cumulative dose, we have used the following formula:

\[
\text{daily hydrocortisone dose (in milligrams or in milligrams/kg)} \times \text{time period}
\]

2.3 Biochemical markers of bone turnover

Serum samples of patients were collected to measure calcium, phosphorus, alkaline phosphatase (ALP), vitamin D, and parathyroid hormone (PTH)).

An ALP level above 150 IU/l was considered as high.

PTH (normal range, 15–65 pg./ml) and vitamin D (normal range, 30–100 ng/ml) were measured by electrochemiluminescence immunoassay (ECLIA).

2.4 BMD

BMD was evaluated using dual-energy X-ray absorptiometry (DEXA), at the lumbar spine (L1–L4) (trabecular bone) and femoral neck (cortical bone) sites, based on a standard protocol.

The results were expressed as BMD in g/cm², T- and Z- scores expressed as standard deviation (SD), in both lumbar and femoral sites.

Referring to the World Health Organization (WHO) classification, osteoporosis is defined as a T-score \(\leq 2.5\) SD and osteopenia as a T-score between \(-2.5\) and \(\leq 1\) SD [10].

2.5 Statistical analysis

Statistical analysis of data was done by using the “Statistical Package for Social Sciences” (SPSS) version 25.

Thus, we performed a univariate analysis based on the comparison of means on paired series using the Student test and the non-parametric Mann–Whitney–Wilcoxon test for unpaired series.

Several regression analyses were achieved to recognize factors impacting BMD in patients with AD. Current BMD was correlated with cumulative and average daily glucocorticoid doses, as well as with clinical and laboratory data.

A point estimate of Odds ratio (OR) with a 95% confidence interval was determined to evaluate the strength of relationship.

Statistical significance was accepted if p-value \(<0.05\).

3. Results

3.1 Clinical descriptive data

Median age of patients was 49.5 ± 13.9 years old with extremes ranging from 18 to 78 years. There were 40 females and 10 males.

The majority of patients (70%) were aged between 40 and 50 years old. Ten percent of patients were smokers.

Two thirds (66%) of patients were not physically active.

Approximately 42.5% of females were postmenopausal. All patients took neither calcium oral supplementation nor estrogen replacement therapy.

Average age at diagnosis of AD was 35.5 ± 14.6 years (range, 0–70 years).
Average AD duration was 13.9 ± 8.7 years (range, 5–35 years).
Patients’ average weight was 72.5 kg (range, 62–107 kg), and average BMI was estimated at 28.1 kg/m² (range, 21.2–45.8 kg/m²).
Overweight was noted in 48% of patients and obesity in 26%.

3.2 Glucocorticoid treatment

Average daily HC dose at the time of AD diagnosis was 25.7 ± 9.1 mg (range, 15–50 mg) corresponding to 0.47 ± 0.23 mg/kg (range, 0.8–1.08 mg/kg) and an average daily dose adjusted for body surface area of 16.29 ± 7.54 mg/m² (range, 15.6–37.94 mg/m²).
HC was prescribed twice a day for 67% of patients with an initial daily dose greater than 30 mg in 44% of patients.
During follow-up, the average daily HC dose was 27.4 ± 6.7 mg (range, 15–42.1 mg) corresponding to 0.38 ± 0.128 mg/kg (range, 0.175–0.711 mg/kg) and a mean dose per body surface area of 14.83 ± 4.658 mg/m² (7.486–31.460 mg/m²) (Figure 1).
Thirty-nine (78%) patients received a mean daily HC dose greater than 11 mg/m².
Cumulative HC dose was 374.636 ± 283.821 mg (range, 60–1184, 94 mg) corresponding to 5.924 ± 4.648 mg/kg (range, 0.875–17.238 mg/kg).

3.3 Bone turnover markers

Mean serum calcium and phosphorus levels were 2.29 ± 0.13 mmol/l (range, 1.9–2.55 mmol/l) and 1.10 ± 0.18 mmol/l (range, 0.8–1.66 mmol/l), respectively.

