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Clinical Research Article

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Empiric Determination of the Daily Glucocorticoid Replacement Dose in Adrenal Insufficiency

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Abbreviations: AI, adrenal insufficiency; BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; DCPR, daily cortisol production rate; DGRD, daily glucocorticoid replacement dose; HC, hydrocortisone; PRED, prednisone; SBP, systolic blood pressure.

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Abstract

Background: For the treatment of adrenal insufficiency (AI) in adults, the Endocrine Society's recommended daily glucocorticoid replacement dose (DGRD) is 15 to 25 mg hydrocortisone (HC), which is approximately 1.7 times the reported mean daily cortisol production rate. Prolonged glucocorticoid overtreatment causes multiple morbidities.
Hypothesis: We tested the hypotheses that the DGRD, empirically determined by individual patient titration, is lower than that of the Endocrine Society guidelines and tolerated without evidence of glucocorticoid under-replacement.
Methods: We empirically determined the DGRD in 25 otherwise healthy adults with AI by titrating the DGRD to the lowest dose tolerated as judged by body mass index, blood pressure, serum sodium concentration and AI symptoms. Patients received either HC or prednisone (PRED). The HC equivalent of PRED was assumed to be 4:1.
Results: The mean empirically determined DGRD, expressed as HC equivalent, was significantly less than the midpoint of the Endocrine Society's recommended DGRD (7.6 ± 3.5 mg/m^2 vs 11.8 mg/m^2; $P < 0.001$). The DGRD in the adrenalectomy group was not significantly different than the DGRD of those with other AI causes (7.9 ± 4.0 mg/m^2 vs 7.3 ± 3.1 mg/m^2; P = ns), demonstrating that the empirically determined DGRD was not biased by residual cortisol secretion. There was no evidence of glucocorticoid under-replacement as determined by measured biometrics and AI symptoms.

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Conclusions: We conclude that an empirically determined DGRD is significantly lower than that of the Endocrine Society guidelines and tolerated without evidence of glucocorticoid under-replacement.

Key Words: adrenal insufficiency, glucocorticoid replacement dose

The optimum daily glucocorticoid replacement dose (DGRD) is critical for adult patients with adrenal insufficiency (AI). Under-replacement may result in weight loss, hypotension, hyponatremia, and death [1, 2]. In contrast, excess glucocorticoids cause osteoporosis, diabetes, hypertension, immune suppression, venous thrombosis, and predispose to premature death [3-6]. The optimum DGRD remains unknown.

The current Endocrine Society AI guidelines recommend an adult DGRD of 15 to 25 mg of hydrocortisone (HC) [1]. Assuming an average body surface area (BSA) of 1.7 m^2, this is a DGRD of 8.8 mg cortisol/m^2 to 14.7 mg/m^2 (midpoint = 11.8 mg/m^2). In the largest group of patients evaluated using stable isotope dilution technologies, the mean daily cortisol production rate (DCPR), is 7.0 mg/m^2 [7]. The midpoint of the Endocrine Society's recommended DGRD is approximately 1.7 times higher than this DCPR. The DGRD recommended by the Endocrine Society and the slightly greater replacement doses suggested by others [8] prevent complications of glucocorticoid under-replacement but exceed normal DCPR and may not be benign. For example, some large registry-based studies have found that patients with both primary and secondary AI on standard glucocorticoid replacement have a 2-fold greater mortality due to cardiovascular, infectious, and malignant diseases that are potentially due to over-replacement with glucocorticoids [3-5]. More recently there are concerns that excess glucocorticoid replacement may interfere with immune modulating antitumor responses and predispose to SARS-CoV-2 [8, 9]. A DGRD exceeding the DCPR may cause these adverse outcomes. However, it is not known if AI patients will tolerate lower replacement doses.

In our practice, the DGRD of each AI patient is titrated to the lowest tolerated glucocorticoid dose. Therefore, we are in a position to test the hypotheses that an empirically determined DGRD is lower than that of the Endocrine Society guideline, similar to that of DCPR, and tolerated without evidence of glucocorticoid under-replacement.

