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Effects of Short-Term Glucocorticoids on Cardiovascular Biomarkers

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Context: Glucocorticoids are known to acutely increase blood pressure, suppress inflammation, and precipitate insulin resistance. However, the short-term effects of glucocorticoids on other cardiovascular risk factors remain incompletely characterized.

Objective: Our objective was to determine the effects of a short course of dexamethasone on multiple cardiovascular biomarkers and to determine whether suppression of morning cortisol in response to low-dose dexamethasone is correlated with cardiovascular risk markers in healthy volunteers.

Design: We conducted a randomized, double-blind, placebo-controlled study.

Setting: The study took place in a tertiary care hospital.
Study subjects: Twenty-five healthy male volunteers, ages 19–39 yr, participated in the study.

Intervention: Subjects received either 3 mg dexamethasone twice daily or placebo for 5 d. Subjects also underwent a low-dose (0.5 mg) overnight dexamethasone suppression test.

Measures: Parameters examined before and after the 5-d intervention included heart rate, blood pressure, weight, fasting lipid variables, homocysteine, renin, aldosterone, insulin resistance (homeostasis model assessment), high-sensitivity C-reactive protein, B-type natriuretic peptide, flow-mediated and nitroglycerin-mediated brachial artery dilatation, and heart rate recovery after exercise. All measurements were done in the morning hours in the fasting state.

Results: Dexamethasone increased systolic blood pressure, weight, B-type natriuretic peptide, and high-density-lipoprotein-cholesterol. Dexamethasone decreased resting heart rate, high-sensitivity C-reactive protein, and aldosterone and tended to attenuate nitroglycerin-mediated vasodilatation. There was no effect on flow-mediated vasodilatation, diastolic blood pressure, triglycerides, low-density-lipoprotein-cholesterol, nonesterified fatty acids, homocysteine, or heart rate recovery. The response of circulating cortisol to low-dose dexamethasone had no significant correlation with any of the cardiovascular risk markers.

Conclusions: Short-term glucocorticoids elicits both favorable and unfavorable effects on different cardiovascular risk factors. Manipulation of specific glucocorticoid-responsive physiological pathways deserves further study. **(*J Clin Endocrinol Metab* 90: 3202–3208, 2005)**

THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) axis is vital for survival in stressful situations such as hemorrhage and sepsis (1). Glucocorticoid deficiency can result in hypotension, weight loss, hypoglycemia, and death, especially in the setting of stress (2). Conversely, exogenous or endogenous glucocorticoid excess can contribute to the development of hypertension, insulin resistance, hyperglycemia, weight gain, hyperhomocysteinemia, and atherosclerosis (3–6). Although epidemiological studies and animal studies suggest accelerated atherosclerosis in the presence of long-term excessive exogenous glucocorticoid exposure (7–9), the extent of inflammation confounds the relationship between glucocorticoid exposure and the atherosclerosis associated with inflammatory diseases (10). In recent years, a growing body of literature suggests that altered endogenous glucocorticoid homeostasis may contribute to the metabolic syndrome and adverse cardiovascular outcomes (11–18), whereas other studies have suggested salutary effects of glucocorticoids on the cardiovascular system (19).

Limited *in vivo* data are available to characterize the effects of glucocorticoids on specific cardiovascular risk factors, except for hypertension and glucose homeostasis, and, with long-term exposure, body fat redistribution. Furthermore, central adiposity resulting from long-term glucocorticoid exposure, rather than glucocorticoids *per se*, may lead to many adverse cardiovascular effects, complicating the assessment of direct glucocorticoid effects on these risk factors (4). Another issue that confounds the evaluation of glucocorticoid-specific regulation of cardiovascular risk factors is that most glucocorticoids used in clinical medicine, such as prednisone, hydrocortisone, and methylprednisolone, have substantial mineralocorticoid effects when used in pharmacological doses. As such, physiological studies using high doses of these agents are, in effect, examining the combined effects of glucocorticoids and mineralocorticoids (8, 20–28).

Based on these limitations of existing literature, we sought

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Abbreviations: BNP, Brain natriuretic peptide; CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA, homeostasis assessment model; HPA, hypothalamic-pituitary-adrenal; LDL, low-density lipoprotein.