Figure 1.
Average daily HC dose during follow up of patients with AD.
Hypocalcemia was observed in 18% of patients after a mean AD duration of 11.9 ± 7.1 years (range, 4–26 years) and a mean cumulative HC dose of 317.7 ± 211.7 mg (range, 75–702 mg).

In fact, hypocalcemia had no significant correlation with none of glucocorticoid replacement duration (p = 0.397) or glucocorticoid dose (p = 0.680).

Mean ALP was 77.2 ± 28.5 IU/l (range, 15–190 IU/l). Patients presenting an increased ALP level (18%) received higher cumulative HC intake but without statistical significance (413.4 ± 348 mg versus 365.5 ± 271 mg, p = 0.7).

Mean vitamin D level was 22.28 ± 14.14 ng/ml (range, 5.6–78.6 ng/ml). Hypovitaminosis D was observed in 66% of patients.

All patients with hypocalcemia had hypovitaminosis D.

Mean PTH level was 51.79 ± 23.84 pg./ml (range, 16.36–139 pg./ml). An elevated PTH level was observed in 20% of patients who presented with all vitamin D deficiency.

Finally, biochemical parameters of bone turnover in patients with AD showed no significant correlation with none of AD duration or glucocorticoid dose.

### 3.4 BMD in patients with AD

The average BMD at lumbar spine and femoral neck was 0.928 ± 0.174 g/cm² (range, 0.596–1.287 g/cm²) and 0.945 ± 0.145 g/cm², (range, 0.687–1.265 g/cm²), respectively.

The data on BMD at both lumbar spine and femoral neck are shown in Table 1.

The T-scores at lumbar spine were lower than at femoral neck. Similarly, lumbar spine Z-scores were lower than at femoral site.

Twenty-four (48%) patients had reduced BMD (less than 2 standard deviations [SD] of the mean value of an age-matched reference population). Among these patients, 12 had osteoporosis, corresponding to 24% of all patients including in our study. Also, osteopenia was observed in 24% of patients.

But, none had a history of spontaneous or traumatic fracture.

### 3.5 Predictive factors for low BMD in patients with AD

Patients with low BMD were significantly older than those with normal BMD (53.6 ± 11.8 years versus 45.17 ± 15.04 years, p = 0.04).

As well, BMD was significantly more frequent in postmenopausal women (risk ratio = 3.7, p = 0.049) (p = 0.049).

No significant BMD variation was observed according to BMI (p = 0.71) or AD duration (p = 0.79).

PTH level was higher in patients with decreased BMD but without a statistically significant association (56 ± 21.8 pg./ml versus 48.1 ± 25.4 pg./ml, p = 0.1).

<table>
<thead>
<tr>
<th>Scores (SD)</th>
<th>Mean ± SD</th>
<th>Minimum–Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-score lumbar spine (L1–L4)</td>
<td>-1.18 ± 1.33</td>
<td>4.2–1.1</td>
</tr>
<tr>
<td>T-score femoral neck</td>
<td>-0.61 ± 1.06</td>
<td>-2.9–1.3</td>
</tr>
<tr>
<td>Z-score lumbar spine (L1–L4)</td>
<td>-0.92 ± 1.18</td>
<td>3.5–1.3</td>
</tr>
<tr>
<td>Z-score femoral neck</td>
<td>-0.28 ± 0.79</td>
<td>-1.8–1.3</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.

Table 1. Results of bone densitometry in lumbar spine and femoral neck.
Also, vitamin D level was lower in patients presenting low BMD compared to those with normal BMD but still without statistically significant correlation (19 ± 10.2 ng/ml versus 25.2 ± 16.6 ng/ml, p = 0.2).

As for glucocorticoid therapy dose, although it was higher in patients with reduced BMD, no correlation was observed between cumulative HC dose and low BMD. Table 2 shows daily and cumulative glucocorticoid dose variation between patients with normal BMD and those with low bone mass.