1. Methods

A. Patients

This study was approved by the Institutional Review Board at the University of Connecticut Health Center. We retrospectively identified and analyzed 25 otherwise healthy adult patients (16 women and 9 men) with AI. Data were collected from the records of the University of Connecticut Health Center, Department of Endocrinology from January 1, 2000 to May 22, 2020. AI was assumed for those patients who had undergone bilateral adrenalectomy. In all others, AI was confirmed by a 250 mcg cosyntropin stimulation test or an insulin hypoglycemic test. Consistent with the Endocrine Society guidelines, all patients with AI had a serum cortisol concentration ≤17 mcg/dL (470 nmol/L), when maximally stimulated at 60 minutes following cosyntropin or 30 minutes following a nadir glucose <40 mg/dL (2.22 mmol/L) on an insulin hypoglycemia test. Nineteen patients (76%) had primary AI due to bilateral adrenalectomy (n = 13), autoimmune destruction (n = 5), or hemorrhage due to antiphospholipid antibody syndrome (n = 1). Six (24%) patients had secondary AI due to pituitary fossa tumors with pituitary surgery (n = 5) or pituitary hemorrhage (n = 1). Patients with other significant active medical problems were excluded. In particular, we excluded patients with active malignancies, who had developed AI on immune therapies, and patients with other metastatic disease. Patients with pituitary disorders and AI based on an abnormal cosyntropin stimulation test or insulin hypoglycemia test were excluded, if they did not require any daily glucocorticoid replacement to treat clinical features of AI. These individuals were considered as having partial secondary AI. None of the patients with secondary AI were patients with pituitary Cushing disease in whom the axis might recover. No patients were being treated with antiseizure medications, antiviral medications or other medications that would alter CYP3A4 activity [10].

About half of the patients in this study had undergone bilateral adrenalectomy. This relatively high proportion is due to one of the investigator's (C.D.M.) patient population that is enriched in adrenal disorders that required bilateral adrenalectomy. Diagnoses included bilateral pheochromocytoma, Cushing disease that had failed medical and pituitary directed therapies, and Cushing syndrome caused by bilateral micronodular dysplasia, bilateral macronodular hyperplasia, or bilateral adrenal adenomas.

Individual patient data regarding type of adrenal insufficiency, titration duration and treatment, and biometric measurements are reported in Table 1.

Table 1. Individual Patient Data

Subject	*Age* (y)	*Sex*	*AI*	*Time Intervals* (y)		*HC Equivalence* (mg)		*Fludrocortisone* (mg)		*BMI* (kg/m^2)		*SBP* (mm Hg)		*DBP* (mm Hg)		*Serum [Na$^+$]* (mmol/L)	
				Titration Time	*Time on Lowest Dose*	*Initial*	*Final*	*Initial*	*Final*	*Initial*	*Final*	*Initial*	*Final*	*Initial*	*Final*	*Initial*	*Final*
1	31	M	2°	0.7	10.8	20	16	0	0	35.7	35.5	120	104	85	76	141	140
2	62	M	2°	6.5	8.3	16	8	0	0	63.6	45.9	130	114	80	60	---	137
3	74	M	2°	10.3	3.1	20	15	0	0	32.4	30.8	120	140	62	60	138	137
4	64	M	2°	4.4*	1.3	12	12	---	0	---	23.9	---	134	---	82	---	139
5	70	F	2°	0.1	10.7	16	12	0	0	20.9	27.3	120	118	80	78	139	136
6	45	F	2°	6.8*	13.8	15	15	0	0	---	26.2	---	136	---	91	---	137
7	37	F	1°	2.4	2.9	40	4	0.1	0.1	34.4	35	128	120	80	80	139	138
8	67	F	1°	4.9*	14.8	20	20	0.1	0.1	24.1	23.4	110	148	75	100	140	145
9	53	F	1°	13.8	0.5	15	10	0.1	0.1	27.4	28.4	118	105	80	70	---	141
10	62	F	1°	9.4*	8.3	20	20	0.2	0.1	---	19.9	---	130	---	80	---	138
11	49	F	1°	4.1	8.8	40	5	0.1	0.1	29.9	24.7	110	116	70	80	143	133
12	29	F	1°	4.3	0.5	40	8	0.1	0.2	40.6	32.1	120	118	82	58	138	137
13	88	F	1°	19.6*	7.8	20	20	0.05	0.1	---	32.7	---	120	---	50	---	136
14	78	F	1°	2.3	5.2	40	12	0.1	0.1	37.3	22	122	150	70	70	139	135
15	28	F	1°	1.8	0.5	40	8	0.1	0.1	41.4	34.4	110	107	75	71	141	139
16	38	M	1°	1.5	0.8	80	16	0.1	0.1	36.8	31	130	110	85	80	136	140
17	54	F	1°	12.3	2.3	10	7.2	0.2	0.2	25.5	26.2	100	90	70	66	138	139
18	61	F	1°	16.4*	14.4	20	20	0.2	0.2	---	24.2	---	110	---	68	---	134
19	59	M	1°	0.7	1.5	40	20	0.1	0.1	24.6	23.7	130	114	80	78	137	136
20	32	F	1°	1.8	10.5	20	10	0.2	0.1	33.8	39.6	145	98	110	62	---	138
21	71	F	1°	1.5	2.8	40	12	0.1	0.1	26.7	28.7	128	132	74	88	134	141
22	64	F	1°	10.3*	7.4	20	20	0.2	0.2	---	26.5	---	124	---	84	---	140
23	66	M	1°	9.8*	15.1	15	15	0.1	0.1	---	24.5	---	126	---	76	---	137
24	49	M	1°	6.4	5.3	40	12	0.1	0.2	27.6	27.6	120	150	85	88	135	134
25	60	M	1°	0.9	5.2	35	30	0.1	0.1	25.2	23.7	150	142	80	82	141	141

