Increased Adrenal Androgen Secretion With Inhibition of 11-Beta hydroxylase in HIV-Infected Women

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Abstract

Adrenal androgen production is reduced in association with disease severity in HIV-infected women. This response may be maladaptive in terms of maintenance of lean body mass, functional status and immune function. The aim of the present study was to assess whether the use of an adrenal enzyme inhibitor of 11-beta hydroxylase might increase androgen production in this population. We conducted a randomized, double-blind, placebo-controlled study of metyrapone 500 mg PO QID or placebo for 2 weeks in ten HIV-infected women with AIDS wasting (weight < 90% IBW or weight loss > 10%) and reduced androgen levels. Basal and ACTH stimulated androgen, mineralocorticoid and glucocorticoid levels were measured at baseline and after 14 days of treatment.

Subjects were similar in age (40.9±0.9 years), weight (91.7±3.5%IBW) and hormone concentrations at study entry. Total testosterone (84±54 vs. –0.4±2 ng/dL, P=0.024), free testosterone (6.5±2.8 vs. 0.1±0.1 pg/mL, P=0.024), DHEA (5.0±3.2 vs. –0.6±0.5 (µg/L, P=0.024) and 11-deoxycortisol (2145±820 vs. –14±22 ng/dL, P=0.024) levels increased in response to metyrapone compared to placebo treatment. In response to ACTH, significant increases in the DHEA:cortisol ratio (174±48 vs. 3±3, P=0.008) were seen in the metyrapone group compared to placebo. Blood pressure and electrolytes did not change and signs of adrenal insufficiency were not apparent.

These data demonstrate that inhibition of 11B hydroxylase with metyrapone increases adrenal androgen secretion in HIV-infected women. Further studies are needed to assess the physiologic effects of this strategy to increase anabolic hormone levels in
severe stress, including detailed testing to rule out the potential risk of concomitant adrenal insufficiency.
Introduction

Stress, such as that associated with severe illness, results in increased cortisol, and decreased androgen synthesis (24). Women with acquired immune deficiency syndrome (AIDS) wasting demonstrate reduced androgen levels which may contribute to reduced muscle mass and quality of life in this population (10) (20). Androgen deficiency among HIV-infected women may be related to an effect of severe illness on the hypothalamic pituitary gonadotrophic axis (27), but normal ovarian responses to HCG have been shown in this population (11). In contrast, we have demonstrated significant reduction in adrenal androgen secretion and a relative increase in cortisol, in association with low CD4 count, an index of illness severity, in a prior study among HIV-infected women (11). In men with AIDS wasting, a similarly altered pattern of adrenal steroid biosynthesis has been reported (19) (7), potentially as a result of altered P450c17 lyase activity. Prior studies suggest that reduced adrenal androgen synthesis in HIV-infected patients is associated with reduced immune function (2, 3, 6). The relative increase in cortisol and decrease in adrenal androgens may favor a shift from Type 1 to Type 2 immune response in association with HIV disease progression (4). DHEAS is also thought to have antiglucocorticoid activity, and may inhibit glucocorticoid induced lymphocyte apoptosis and help to prevent infections (1). In addition, androgens are anabolic to muscle, resulting in nitrogen retention and increased protein synthesis (6). In contrast, cortisol is a catabolic hormone that reduces muscle protein synthesis (22). Taken together, these studies suggest a mechanism whereby severe stress results in increased cortisol and decreased androgen secretion. This response may be maladaptive in terms of maintenance of lean body mass, functional status and immune function.
In order to address this relative imbalance of adrenal steroid metabolism, we hypothesized that administration of metyrapone, an inhibitor of adrenal 11- Beta hydroxylase that inhibits conversion of 11-deoxycortisol to cortisol in the final step of adrenal glucocorticoid synthesis, would result in increased adrenal androgen secretion and overall androgen levels HIV-infected women. Our results indicate that metyrapone significantly increased adrenal androgen secretion over a 2-week administration. Further studies are necessary to assess the physiologic effects of 11-Beta hydroxylase inhibition and increased adrenal androgen production in chronic severe illness.