### 3.6 Predictive factors for osteoporosis in patients with AD

Patients who developed osteoporosis were significantly older than those with normal BMD (p = 0.018). The menopause was also a significant predictor of incident osteoporosis (p = 0.006). Furthermore, osteoporosis was significantly more prevalent

<table>
<thead>
<tr>
<th>Glucocorticoid dose</th>
<th>Normal BMD (n = 30)</th>
<th>Low BMD (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose (mg)</td>
<td>25.6 ± 6.3</td>
<td>26.0 ± 7.3</td>
<td>0.969</td>
</tr>
<tr>
<td>Daily dose (mg/kg)</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.336</td>
</tr>
<tr>
<td>Daily dose per body surface (mg/m²)</td>
<td>15.0 ± 4.8</td>
<td>14.7 ± 4.6</td>
<td>0.892</td>
</tr>
<tr>
<td>Cumulative dose (mg)</td>
<td>338.9 ± 236.8</td>
<td>408.9 ± 324</td>
<td>0.774</td>
</tr>
<tr>
<td>Cumulative dose (mg/kg)</td>
<td>5.0 ± 3.9</td>
<td>6.8 ± 5.2</td>
<td>0.322</td>
</tr>
</tbody>
</table>

Abbreviation: BMD, bone mineral density.

Table 2.
Correlation between glucocorticoid dose and BMD.

<table>
<thead>
<tr>
<th>Clinical/Laboratory data</th>
<th>No osteoporosis (n = 30)</th>
<th>Osteoporosis (n = 12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>46.7 ± 13.6</td>
<td>58.4 ± 11.4</td>
<td>0.018</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (20%)</td>
<td>0 (0%)</td>
<td>0.046</td>
</tr>
<tr>
<td>Female</td>
<td>28 (56%)</td>
<td>12 (24%)</td>
<td></td>
</tr>
<tr>
<td>Menopause</td>
<td>8 (21%)</td>
<td>9 (75%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Normal BMI (5–25)</td>
<td>23 (54.8%)</td>
<td>7 (16.7%)</td>
<td>0.514</td>
</tr>
<tr>
<td>Overweight (25–30)</td>
<td>7 (16.7%)</td>
<td>1 (2.4%)</td>
<td></td>
</tr>
<tr>
<td>Obesity (&gt;30)</td>
<td>2 (4.8%)</td>
<td>2 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>13.2 ± 8.0</td>
<td>16.4 ± 10.9</td>
<td>0.412</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml)</td>
<td>50.6 ± 23.9</td>
<td>55.8 ± 24.3</td>
<td>0.375</td>
</tr>
<tr>
<td>Vitamin D (ng/ml)</td>
<td>23.7 ± 14.9</td>
<td>17.3 ± 9.9</td>
<td>0.175</td>
</tr>
<tr>
<td>Calcemia (mmol/l)</td>
<td>2.3 ± 0.1</td>
<td>2.3 ± 0.1</td>
<td>0.510</td>
</tr>
<tr>
<td>Phosphoremia (mmol/l)</td>
<td>1.1 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>0.122</td>
</tr>
<tr>
<td>Alcaline phosphatase (IU/I)</td>
<td>72.3 ± 20.3</td>
<td>92.9 ± 43.2</td>
<td>0.275</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index.

Table 3.
Relationships between osteoporosis and patients’ clinical/laboratory data.
among females ($p = 0.046$). No significant association was found between osteoporosis and AD duration as shown in Table 3.

Then, we studied the effect of glucocorticoid replacement therapy on BMD and the occurrence of osteoporosis in patients with AD. Daily and cumulative HC doses were higher in patients with osteoporosis than those with normal osteodensitometry ($26.5 \pm 8.3\text{ mg/day}$ versus $25.6 \pm 6.3\text{ mg/day}$; $462.2 \pm 373.2\text{ mg}$ versus $344.6 \pm 245.5\text{ mg}$), but none of these factors had a significant impact on the occurrence of osteoporosis as shown in Table 4.

### 4. Discussion

#### 4.1 Glucocorticoid effects on calcium-phosphorus metabolism and bone health

Glucocorticoid therapy is the primary cause of secondary osteoporosis. This complication is essentially dependent on the dose and duration of glucocorticoid treatment [12].