Individual patients data regarding type of adrenal insufficiency (AI), titration duration and treatment, and biometric measurements are reported. Time intervals are given as titration time (the duration from the start of titration—labeled as "initial" – to the start of the lowest glucocorticoid dose given), and the time on the lowest dose (the duration from the start of the lowest glucocorticoid dose to the most recent encounter on the lowest dose—labeled as "final"). Total time of treatment can be calculated by adding the titration time and with the time on the lowest dose. Patient's data include hydrocortisone (HC) equivalence dose, fludrocortisone dose, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and serum sodium concentration. 1° indicates primary AI; 2° indicates secondary AI. (*) indicates biometric variables are no longer available in the patient's current chart. F indicates female; M indicates male. The patient's age indicates the time of the most recent data extraction.

B. Determination of Each Patient's DGRD

Patients received either HC or prednisone (PRED). The HC equivalent of PRED was assumed to be the standard 4:1 ratio, which is based on the relative potency of prednisolone (the active metabolite of PRED) to HC, the duration of the glucocorticoid effect, and the bioavailability of oral HC and PRED of 100% and 80%, respectively [9, 11-13]. The choice of glucocorticoid was dependent on cost, availability, and patient preference. Fifteen patients were treated with PRED, and 10 patients were treated with HC.

The DGRD for each patient was determined by titrating the glucocorticoid replacement to the lowest possible dose tolerated by the patient or to the prespecified lower titration limit of 1 mg/d for PRED or 5 mg/d for HC. Both PRED and HC were divided into twice-a-day doses except for patients on 1 mg/d PRED or 5 mg/d HC, when it was given once daily. The duration of the empirically determined DGRD treatment ranged from 0.5 to 15.1 years (mean ± standard deviation [SD] = 6.5 ± 4.9 years).

Adjustments of the glucocorticoid replacement were dependent on the clinical situation. In general, following surgical procedures such as bilateral adrenalectomy, glucocorticoid replacement doses were decreased over a period of weeks to a HC equivalent of 30 mg/d. For all patients on about 30 mg/d HC equivalent, decreases of approximately 5 mg/d of HC equivalent were made at approximately 2- to 12-month intervals, although occasionally a further decrease was made after the patient had been on a consistent dose for years. Under-replacement and need

for increased dose of glucocorticoid replacement were the following: body mass index (BMI) <18.5 kg/m^2, systolic blood pressure (SBP) < 90 mm Hg, diastolic blood pressure (DBP) < 50 mm Hg, serum sodium concentration <133 mmol/L, and AI symptoms (nausea, vomiting, anorexia, and fatigue not due to other identifiable causes). For patients with primary AI, the fludrocortisone dose was titrated to normalize the plasma renin activity.