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to determine the specific short-term effects of glucocorticoids on cardiovascular biomarkers in healthy volunteers in whom active inflammatory diseases were absent. We used dexamethasone because it has negligible mineralocorticoid effects (29, 30), and we chose a dose of dexamethasone that would be comparable to maximal stress-induced endogenous hydrocortisone production (such as seen in sepsis), approximately 150- to 300-mg hydrocortisone equivalents daily (31, 32). We hypothesized that insulin resistance induced by dexamethasone would adversely affect endothelial function, lipid parameters (particularly triglycerides and nonesterified fatty acids), B-type natriuretic peptide (BNP), and heart rate recovery after exercise. We also sought to determine whether dexamethasone would affect C-reactive protein (CRP) in healthy subjects (with low baseline CRP values), given that glucocorticoids directly stimulate hepatic CRP production (33) while simultaneously suppressing inflammation. We were concerned with the direction of change in these parameters (increase *vs.* decrease) and not with the magnitude of the changes from baseline, which would be affected primarily by the dose and duration of treatment defined by the protocol.

Based on preliminary work by others (14, 34), we also sought to relate these risk markers to the tone of the HPA axis, measured by low-dose dexamethasone suppression testing, to attempt to validate the hypothesis that subtly impaired suppression of endogenous cortisol is related to the metabolic syndrome. We hypothesized that features of the metabolic syndrome, including high waist-to-hip ratio, high body mass index, blood pressure, the ratio of triglyceride to high-density lipoprotein (HDL)-cholesterol, insulin resistance, and endothelial dysfunction, would be negatively correlated with the magnitude of the decrease in circulating cortisol in response to low-dose dexamethasone.

Subjects and Methods

Study design

We conducted a randomized, double-blind, placebo-controlled study in healthy young men. Subjects were treated with 3 mg dexamethasone twice daily for 5 d or with placebo. Multiple physiological markers were assessed before and after the intervention. Additionally, we conducted a low-dose dexamethasone test before the pharmacological intervention; all subjects received 0.5 mg dexamethasone at bedtime (2300 h) followed by assessment of plasma cortisol the following morning at 0800 h.

Subjects

We recruited healthy nonsmoking men, ages 19–39 yr, by local advertisements; volunteers were given a stipend for participation. Potential subjects were excluded if they had any of the following: ongoing medical or psychiatric illnesses, regular use of prescription or nonprescription medications, illicit drug use or excessive alcohol use, surgery or hospitalization in the preceding 3 months, exposure to exogenous glucocorticoids in the preceding year, or nontraditional sleep/wake habits (*e.g.* night-shift work or frequent travel across time zones). Subjects underwent a full history and physical examination, including measurement of height, weight, and waist and hip circumferences. Subjects were advised to maintain their usual sleep-wake schedule, exercise, and dietary habits during the study and to report any changes in their health status or perceived adverse effects of study participation. A structured poststudy questionnaire allowed the subjects to report perceived effects of the study medication on health-related behaviors. Subjects were advised not to take any prescription medications, over-the-counter medications, or alcohol during the protocol. All subjects provided written informed consent. The Cleveland Clinic Foundation Institutional Review Board approved the protocol.

Randomization and blinding

Subjects were randomized by computer to receive dexamethasone or placebo. Investigators and subjects were unaware of treatment assignments. At study completion, all subjects were asked to report whether they believed they received dexamethasone or placebo. Compliance was confirmed by measuring posttreatment cortisol levels (expected to be undetectable in all subjects assigned to dexamethasone). Prospective power analysis indicated that 12 subjects per group would provide 80% power to detect a difference of at least 1.2 SD in the mean change from baseline between the placebo and dexamethasone groups, assuming unequal group variances. At this sample size, we had 80% power to detect a mean change from baseline within each group of at least 0.9 SD and over 80% power to detect Pearson correlation coefficients between continuous measures of at least 0.50 (r^2 at least 0.25).