According to the medical literature, bone loss occurs in two stages: an early stage characterized by a sharp decline in BMD of between 6 and 12% over the first year of treatment, followed by a long-term phase where BMD slowly declines at a rate of roughly 3% per year [12, 13].

Thus, early in the course of treatment, osteoporotic fractures are significantly more common as a result of high-dose synthetic corticosteroid therapy [14, 15].

The bone effects of glucocorticoid are complex, resulting from direct effects on bone tissue and indirect repercussions on calcium homeostasis and sex steroid production. Glucocorticoids exert a proapoptotic effect on osteoblasts and osteocytes [16]. Type I collagen, a vital component of bone, cannot be synthesized.

The main impact of glucocorticoids on bone cell function is the reduction of osteoformation activity by osteoblasts, resulting in a low osteocalcin level [16].

Glucocorticoids also promote bone resorption through other various mechanisms, such as raising RANKL (Receptor Activator of Nuclear Factor κB Ligand) synthesis and reducing in osteoprotegerin level, an osteoclastogenesis inhibitor.

In addition, glucocorticoids affect phosphocalcic metabolism by decreasing intestinal calcium absorption by inhibiting its transport and increasing renal calcium excretion [4, 17]. This leads to hypocalcemia and consequently secondary hyperparathyroidism [11, 18].

Finally, glucocorticoids influence gonadal hormone production by inducing hypogonadism and may in some situations also reduce adrenal androgens production [16].
In fact, sex steroids promote osteoblast proliferation and maturation, while they inhibit osteoclastic activity conversely, which results in an optimal concentration of calcium at sites of bone mineralization. Estrogens also act directly on bone tissue where their main effect is to inhibit osteoclastic activity [19].

As prescribed at supraphysiological levels, glucocorticoid replacement therapy in AD could have similar effects on phosphocalcic metabolism and the same induced bone side repercussions [20, 21].

4.2 Bone turnover markers in patients with AD

In our study, 18% of the patients had hypocalcemia after a mean disease duration of 11.9 ± 7.1 years, without statistically significant association with HC dose or disease duration.

Our findings are in agreement with those of Suliman et al. [22] reporting low levels of ionized calcium in patients with AD compared to controls (p < 0.001) but without a significant association with HC dose.

Indeed, hypocalcemia is uncommon in isolated AD. The majority of reported cases of hypocalcemia were part of an autoimmune polyendocrinopathy (AIP) associating AD with celiac disease or hypoparathyroidism [23, 24].

In our study, the vitamin D deficiency observed in 66% of patients could partly explain this hypocalcemia.

Some data in medical literature suggested an association between vitamin D deficiency and AD. Ramagopalan et al. [25] observed a significantly high prevalence of autoimmune diseases including AD among 13,260 patients hospitalized for hypovitaminosis D in a British center. It was proposed that vitamin D deficiency may disrupt the immune response and induce inflammatory responses that would trigger the development of autoimmune diseases.

In addition, it has recently been demonstrated that skin hyperpigmentation reduces the skin’s capacity to generate vitamin D3 when ultraviolet B radiation is present [26].

The high melanin content of their skin may account for hypovitaminosis D, which often observed in patients with AD.

4.3 BMD in patients with AD

Several researches have been interested in assessing BMD in AD.

In our series, low BMD was observed in almost half of the patients (48%) of whom 24% had femoral and/or vertebral osteoporosis.

The mean lumbar spine and femoral neck Z-scores were low (−0.92 ± 1.18 and − 0.28 DS, respectively) but remained within the normal range (between −2 and + 2).

Despite the fact that their findings are conflicting, the majority of studies revealed that patients with AD experience a more frequent decline in BMD than the general population [27–30].

Zelissen et al. [6] were the first to find in 1994 the bone loss in 91 patients with AD, with an estimated prevalence of 32% in women and 7% in men.