C. Biometric Variables

For each patient, measurements were made of BMI, age, SBP, DBP, and serum concentration of sodium, after the patient had been on a stable glucocorticoid and mineralocorticoid replacement dose for at least 6 months. Arm blood pressure measurements were performed manually in the office by one of the authors (C.D.M.) after the patient had been sitting quietly for more than 15 minutes. BSA was calculated using both the standard Mosteller formula [14] and the Schlich formula that accounts for gender [15].

D. Calculation of the Endocrine Society's DGRD Normalized to BSA

The Endocrine Society's recommended DGRD of 15 mg/d to 25 mg/d of HC was normalized to BSA by assuming a population of half women and half men. BSA was calculated from the average United States height (175 cm for men and 162 cm for women) and ideal body weight (70 kg for men and 54 kg for women). The average BSA was 1.70 m^2 using the gender-neutral Mosteller formula and 1.61 m^2 using the gender-sensitive Schlich formula. Hence, the Endocrine Society's recommended DGRD is 8.8 to 14.7 mg/m^2 using the gender-neutral Mosteller formula [14] and 9.3 to 15.5 mg/m^2 using the gender-sensitive Schlich formula [15].

E. Frequency of Adrenal Crisis

A chart review for the duration (up to a maximum of 5 years) that each patient had been on the lowest DGRD was performed to identify episodes of adrenal crisis. Adrenal crisis was defined as an acute deterioration in health status associated with absolute hypotension (SBP <100 mm Hg) or relative hypotension (SBP ≥20 mm Hg lower than usual), or hyponatremia resolving rapidly with parenteral glucocorticoids. This definition is somewhat broader than that used by Rushworth et al [10].

F. Statistical Analysis

The one-sample t-statistic was used to test the null hypotheses that the empirically determined DGRD is not different than the midpoint DGRD recommended by the Endocrine Society, and that the empirically determined DGRD is not different from the mean reported DCPR.

Comparisons were performed within the AI group. Ordinary least squares linear regression analysis was performed to determine if there were any correlations of the DGRD with age and with the 4 different biometric variables that might indicate glucocorticoid under-replacement. The 2-group t-statistic was used to compare the DGRD in the adrenalectomy group patients to those with other causes of AI and to compare the DGRD in patients treated with PRED to those treated with HC. To account multiple testing within the AI patient group, a Bonferroni correction was used; alpha (0.05) was divided by the number of additional comparisons (total of 7) to yield critical p value for evaluating statistical significance of $P < 0.0071$).

2. Results

The primary goal of this study was to compare the empirically determined DGRD with both the DGRD recommended by the Endocrine Society and the reported DCPR determined by stable isotope methodology. As shown in Fig. 1, the empirically determined DGRD (mean ± SD), expressed as HC equivalent dose and adjusted for BSA (Mosteller formula), was 7.6 ± 3.4 mg/m^2 (range, 1.9-14.4). This empirically determined DGRD was significantly less than the midpoint of the Endocrine Society's recommended DGRD (11.8 mg/m^2; $P < 0.0001$) and closely approximated the reported DCPR mean (7.0 mg/m^2; $P = 0.4$) and range (2.7-14 mg/m^2) [7].

To compare DGRD with DCPR, it was necessary to correct for BSA. However, this adjustment may have biased our comparison to the Endocrine Society recommended DGRD, since the average BSA of our specific study group

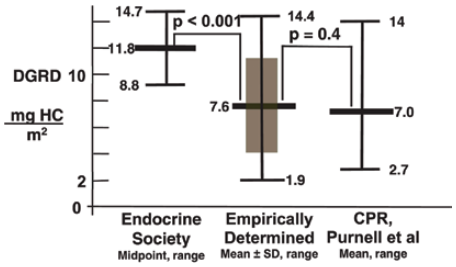

Figure 1. Daily glucocorticoid replacement dose (DGRD) comparisons. The DGRD is expressed as mg hydrocortisone (HC) or HC equivalent normalized for body surface area. The empirically determined DGRD (mean, SD, and range) reported in this study is compared with Endocrine Society Guideline midpoint and range [1] and to the daily cortisol production rate (DCPR; mean and range) reported by Purnell, et al [7]. The empirically determined DGRD (7.6 ± 3.5 mg/m^2) was significantly less ($P < 0.01$) than the midpoint of that recommended in the Endocrine Society Guideline (11.3 mg/m^2) [1], but not significantly different from the mean DCPR of 7.0 mg/m^2 reported by Purnell, et al [7]. The empirically determined DGRD range was similar to the DCPR range determined by Purnell, et al [7].