Laboratory data

Fasting 0800-h blood samples were obtained before and after the 5-d intervention. All samples were promptly centrifuged and stored at −70 C for batch analysis. Plasma BNP was assayed using an automated two-site sandwich immunoassay using direct chemiluminescence (ADVIA Centaur; Bayer Healthcare, Newbury, UK). Serum high-sensitivity CRP was assayed using an immunoturbidometric assay (Modular Analytics; Roche Diagnostics, Indianapolis, IN). Serum triglycerides, total cholesterol, and direct low-density lipoprotein (LDL)-cholesterol were determined enzymatically (Modular Analytics), and HDL-cholesterol was determined using the Friedewald formula. Insulin levels were determined using an enzyme immunoassay (AIA NexIA; Tosoh Bioscience, South San Francisco, CA). Cortisol was measured using a chemiluminometric immunoassay (AIA NexIA). Enzyme colorimetry (WAKO; Alpha Laboratories, Hampshire, UK) was used to determine serum nonesterified fatty acid concentrations. Glucose was measured with an automated oxidation assay (Modular Analytics). Plasma aldosterone was measured by RIA (Diagnostic Products Corp., Los Angeles, CA). Plasma renin was measured as direct active renin by a monoclonal antibody-based two-site immunochemiluminometric assay on the automated Nichols Advantage System (Nichols Diagnostics, San Juan Capistrano, CA). The assay is calibrated against the international reference preparation distributed by the World Health Organization (WHO IRP 68/356), and results are expressed as mU/liter. Both inter- and intraassay variations were well under 8%, and the assay has a functional sensitivity of 0.8 mU/liter. The homeostasis model assessment (HOMA) was used to determine insulin resistance, calculated as [fasting insulin (μU/ml)] × [fasting glucose (mmol/liter)]/22.5 (35).

Blood pressure, heart rate, and weight

Blood pressure and heart rate were determined in triplicate in a rested sitting position using a single automated cuff (DINAMAP); the mean value of the three measurements of diastolic blood pressure, systolic blood pressure, and pulse rate were used in data analysis. Heart rate was also determined while supine, after quietly resting for 15 min. Weight and height were determined manually using a single balance scale.

Brachial artery reactivity

Endothelium-dependent vasodilatation was assessed noninvasively using a 13-MHz harmonic imaging transducer (Acuson Sequoia, Mountain View, CA). Two-dimensional and Doppler flow images of the brachial artery were digitally stored in cine-loop DICOM format and transferred to a workstation for off-line analysis (ProSolv Cardiovascular version 3.0, Indianapolis, IN). A blinded investigator measured the brachial artery diameter before and after proximal arterial occlusion. Transient arterial occlusion was accomplished using a blood pressure cuff placed 4 cm above the antecubital crease and inflated to 180 mm Hg for 5 min and then rapidly deflated. Anatomic landmarks were used to maintain consistent positioning of the probe. Flow-mediated vasodilatation was defined as the percent increase in arterial diameter in response to this ischemic stressor. After a 15-min supine resting period,

non-endothelium-mediated vasodilatation was assessed in a similar fashion in response to a single 0.4-mg dose of sublingual nitroglycerin.

Heart rate recovery

Subjects underwent a standard Bruce treadmill protocol. To ensure that each subject exercised for the same amount of time (and reached the same workload) before and after the intervention, we did not exercise subjects to exhaustion. Instead, during the index study, subjects exercised 1 min beyond achieving 90% of their age-predicted maximum heart rate (220 beats/min minus age in years) (36). Subjects exercised for an identical duration of time during the postintervention assessment, regardless of heart rate. Heart rate recovery was defined as the peak heart rate (at the termination of exercise) minus the heart rate 1 min into the recovery phase of the Bruce protocol (37). This parameter is considered an index of parasympathetic reactivation after exertion (38).

Statistical analysis

We computed the change from baseline to post intervention in each measured variable; variables with highly skewed distributions were log-transformed before this calculation. We compared the placebo and dexamethasone groups on change from baseline using two-sample unequal variance *t* tests. As a secondary analysis, we assessed whether the mean change from baseline within the dexamethasone group was equal to zero using one-sample *t* tests. We assessed the relationships among continuous variables using Pearson correlation coefficients. All tests were two-tailed and performed at a significance level of 0.05. Statistical analyses were performed using JMP 5.1 (SAS Institute, Cary, NC).