According to Leelarathna et al. [28], more than 50% of AD patients included in their study (n = 292) had osteopenia, and one patient out of 5 developed osteoporosis. Bone demineralization was predominant in the lumbar spine, in agreement with our results.
Other studies did not observe a significant decrease in BMD in patients with AD [8, 31]. Camozzi et al. [32] analyzed BMD in 87 patients with AD compared to 81 healthy controls, and no higher risk of reduced BMD was found in AD patients in comparison with controls. 

Table 5 summarizes the results of several studies that have analyzed BMD in patients with AD.

Some studies have also investigated the risk of osteoporotic fractures in AD patients.

<table>
<thead>
<tr>
<th>Study, reference number</th>
<th>Year</th>
<th>Country</th>
<th>Population</th>
<th>Study design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florkowski [33]</td>
<td>1994</td>
<td>New Zealand</td>
<td>14 AD</td>
<td>Observational</td>
<td>Women with AD showed a higher risk of low BMD in comparison with males.</td>
</tr>
<tr>
<td>Braatvedt [30]</td>
<td>1999</td>
<td>New Zealand</td>
<td>29 AD</td>
<td>Observational</td>
<td>A significant decrease in BMD in males</td>
</tr>
<tr>
<td>Heureux [27]</td>
<td>2000</td>
<td>France</td>
<td>24 AD</td>
<td>Prospective</td>
<td>More than half of patients (58%) had osteoporosis.</td>
</tr>
<tr>
<td>Jódar [31]</td>
<td>2003</td>
<td>Spain</td>
<td>25 AD</td>
<td>Cross-sectional</td>
<td>No significant reduction of BMD in patients with AD.</td>
</tr>
<tr>
<td>Levás [29]</td>
<td>2009</td>
<td>Norway United Kingdom New Zealand</td>
<td>292 AD</td>
<td>Cross-sectional</td>
<td>Z-score was significantly reduced at both femoral neck (−0.28 SD in Norway and −0.21 SD in New Zealand) and lumbar spine (−0.17 SD in Norway and −0.57 SD in New Zealand).</td>
</tr>
<tr>
<td>Leelarathna [28]</td>
<td>2010</td>
<td>United Kingdom</td>
<td>48 AD</td>
<td>Retrospective</td>
<td>More than half of patients with AD had osteopenia and 1 in 5 patients had osteoporosis.</td>
</tr>
<tr>
<td>Chandy [34]</td>
<td>2016</td>
<td>India</td>
<td>41 AD</td>
<td>Cross-sectional</td>
<td>Osteoporosis was observed in 43% of patients with AD versus 25% in control patients.</td>
</tr>
<tr>
<td>Camozzi [32]</td>
<td>2018</td>
<td>Italy</td>
<td>87 AD</td>
<td>Cross-sectional</td>
<td>No significant difference in BMD was observed between patients with AD and healthy controls.</td>
</tr>
<tr>
<td>Our study</td>
<td>2021</td>
<td>Tunisia</td>
<td>50 AD</td>
<td>Cross-sectional</td>
<td>Low BMD was observed in 48% of patients, 24% of whom had osteoporosis.</td>
</tr>
</tbody>
</table>

Abbreviation: AD, Addison Disease; CI, Corticotropic Insufficiency; BMD, Bone Mineral Density.

Table 5. Synopsis of main clinical studies analyzing BMD in patients with AD.
A Swedish study examined the risk of hip fracture in patients with AD who showed a higher risk compared to healthy controls (6.9 vs. 2.7% in controls; p < 0.001) [35].

Similarly, Camozzi et al. [32] showed that 31.1% of patients with AD had at least one vertebral fracture related to osteoporosis, compared with only 12.8% of control subjects (odds ratio = 3.09).

4.4 Predictive factors of low BMD in patients with AD

*Disease duration*

Lee et al. [36] have demonstrated that bone loss occurs early in AD, even before diagnosis, since glucocorticoids promote osteoblastic precursor differentiation, and therefore, hypocorticism might result in osteoblastic immaturity and reduced bone mass.

Studies investigating the correlation between the age of AD and bone status are heterogeneous, and their results are contradictory. However, the majority of findings have not reported a correlation between disease duration and BMD in patients with AD [6, 8, 28, 31, 34].