(1.88 m^2) is greater than the idealized BSA (1.7 m^2) used to normalize the Endocrine Society recommended DGRD. To account for this potential bias, we used 2 different approaches to compare the empirically determined DGRD to the Endocrine Society DGRD. First, we compared the raw DGRD in mg of HC equivalent/d. The difference between the empirically determined DGRD and the midpoint of the Endocrine Society DGRD remains highly significant (13.9 ± 6 mg vs 20 mg, respectively; $P < 0.001$). Second, we used the mean BSA specific to our study group (1.88 m^2) to correct the Endocrine Society midpoint DGRD for BSA. In this case, the difference between the empirically determined DGRD and the Endocrine Society DGRD midpoint still remains highly significant (7.6 ± 3.5 mg/m^2 vs 10.6 mg/m^2, respectively; $P < 0.001$). Therefore, the difference between the empirically determined DGRD and the Endocrine Society recommended DGRD is not due to a bias inherent in the BSA adjustment.

To be certain that the DGRD was not biased by residual cortisol secretion necessitating lower replacement doses, we compared the DGRD in the 13 patients who had undergone bilateral adrenalectomy to the 12 patients with other AI causes. Figure 2 shows that there is no significant difference between the empirically determined DGRD in the adrenalectomy group and the empirically determined DGRD in those with other causes of AI (7.9 ± 4.0 mg/m^2 vs 7.3 ± 3.1 mg/m^2; $P = 0.70$).

Fifteen patients were treated with PRED and 10 with HC. We compared the empirically determined DGRD of these 2 groups to confirm that the empirically determined DGRD was independent of the choice of glucocorticoid. Figure 3 shows that there is no significant difference between the empirically determined DGRD in those patients treated with PRED as compared with those treated with HC (7.3 ± 3.2 mg/m^2 vs 8.7 ± 3.6 mg/m^2; $P = 0.32$).

Since older individuals have been reported to produce more cortisol than younger individuals, we evaluated the relationship between the empirically determined DGRD and age. As shown in Fig. 4, there was a nonsignificant trend for the empirically determined DGRD to correlate with age ($r^2 = 0.27$; $P = 0.008$).

To evaluate for tolerability of the low DGRD, we looked for evidence of glucocorticoid under-replacement by determining the mean, SD, and range of each of the biometric parameters and also by examining the correlation of DGRD with BMI, SBP, DBP, and serum sodium concentration. As shown in Table 2, the mean of each biometric variable was in the normal range, and there were no significant correlations to suggest under-replacement. Three patients had a serum sodium concentration <135 mmol/L: 2 were 134 mmol/L, and 1 was 133 mmol/L. Unexpectedly, as shown in Fig. 5, there was a significant negative correlation of BMI with DGRD ($r^2 = 0.30$; $P = 0.005$). When using the Schlich BSA formula to account for gender, the correlation of BMI with DGRD was no longer statistically significant ($r = 0.51$; $P = 0.009$). No other correlations or trends were created or lost using this gender-dependent BSA formula.

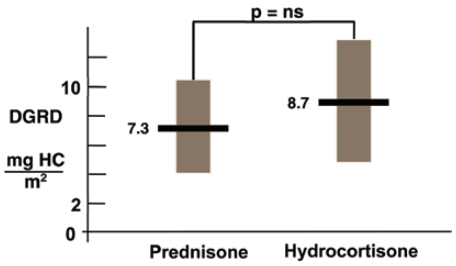

Figure 3. DGRD administered as prednisone (PRED) or hydrocortisone (HC). There is no significant difference in the DGRD of AI patients being treated with PRED (n = 15) as compared to those being treated with HC (7.3 ± 3.2 mg/m^2 vs 8.7 ± 3.6 mg/m^2, respectively; $P = 0.32$). The DGRD is expressed as mg hydrocortisone (HC) or HC equivalent normalized for body surface area.