Results

Subjects, randomization, and protocol completion

Twenty-five subjects were enrolled in the protocol; 13 were randomized to receive dexamethasone and 12 to placebo. All subjects completed the protocol, and compliance was confirmed in all 13 dexamethasone-treated subjects via undetectable postintervention serum cortisol. Brachial artery reactivity data were incomplete for two subjects, one in each group; one subject refused to take nitroglycerin during the postintervention assessment because of a headache during the baseline study, and technical difficulties affected the data for the other subject.

Unblinding and self-reported effects of the intervention

In the structured postintervention survey, three subjects in each group believed they had received the active drug; seven dexamethasone-treated subjects and four placebo-treated subjects believed they had received placebo. The remaining eight subjects were unsure. Nineteen of the subjects reported no change whatsoever in sleeping, eating, and exercise behaviors; the other six subjects reported minor changes in one or more of these behaviors. Increased appetite was reported in two dexamethasone-treated subjects and one placebo-treated subject ($P > 0.99$).

Effects of the intervention on cardiovascular risk markers (Fig. 1)

The baseline values of the various measured parameters are shown in Table 1; the effects of the intervention are also presented in Table 1. Among subjects treated with dexamethasone, the change in BNP was not significantly correlated with the change in systolic blood pressure ($r^2 = 0.01$; $P = 0.72$), suggesting that increased afterload alone did not account for the change in BNP. Similarly, the change in systolic blood pressure was not significantly related to the change in supine heart rate ($r^2 = 0.05$; $P = 0.26$) or sitting heart rate ($r^2 = 0.01$; $P = 0.70$).

Brachial artery reactivity

As shown in Table 1, flow-mediated vasodilatation was similar in dexamethasone- and placebo-treated subjects, suggesting that short-term dexamethasone did not significantly impair endothelial function.

Low-dose dexamethasone testing

We examined correlations between the absolute change in cortisol from baseline and the various cardiovascular biomarkers. We also examined correlations between each biomarker and the percent decrement of cortisol from baseline. We found no significant correlations between the responsiveness of the HPA axis to low-dose dexamethasone and any of the metabolic-syndrome-associated parameters. Correlation coefficients between specific biomarkers and the absolute change in morning cortisol after 0.5 mg dexamethasone (our hypothesized index of HPA-axis tone) are shown in Table 2. Also shown are the correlation coefficients between baseline cortisol levels and absolute postdexamethasone cortisol levels.

Discussion

Our data suggest that glucocorticoids acutely decrease resting heart rate, increase circulating BNP, lower CRP, and increase HDL-cholesterol without affecting LDL-cholesterol, free fatty acids, or triglycerides. These changes occurred in the setting of a marked increase in insulin secretion but no significant change in circulating glucose levels. We did not find any evidence that short-term glucocorticoids adversely affect endothelial function. Before we address some key differences between our findings and those of other researchers, it is important to recognize that we used a drug (dexamethasone) with negligible mineralocorticoid activity (29, 30) that suppresses endogenous cortisol (which has substantial mineralocorticoid activity). Therefore, it is conceivable that some of the effects we observed might have been mediated in part by decreased mineralocorticoid activity rather than glucocorticoid effects *per se*. In keeping with this, we did observe a significant reduction in aldosterone concentrations in the dexamethasone-treated subjects. Nevertheless, given the well-characterized adverse cardiovascular effects of mineralocorticoids (39), we believe that the use of dexamethasone is a major strength of our study. Indeed, other researchers who attempted to examine the effects of glucocorticoids on cardiovascular risk factors may have unknowingly generated findings that were mediated in part by mineralocorticoid effects of the drugs they chose (such as hydrocortisone and prednisone) (8, 20–28).