*Age*

Bone demineralization in the general population begins progressively from the age of 25 years and increases linearly with age.

In fact, aging leads to an osteoformation decrease by a reduction of osteoblast activity as well as an acceleration of bone resorption due to a state of hyperparathyroidism secondary to the hypovitaminosis D frequently observed in the elderly subject.

This bone loss increases rapidly after menopause in women and remains constant in men [37, 38].

In AD patients, the curve of bone mass evolution according to age is similar to that of the general population.

Thus, Jodar et al. [31] observed that no BMD variation according to age was found. Similarly, Valero et al. [39] in their cross-sectional study of 30 AD patients with an average age of 52.2 years reported the same result.

In our study, patients with low BMD were older than those with normal BMD but without significant differences.

*Menopause*

Various studies studying BMD in AD patients reported a more frequent bone loss (osteopenia and/or osteoporosis) in menopausal women [5, 32, 33, 39].

In a comparative study reported by Camozzi et al. [32], none of the menopausal women in the control group experienced an osteoporotic fracture, while menopausal AD women had a fracture rate of 53%.

This finding suggests a major impact of glucocorticoid replacement therapy in the occurrence of atraumatic fractures in menopausal AD women.

*Glucocorticoid dose*

Most of studies concur that optimal glucocorticoid replacement therapy requires a daily dose of 15 to 20 mg equivalent to 10–12 mg/m² [1, 40].

A recent Endocrine Society Clinical Practice Guideline recommended a daily HC dose of 15–25 mg for patients with AD [2]. But most of AD patients seemed to be on supraphysiological glucocorticoid doses, resulting in catabolic repercussions on bone health.

In our study, 78% of patients received a daily HC dose greater than 11 mg/m². Higher mean cumulative HC doses, particularly in patients with osteoporosis, were observed in patients with low BMD.
Several studies have examined the impact of HC dose on bone health in patients with AD [5, 6, 30, 41].

In a study involving 91 patients with AD, Zelissen et al. [6] observed that mean BMD was negatively correlated with current glucocorticoid dose but only in men (p = 0.032). Patients treated with a daily HC dose of less than 13.6 mg/m$^2$ had normal BMD instead of those receiving more than 16.4 mg/m$^2$.

In another prospective study, Schulz et al. [5] reported that HC dose reduction from 30.8 ± 8.5 mg/d to 21.4 ± 7.2 mg/d induced a significant improvement in lumbar spine and femoral Z-scores in 90 AD patients (from $-0.93 ± 1.2$ to $-0.65 ± 1.5$ (p < 0.05) and from $-0.40 ± 1.0$ to $-0.28 ± 1.0$ (p < 0.05), respectively) [5].

In contrast, Koetz et al. observed that lower glucocorticoid dose did not improve BMD in 81 AD patients [8].

These same findings were also reported by Jodar et al. [31], Florkowski et al. [33], Valero et al. [39], and Chandy et al. studies [34].

Finally, the vast majority of medical researches concur that high cumulative glucocorticoid dose is associated with an increased prevalence of bone demineralization in AD patients.

Table 6 summarizes several studies assessing glucocorticoid dose’s impact on BMD in patients with AD.