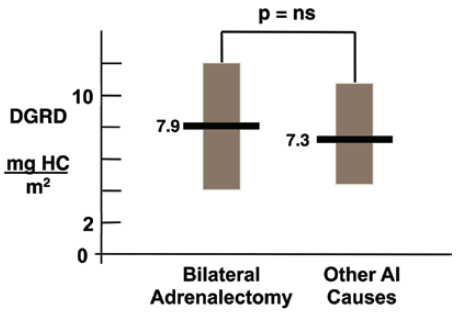

Figure 2. DGRD in bilateral adrenalectomy patients. The empirically determined DGRD in patients who had undergone bilateral adrenalectomy (n = 13) was not significantly different from the empirically determined DGRD for the patients with all other causes of AI (7.9 ± 4.0 mg/m^2 vs 7.3 ± 3.1 mg/m^2, respectively; $P = 0.70$). The DGRD is expressed as mg hydrocortisone (HC) or HC equivalent normalized for body surface area.

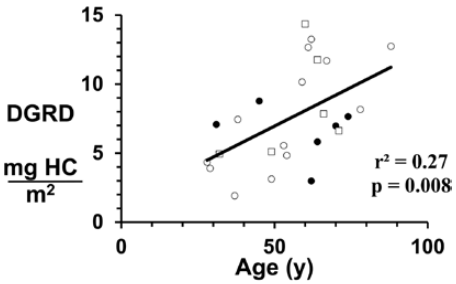

Figure 4. Relationship of DGRD with age. There is a nonsignificant trend for the empirically determined DGRD to correlate with patient age ($r^2 = 0.27$; $P = 0.008$). The DGRD is expressed as mg hydrocortisone (HC) or HC equivalent normalized for body surface area. Solid circles represent patients with secondary AI, open circles represent patients with primary AI due to bilateral adrenalectomy, and squares represent patients with primary AI due to autoimmune disorders.

Table 2. Biometric Measurements (mean, SD, range) and Correlation With DGRD

Biometric	*Mean*	*SD*	*Range*	*r*	*P*	*Summary*
BMI (kg/m^2)	29	6.0	20-46	0.55	0.005	Negative correlation
Age (years)	56	16	28-88	0.52	0.008	Positive trend
SBP (mm Hg)	122	16	90-150	0.35	0.09	Weak positive trend
Serum sodium concentration (mmol/L)	138	2.7	133-145	0.18	0.38	No correlation
DBP (mm Hg)	75	12	50-100	0.18	0.39	No correlation

Biometric measurements evaluated include body mass index (BMI), age, systolic blood pressure (SBP), serum sodium concentration, and diastolic blood pressure (DBP).

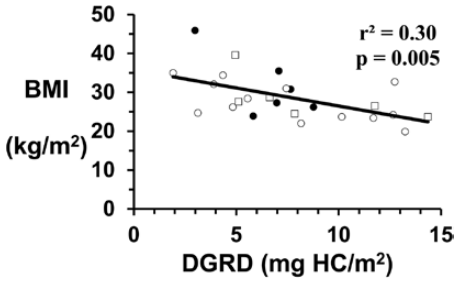

Figure 5. Relationship of DGRD with body mass index (BMI). There is a negative correlation of BMI with DGRD (r^2 = 0.30; P = 0.005). The DGRD is expressed as mg hydrocortisone (HC) or HC equivalent normalized for body surface area. Solid circles represent patients with secondary AI, open circles represent patients with primary AI due to bilateral adrenalectomy, and squares represent patients with primary AI due to autoimmune disorders.

We considered the possibility that the glucocorticoid effect of fludrocortisone substantially influenced the empirically determined DGRD. In those patients with primary AI, there was no correlation between the empirically determined DGRD and the fludrocortisone dose (r = 0.07; P = 0.79).

To determine the frequency of adrenal crisis during treatment with the lowest titrated DGRD, the chart review identified 2 episodes of adrenal crisis, in a total of 95 patient-years for a rate of 2.1 per 100 patient-years.