Several of our findings deserve comment. Our intervention demonstrates that hyperinsulinemia *per se*, induced by a short course of glucocorticoids, does not invariably lead to the lipid changes typically associated with insulin resistance (high triglycerides, raised nonesterified fatty acids, and low HDL). Rather, glucocorticoids promote insulin secretion,

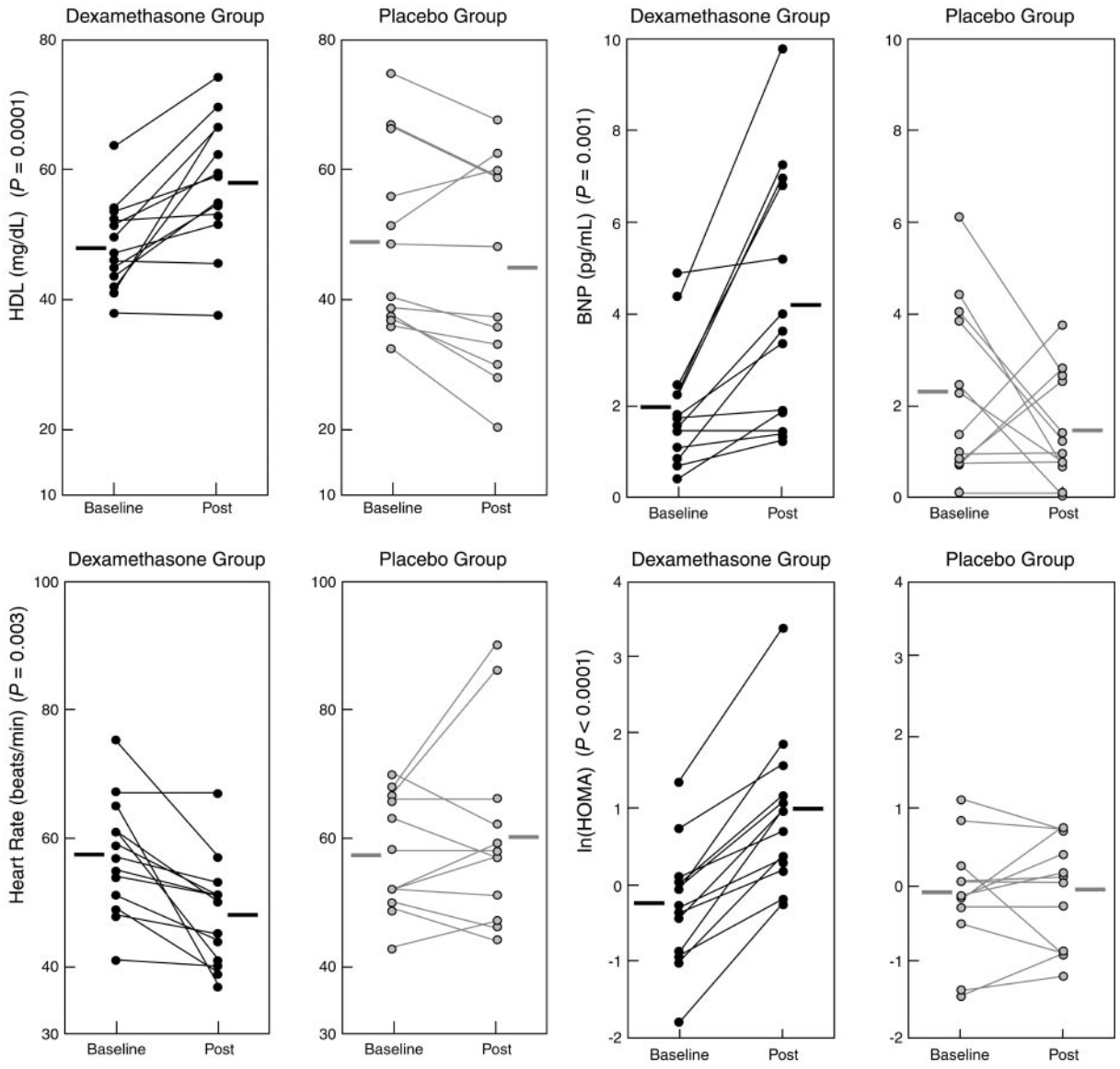

FIG. 1. Dexamethasone-mediated changes in selected cardiovascular biomarkers. The *P* values are for two-sided intergroup comparisons. Means are shown by the *horizontal lines* in the figure *margins*.

which at the level of the liver is likely to limit the action of hepatic lipase, decreasing HDL catabolism (40). Our lipid findings are consistent with one small, nonrandomized study of prednisone-treated patients with systemic inflammatory diseases (20) but differ from other nonrandomized reports that corticosteroid treatment raises triglycerides and LDL (21, 41). The placebo-controlled nature of our study, the short duration of treatment, and the use of healthy volunteers (rather than patients with inflammatory diseases) may explain the differences between our findings and those of other researchers. Additionally, the mineralocorticoid effects of the steroids used in these other studies may have affected lipid parameters, given the known metabolic effects of drugs affecting the renin-angiotensin-aldosterone system (42, 43).