Methods

Study Design

Ten HIV infected women between 18–45 yr meeting the CDC definition of AIDS wasting (weight <90% of ideal body weight or weight loss >10% from pre-illness baseline) with relative androgen deficiency free testosterone < 3 pg/mL (<10.4 pmol/liter), on stable antiretroviral regimen for 3 months were studied (Table I).

Subjects were excluded if they were pregnant or receiving estrogen, progesterone, megestrol acetate, glucocorticoid, mineralocorticoid, androgens, or any drugs known to affect the hypothalamic-pituitary-gonadal or adrenal axes within 3 months of the study. Subjects were also excluded if they used any anabolic agent, including testosterone, GH, or megestrol acetate within 3 months of the study or were active substance abusers. Subjects were excluded if they had obvious clinical lipodystrophy, were pregnant, breastfeeding, or were trying to become pregnant. Subjects were required to use an acceptable form of birth control during the metyrapone treatment period. Acceptable forms of birth control include IUD’s, barrier devices (condoms, diaphragms), and long-term abstinence. Subjects were additionally excluded for Hgb < 9.0
mg/dL, creatinine > 1.5 mg/dL, adrenal insufficiency as established by cosyntropin stimulation testing (cortisol < 18.0 mg/dL at 60 minutes after IV cosyntropin injection of 250 µg). Written consent was obtained from all subjects, and the study was approved by the Subcommittee on Human Studies of the Massachusetts General Hospital.

**Screening Visit**

Eligibility was determined by medical history, physical exam, free testosterone level, complete blood count, urine pregnancy test, cosyntropin stimulation test, creatinine, and weight at a baseline screening visit. Subjects meeting all the eligibility requirements with a free testosterone level less than 3.0 pg/ml (<10.4 pmol/liter) were subsequently enrolled into the study.

**Baseline Testing Prior to Randomization**

Eligible subjects were admitted to the General Clinical Research Center of the Massachusetts General Hospital. Eumenorrheic subjects were admitted within the follicular phase. One day prior to baseline visit, subjects began a 24 hour urine collection for urine free cortisol and creatinine that was completed on the morning of Day 1 (Table 2).

**Day 1**

A urine pregnancy test was obtained from all participants. At 0800 h, measurements were made of baseline testosterone, free testosterone, SHBG, cortisol, DHEA, aldosterone, 11-deoxycortisol, estradiol, HIV test, viral load, CD4 and complete blood count. Dexamethasone (1 mg PO) was administered at 2400 h.
Day 2

At 0800 h, measurements of cortisol, DHEA, androstendione and aldosterone were made. Cosyntropin [ACTH-(1–25); 250 µg, iv) was administered, and repeat measurements of hormone levels were made at 0, 30, 60, 90 and 120 minutes.

Randomization

Following completion of testing on Day 2, subjects were randomized to placebo vs. metyrapone 500 mg PO QID x 14 days. Randomization was double-blinded and stratified by weight < 90% IBW.

Days 3 and 4

During Days 3 and 4, after initiation of study drug, subjects remained as inpatients at the MGH GCRC for safety monitoring and underwent blood work daily for chemistry labs including sodium and potassium and q4h vital sign monitoring until discharge on Day 4.

Days 5-14

Subjects continued taking the study drug metyrapone vs. placebo 500 mg po q6h and returned every morning to the GCRC at MGH for blood work to check electrolytes and blood pressure. On the morning of day 14 subjects began a 24 hour urine collection for urine free cortisol and creatinine which they brought to the hospital on the morning of Day 15.

Day 15 and Day 16 (testing identical to Days 1 and 2).

On the morning of Day 15, subjects returned to the MGH GCRC for an overnight stay. Testing on Day 15 was identical to baseline testing on Day 1 and subjects also received dexamethasone 1 mg PO at 2400 h on the evening of Day 15. The following morning at 0800 h, measurements of cortisol, DHEA, androstenedione and aldosterone were made. Cosyntropin
[ACTH-(1–25); 250 µg, iv) was administered, and repeat measurements of hormone levels were made at 0, 30, 60, 90 and 120 minutes min, identical to Day 2. Subjects underwent DXA scan as during the baseline visit. Subjects were discharged home after all testing was complete.