This study was not designed to determine if there were adverse effects of excess glucocorticoid replacement. Interestingly, a positive weak trend was seen with SBP and DGRD (r = 0.35; P = 0.09). Furthermore, after excluding elevated BMI, disorders that potentially could have been exacerbated by excess glucocorticoids were found in 5 patients: 2 with hypertension, 1 with hypertension plus type 2 diabetes, 1 with unexplained pulmonary embolus, and 1 with osteoporosis. All 5 patients in this group were being treated with a DGRD that was above the mean empirically determined DGRD. There was a nonsignificant trend for the mean DGRD in this group with potential glucocorticoid complications to be greater than that of the remaining 20 AI patients (10.3 ± 2.4 mg/m^2 vs 6.8 ± 3.2 mg/m^2; P = 0.03).

3. Discussion

The discrepancy between currently recommended DGRD and the DCPR is, in part, historical. Initial measurements of DCPR ranged from about 12 to 15 mg/m^2, with subsequent DGRD recommendations equaling these estimates (about 20-30 mg HC or its equivalent). These early DCPR measurements were subject to multiple sources of error as discussed elsewhere [16]. Subsequent studies in the 1990s using deconvolution analysis in young men determined a mean DCPR of 5.3 ± 0.5 mg/m^2 [17] that was similar to the DCPR of 5.7 ± 1.3 mg/m^2 observed for a group of young men and young women using steady state, stable isotope tracer infusion of deuterium-labeled cortisol [16]. Using this same methodology in a larger group of adult men and women (n = 54) with a broad age range (19-70 years), the reported mean DCPR is 7.0 mg/m^2 (range, 2.7-14 mg/m^2) [7]. The clinical response to these more recent DCPR measurements has been mixed. Some clinicians have suggested continuing replacement at the previously recommended 20 to 30 mg/d of HC or its equivalent [8]. Others have suggested that this dose is too high for most patients and have proposed titrating to a DGRD more closely approximating the DCPR with some adjustment for BSA [18]. The Endocrine Society and others have compromised, recommending 15 to 25 mg/d of HC [1, 2, 19]. Although a number of studies have been directed toward the timing of the glucocorticoid dose [20], there has been less attention directed toward the total dose.

In this study, we found that the empirically determined DGRD is significantly below most recommendations [1, 8] but closely approximates the reported DCPR both in mean value and range [7]. Glucocorticoid over-replacement is difficult to determine, since the adverse effects are nonspecific and make take years to decades to develop. In contrast, under-replacement is more easily identified. The relatively specific and easily quantitated biomarkers include low BMI, hyponatremia, hypotension, and AI symptoms. Only fatigue is a less specific marker. The DGRD for each patient was titrated based upon objective and subjective tolerability, an approach consistent with Endocrine Society guidelines

[1]. We elected not to titrate the glucocorticoid replacement dose based upon serum cortisol concentrations, since the normal range is quite broad and serum cortisol concentrations change rapidly with time following oral administration. There was no evidence of under-replacement in either the entire AI group or those individuals on the very lowest DGRD. Within-group comparisons of HC and PRED suggest that the empirically determined DGRD is not biased by choice of glucocorticoid.

The range of the empirically determined DGRD varies by 7.6-fold as compared to the Endocrine Society guidelines, in which the DGRD varies by only 1.7-fold. The reasons for this difference are likely multifactorial. Furthermore, this difference has important clinical implications. First, if we correctly titrated each patient to his personalized DGRD, then the empirically determined DGRD range is expected to approximate the DCPR range that varies by 5.2-fold. Another reason for the broad range is that some patients refused further titration due to fatigue unexplained by other causes. Fatigue is a very nonspecific symptom, and we may be treating some patients with excessive glucocorticoid doses. This wide range in DGRD has an important clinical implication as well. It should not be assumed that all patients should be titrated to the mean empirically determined DGRD as some will require higher or lower glucocorticoid doses.

There was a trend for the empirically determined DGRD to correlate with age. A significant positive correlation of the DCPR and age has been demonstrated and is due to an increase in cortisol production after the noon meal and from midnight to 6:00 AM in older individuals [7]. This relationship might be considered when adjusting glucocorticoid replacement in older individuals.