In our subjects, hyperinsulinemia *per se* did not increase sympathetic-parasympathetic balance (based on heart rate measurements). In contrast, the hyperinsulinemia induced by dexamethasone was associated with decreased heart rate at rest and no change in heart rate recovery after exercise. Although hyperinsulinemia during a euglycemic clamp is associated with increased sympathetic tone (44), it is possible that this is caused in part by depletion of other circulating substrates from the circulation, such as fatty acids, protein or potassium, rather than from hyperinsulinemia itself. Alternatively, it may be that dexamethasone is capable of reducing sympathetic tone in the face of hyperinsulinemia. Although the mechanism for this finding is uncertain, it is possible that suppression of CRH by dexamethasone attenuated sympathetic nervous system activity (45) or that increased blood pressure elicited a reflex inhibition of sympathetic tone. Because change in blood pressure was not significantly correlated with decrease in heart rate, this latter mechanism may be less likely but remains possible. Regardless of the mechanism, a reduction in central sympathetic tone may explain

TABLE 1. Effects of dexamethasone treatment on cardiovascular biomarkers

Parameter	Mean (SD) baseline value		Mean (SD) change from baseline		*P* values for dexamethasone-mediated change from baseline[a]	
	Dexamethasone (n = 13)	Placebo (n = 12)	Dexamethasone (n = 13)	Placebo (n = 12)	Between groups	Within group[b]
Age (yr)	23.5 (5.4)	24.9 (5.6)	N/A	N/A	N/A	N/A
Anthropometric measures						
Weight (kg)	79.6 (13.6)	72.1 (13.0)	+1.3 (1.5)	−0.02 (0.7)	0.008	0.006
Height (cm)	178.1 (9.1)	177.4 (7.4)	N/A	N/A	N/A	N/A
Body mass index (kg/m^2)	25.0 (3.3)	22.9 (3.6)	N/A	N/A	N/A	N/A
Waist-to-hip ratio	0.90 (0.09)	0.87 (0.06)	N/A	N/A	N/A	N/A
Heart rate (beats/min)						
Supine	57.2 (9.0)	57.5 (9.0)	−9.0 (8.4)	+2.8 (9.5)	0.003	0.002
Sitting	64.9 (7.9)	71.1 (14.1)	−9.1 (7.5)	−2.7 (9.5)	0.08	0.001
Peak exercise heart rate	180.2 (13.2)	186.3 (7.5)	−7.8 (6.0)	−8.6 (8.4)	0.79	0.0006
Heart rate recovery at 1 min	26.3 (7.9)	28.0 (12.6)	+1.8 (7.6)	+3.1 (5.5)	0.63	0.42
Blood pressure (mm Hg)						
Systolic	121.9 (10.9)	121.7 (8.8)	+6.5 (9.2)	−5.6 (6.0)	0.0008	0.02
Diastolic	69.4 (7.8)	72.3 (4.4)	−0.2 (4.8)	−1.8 (5.2)	0.42	0.13
Brachial artery dilatation (%)						
Flow-mediated	9.9 (5.2)	7.1 (3.6)	−1.7 (4.0)	−0.1 (3.8)	0.32	0.23
Nitroglycerin-mediated	27.8 (8.5)	26.1 (6.1)	−10.2 (6.6)	−5.5 (6.9)	0.11	0.0002
Glucose homeostasis						
Fasting insulin (μU/ml)[c]	5.06 (4.21)	5.49 (4.06)	+14.3 (23.2)	+0.1 (2.6)	<0.0001	<0.0001
Fasting glucose (mg/dl)	79.2 (8.3)	80.1 (7.5)	+6.8 (14.6)	+0.2 (11.7)	0.22	0.12
HOMA[c]	1.03 (0.99)	1.10 (0.83)	+3.5 (6.7)	+0.02 (0.6)	<0.0001	<0.0001
Lipids						
Triglycerides (mg/dl)	81.2 (26.2)	112.8 (75.9)	+4.8 (25.5)	+8.3 (65.7)	0.79	0.51
HDL-cholesterol (mg/dl)	48.1 (6.8)	48.7 (14.3)	+9.8 (8.1)	−3.7 (6.3)	0.0001	0.0009
LDL-cholesterol (mg/dl)	100.0 (30.2)	105.4 (26.5)	+1.8 (16.9)	−1.1 (9.6)	0.60	0.70
Nonesterified fatty acids (ng/dl)	13.6 (4.6)	15.2 (4.1)	+1.7 (1.4)	−1.2 (4.7)	0.15	0.25
Sodium/volume homeostasis						
BNP (pg/ml)	6.9 (4.6)	8.0 (6.5)	+7.7 (7.0)	−2.9 (7.6)	0.001	0.002
Plasma renin (direct) (μU/ml)[c]	21.9 (11.9)	16.3 (10.2)	−5.4 (14.8)	+7.8 (10.5)	0.02	0.20
Plasma aldosterone (ng/dl)[c]	10.4 (4.5)	8.9 (4.9)	−3.0 (2.7)	+4.5 (7.0)	0.0007	0.001
Aldosterone:renin ratio (ng/dl ÷ μU/ml)	0.52 (0.21)	0.60 (0.22)	−0.07 (0.26)	+0.11 (0.43)	0.49	0.38
CRP (mg/liter)[c]	0.74 (0.90)	0.79 (0.72)	−0.47 (0.60)	−0.19 (0.68)	0.04	0.004
Homocysteine (mg/liter)	1.41 (0.30)	1.70 (0.91)	+0.05 (0.39)	−0.15 (0.78)	0.43	0.68