<table>
<thead>
<tr>
<th>Study, reference number</th>
<th>Year</th>
<th>Country</th>
<th>Population</th>
<th>Study design</th>
<th>HC dose</th>
<th>Impact of glucocorticoid dose on BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zellissen [6]</td>
<td>1994</td>
<td>Netherlands</td>
<td>91 AD</td>
<td>Cross-sectional</td>
<td>29.2 ± 7.0 mg/day</td>
<td>Significant correlation between daily HC dose and low BMD (p = 0.032) in men.</td>
</tr>
<tr>
<td>Valero [39]</td>
<td>1994</td>
<td>Spain</td>
<td>25 AD</td>
<td>Cross-sectional</td>
<td>30 mg/day</td>
<td>No correlation was found</td>
</tr>
<tr>
<td>Florkowski [33]</td>
<td>1994</td>
<td>New Zealand</td>
<td>14 AD</td>
<td>Cross-sectional</td>
<td>27.6 ± 6.1 mg/day</td>
<td>No correlation was found</td>
</tr>
<tr>
<td>Braatvedt [30]</td>
<td>1999</td>
<td>New Zealand</td>
<td>29 AD</td>
<td>Observational</td>
<td>24 ± 2.4 mg/day CD:2.28 ± 0.64 g/kg</td>
<td>Negative correlation between daily and cumulative glucocorticoid dose and BMD</td>
</tr>
<tr>
<td>Jodar [31]</td>
<td>2003</td>
<td>Spain</td>
<td>25 AD</td>
<td>Cross-sectional</td>
<td>21.9 ± 13.3 mg/day</td>
<td>No correlation was found</td>
</tr>
<tr>
<td>Koetz [8]</td>
<td>2012</td>
<td>Germany</td>
<td>122 AD</td>
<td>Cross-sectional</td>
<td>21.9 ± 4.9 mg/day</td>
<td>No correlation was found</td>
</tr>
<tr>
<td>Chandy [34]</td>
<td>2016</td>
<td>India</td>
<td>41 AD</td>
<td>Cross-sectional</td>
<td>13.0 ± 3.0 mg/m²</td>
<td>No correlation between daily glucocorticoid dose and low BMD</td>
</tr>
</tbody>
</table>
5. Conclusions

Glucocorticoid replacement therapy in AD may induce bone loss. Identification of predictive factors of low BMD in patients with AD is useful in the management of long-term glucocorticoid therapy’s bone impact.

Thus, glucocorticoid therapy must be adjusted to the lowest-tolerable dose and regular measurement of bone mineral density may be useful to identify patients at risk for the development of osteoporosis.

Finally, further studies are needed to better analyze these factors and control BMD during the course of AD.

Acknowledgements

We appreciate the cooperation of all patients who participated in this study, especially during the COVID-19 pandemic.

Author contributions

Khouloud Boujelben: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); validation (equal); writing – original draft (equal); writing – review and

---

**Table 6.**

Synopsis of main clinical studies assessing the impact of glucocorticoid dose on BMD in patients with AD.

<table>
<thead>
<tr>
<th>Study, reference number</th>
<th>Year</th>
<th>Country</th>
<th>Population</th>
<th>Study design</th>
<th>HC dose</th>
<th>Impact of glucocorticoid dose on BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schulz [5]</td>
<td>2016</td>
<td>Germany</td>
<td>90 AD</td>
<td>Prospective</td>
<td>30.8 ± 8.5 mg/day</td>
<td>A decrease in daily glucocorticoid dose from 30.8 mg to 21.4 mg induced a significant improvement in BMD at both lumbar spine and femoral neck sites.</td>
</tr>
<tr>
<td>Camozzi [32]</td>
<td>2018</td>
<td>Italy</td>
<td>87 AD</td>
<td>Cross-sectional</td>
<td>35 mg/day</td>
<td></td>
</tr>
<tr>
<td>Our study</td>
<td>2021</td>
<td>Tunisia</td>
<td>50 AD</td>
<td>Cross-sectional</td>
<td>27.4 ± 6.7 mg/day CD: 374.636 ± 283.821 mg 5924 ± 4648 mg/kg</td>
<td>Significant correlation between daily and cumulative dose and low BMD</td>
</tr>
</tbody>
</table>

Abbreviation: Hc, hydrocortisone; BMD, bone mineral density; AD, Addison disease; CD: cumulative dose.
editing (equal). **Dhouha Ben Salah**: Data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing – original draft (equal).

**Conflict of interest**

No author has any conflict of interest.

**Author details**

Dhouha Ben Salah* and Khouloud Boujelben
Department of Endocrinology Diabetology, Hedi Chaker Hospital, Sfax University, Tunisia

*Address all correspondence to: bs.dhoha@gmail.com

© 2023 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References


Clinical Dermatology. 2018;19(2):223-235