The HC equivalent of fludrocortisone is reported to be about 10 to 1 [13, 24-26]. Although we were unable to find a substantial effect of fludrocortisone on the empirically determined DGRD within our subgroup with primary AI, this study may not have been adequately powered to find such an effect.

There are a number of strengths to this study. First, this patient population is enriched in patients with AI due to bilateral adrenalectomy. Therefore, it is unlikely that residual glucocorticoid secretion is the reason that the empirically determined DGRD is below that recommended by the Endocrine Society. Second, we excluded partial secondary AI patients, who required no glucocorticoid replacement, since this might bias the empirically determined DGRD to lower glucocorticoid replacement doses. Third, the clinical features of under-replacement develop relatively rapidly and are consistent across both genders and all ages. Therefore, glucocorticoid under-replacement is likely to have been identified in this study design. Fourth, the patient population is very heterogeneous, varying considerably in age, gender, menopausal status, and previous endocrine abnormality leading to the AI. Therefore, the empirically determined DGRD is likely applicable to most otherwise healthy AI patients. Finally, the DGRD was titrated to relatively inexpensive and commonly collected endpoints, so that this approach can be easily applied in many different clinical situations.

Depending upon the formula used to calculate BSA, there was a significant negative correlation or strong trend for a negative correlation of BMI with DGRD. This relationship may indicate that individuals with endogenous obesity were motivated to down-titrate their DGRD to help control their weight or that we failed to recognize that individuals with normal BMI might be over-replaced. It is exceedingly unlikely that this relationship exists because a low DGRD promotes weight gain. Interestingly, it demonstrates that patients with an endogenous tendency to obesity are able to maintain an elevated BMI on a low DGRD. The reasons for this may be multifactorial and include the current environment that allows easy access to food and minimizes the need to expend calories for survival and increased 11ß-hydroxysteroid dehydrogenase type 1 activity in obesity [27, 28].

There is concern that the empirically determined DGRD of this study may predispose to an increased incidence of adrenal crisis. The incidence of adrenal crisis in our population is possibly less than the reported incidence of adrenal crisis in large populations of about 5 to 8 per 100 patient-years [10, 21-23]. Therefore, the lower DGRD used in this study does not predispose to adrenal crisis.

This study was neither designed nor powered to determine if the higher DGRD of the Endocrine Society guidelines causes adverse outcomes. Since adverse outcomes of excess glucocorticoids are nonspecific and since the patient population is very heterogeneous, it is unlikely that within-group comparisons will identify adverse metabolic, blood pressure, and bone density outcomes in those few patients on the highest glucocorticoid replacement doses. However, we did identify a trend for individuals with possible glucocorticoid-related adverse outcomes to be replaced with a higher DGRD. The current retrospective studies in the literature are mixed. Some, but not all, have found differences in BMI, lipid abnormalities, cardiovascular death, and decreased bone density associated with conventional DGRD [3-6, 29-31]. Association of these metabolic abnormalities with glucocorticoid receptor polymorphisms has generated conflicting results [32, 33]. However, in none of these studies were patients on a DGRD approximating the DCPR compared with those on a conventional DGRD. These conflicting conclusions might be clarified by comparing AI patients on a conventional DGRD with those on a DGRD approximating the DCPR.

There are a number of limitations to this study. Since this is a single-site retrospective analysis, it is subject to possible selection bias. Autoimmune adrenalitis is the most common cause of AI in developed countries [2]. In contrast, our population is enriched in bilateral adrenalectomy patients. We have combined patients with both primary and secondary AI in this study. We have excluded patients with other active medical problems that have not been excluded from other studies of AI. If patients have active infections or metastatic disease, then they may not tolerate these low glucocorticoid replacement doses. Alternatively, in patients in whom a maximum antitumor or anti-infection immune response is beneficial, it may still be helpful to decrease the DGRD as much as possible. This study does not address these conflicting priorities for adjusting the DGRD. Finally, this study does not identify the appropriate glucocorticoid replacement during stress.

4. Conclusion

We conclude that an empirically determined DGRD is significantly lower than that of the Endocrine Society guidelines, similar to that of the reported DCPR and tolerated without clinical evidence of glucocorticoid under-replacement.

Additional Information

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