The metric-SI conversions are as follows: insulin, 1 μU/ml = 6.945 pmol/liter; glucose, 1 mg/dl = 0.0555 mmol/liter; triglycerides, 1 mg/dl = 0.0113 mmol/liter; HDL-cholesterol and LDL-cholesterol, 1 mg/dl = 0.0259 mmol/liter; BNP, 1 pmol/liter = 3.46 pg/ml; nonesterified fatty acids, 1 mmol/liter = 28.2 ng/dl; homocysteine, 1 mg/liter = 0.135 μmol/liter; aldosterone: 1 ng/dl = 36.1 nmol/liter.

[a] Although means and SD are presented for all parameters, log transformations were performed as appropriate before statistical testing.

[b] *P* values apply to dexamethasone-treated subjects.

[c] Variable log-transformed before analysis.

TABLE 2. Pearson correlations (r) between indices of HPA-axis tone and cardiovascular biomarkers

Cardiovascular biomarker	Baseline morning cortisol (mean = 15.2 μg/dl; SD = 4.2 μg/dl)	Morning cortisol after 0.5 mg dexamethasone (mean = 5.2 μg/dl; SD = 4.9 μg/dl)	Absolute decrease in cortisol after 0.5 mg dexamethasone (mean = 10.0 μg/dl; SD = 4.7 μg/dl)
Age	0.00	−0.15	−0.16
Body mass index	−0.14	−0.35	−0.24
Waist-to-hip ratio	−0.15	−0.38	+0.27
Supine heart rate	−0.18	+0.12	+0.28
Heart rate recovery at 1 min	+0.08	+0.10	+0.03
Systolic blood pressure	−0.18	+0.12	+0.28
Flow-mediated brachial artery dilatation	−0.21	+0.03	+0.21
HOMA	−0.37	−0.33	−0.18
Triglycerides	+0.23	+0.04	−0.13
HDL-cholesterol	+0.22	+0.09	−0.11
Nonesterified fatty acids	−0.10	−0.14	−0.07
BNP	−0.11	−0.12	−0.04
CRP	+0.02	−0.15	−0.19
Renin	−0.17	+0.09	−0.23
Aldosterone	+0.20	+0.31	−0.15
Aldosterone:renin ratio	+0.41[a]	+0.23	+0.10

The metric-SI unit conversion for cortisol is 1 μg/dl = 27.6 nmol/liter.

[a] $P < 0.05$; no other *P* values < 0.05.

the observed trend toward a decrease in renin, because renal sympathetic nerves play an important role in stimulating renin release in response to hemodynamic stressors (46). Suppression of ACTH may have further attenuated aldosterone release (47).

We can only speculate about the mechanism of increased blood pressure with dexamethasone, but experimental models suggest that glucocorticoids up-regulate angiotensin II type 1 receptors and α-1 receptors in vascular smooth muscle, may augment adipocyte production of angiotensinogen, and may stimulate angiotensin-converting enzyme expression, while reducing prostacyclin E2 synthesis at the level of the endothelium and vascular smooth muscle (48–50). The decrease in heart rate that we observed with dexamethasone suggests that increased central sympathetic tone did not contribute to the increase in blood pressure we observed. Similarly, we found no evidence that dexamethasone diminished endothelium-mediated vasodilatation.

The finding that dexamethasone increased BNP *in vivo* contrasts with *in vitro* data demonstrating a decrease in BNP in response to dexamethasone (51). Because dexamethasone does not have significant mineralocorticoid effects (29, 30), BNP increases are not readily explained by direct dexamethasone-induced expansion of plasma volume (52). The absence of a significant relationship between change in BNP and change in blood pressure also argues against increased afterload as the primary mechanism for this finding. It is possible that hyperinsulinemia-induced expansion of plasma volume increased BNP and also led to a compensatory reduction in renin-angiotensin-aldosterone system activity (53). The increase in total body weight that we observed is consistent with this mechanistic hypothesis; the dexamethasone-treated subjects gained an average of 1.3 kg over 5 d, which, if this were fat mass, would require the consumption of approximately 2000 additional kilocalories of food per day, an amount that would likely have been noticed and reported by our subjects (54). It is more than likely, therefore, that this weight gain reflects an increase in total body water, but we do not know how much of this water was intravascular.

The absence of an effect of dexamethasone on endothelial function in our subjects contrasts with data suggesting that glucocorticoids can precipitate endothelial dysfunction via inhibition of endothelial nitric oxide release (22, 55). However, the only published *in vivo* study examining this question used hydrocortisone (22), whose mineralocorticoid effects may have led to endothelial dysfunction (22, 56). It is also possible that longer-term glucocorticoid exposure or a different method of assessing endothelial function might have led to different results.

We identified no relationships between the tone of the HPA axis (as determined by response of cortisol to low-dose dexamethasone) and the cardiovascular risk factors we measured. These findings differ from those of Bjorntorp and colleagues (14, 57), who suggest that a blunted diurnal amplitude of circulating cortisol, and in some cases a blunted response of cortisol to low-dose dexamethasone, may be associated with features of the metabolic syndrome, such as central obesity, hypertension, and dyslipidemia. However, these researchers used a larger sample of patients and studied primarily middle-aged men (rather than healthy young men). They also measured salivary cortisol rather than serum cortisol. Any of these factors may explain the discrepancies between our findings and theirs. However, we suspect that other measures of glucocorticoid homeostasis, reflecting glucocorticoid activity at the cellular level, are more closely related to the metabolic syndrome than the response of the HPA axis to low-dose dexamethasone (11, 15, 16).

Strengths of our study include its randomized, double-blind, placebo-controlled design and the use of healthy volunteers without active inflammatory disease as our study subjects. On the other hand, our protocol was limited by its short duration of glucocorticoid exposure, and some biomarkers, such as homocysteine, may have exhibited changes had we kept the subjects on glucocorticoid treatment for two or more weeks. However, we believe that longer exposure might have subjected subjects to unnecessary health risk and that any changes in central fat mass precipitated by long-term glucocorticoids might obscure the direct glucocorticoid effects. Our study was also limited by its relatively small size and lack of power to detect subtle changes in the cardiovascular markers we examined. Nevertheless, our study provides further insights regarding the cardiovascular effects of exogenous, and perhaps endogenous, glucocorticoids, clarifying the potential harms and benefits of these ubiquitous compounds.

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