Body Composition

Body composition was determined to see if there were changes in lean or fat mass. Dual energy x-ray absorptiometry was performed using a model 4500 scanner (Hologic, Inc., Waltham, MA). The precision of this technique in the determination of whole body fat and lean mass is 3% for fat mass and 1.5% for fat-free mass (18).

Biochemical Assays

All samples from the same patient were run in duplicate in the same assay. The free testosterone concentration was determined as the product of the percent free testosterone, measured by equilibrium dialysis, and the total testosterone concentration (Endocrine Sciences, Inc., Calabasas Hills, CA). The intra-assay coefficient of variation of free testosterone was 8.8-9.4 %, and the intra-assay coefficient of variation for total testosterone was 0.72-17.30 %. The intra-assay coefficients of variation (CV’s) were developed using pooled sera covering the range of the assay. The normal range for total testosterone was 10-55 ng/dL (0.4–1.9 nmol/liter), and that for free testosterone was 1.1-6.3 pg/mL (pmol/liter) in adult females. The inter-assay CV for testosterone was 5.6-14.8 %, and that for free testosterone 9.1-11.9 %. The sensitivity of the total testosterone assay was 3 ng/dL (nmol/liter). The sensitivity of the determination of percent free testosterone by this method is 0.1%.
RIA’s were performed for cortisol (intra-assay CV, 6.6-7.7 %; inter-assay CV, 8.8-9.0%; DiaSorin, Inc., Stillwater, MN), DHEA (intra-assay CV, 5.6-10.6%; inter-assay CV, 7.0-10.2%, Diagnostic Systems Laboratories, Inc., Webster, TX), androstenedione (intra-assay CV, 2.8-5.6%; inter-assay CV, 7.0-9.8%; Diagnostics Systems Laboratories, Inc.) aldosterone (intra-assay CV, 3.6-8.3 %; inter-assay CV, 7.3-10.4% Diagnostics Systems Laboratories, Inc.), 11-deoxycortisol (intra-assay CV 2.1-5.9%; inter-assay CV 11.6-13.7%, MP Biomedicals, LLC., Orangeberg, NY), and estradiol (intra-assay CV, 6.5-8.9%; inter-assay CV, 7.5-12.2%, Diagnostic Systems Laboratories, Inc.). SHBG was performed by immunoradiometric assay with an intra-assay CV of less than 4% and an inter-assay CV of 7.8–10.6% (Endocrine Sciences, Inc.). Urinary free cortisol was measured by standardized techniques (15). CD4⁺ count was determined by flow cytometry (Becton Dickinson Biosciences, San Jose, CA) and HIV viral load was determined by ultra-sensitive assay (Amplicor HIV-1 Monitor Assay, Roche Molecular Systems, Branchburg, NJ) with limits of detection 50-75,000 RNA copies/mm³. The complete blood count (CBC) was measured using standard methods. The cross reactivity between cortisol and 11-desoxycortisol was < 1%.

**Statistical Analysis**

Randomization was stratified for weight < 90% IBW, to ensure similar weight in the treatment groups. Baseline comparisons were made between treatment groups using the median rank test. AUC for change in hormone levels during the ACTH test was determined by the trapezoid method. Subjects were selected for the study based on a relative or absolute reduction in free testosterone levels, and the primary endpoint was the
change in free testosterone to assess whether the use of metyrapone improved overall androgen status. Changes in DHEA and androstenedione were also investigated to determine more specifically the effects of metyrapone on adrenal androgen secretion. The change from baseline over 14 days was compared in the treatment and placebo groups by the median rank test. Responses to ACTH between the treatment groups were also compared by the median rank test. One patient in the placebo group elected not to finish the study unrelated to any adverse events. Univariate regression analysis was also used to compare weight with the ratio of the DHEA:cortisol response to ACTH. Results are the mean ± SEM unless otherwise indicated. Statistical analyses were performed using JMP for SAS version 5 (Cary, NC).

Results

Baseline Values

The baseline clinical characteristics are shown in Table I. Subjects were similar in age and weight. Neither androgen nor cortisol levels were different between the study groups at study entry. Duration of ARV use was similar between the groups. None of the HIV-infected subjects demonstrated any clinical characteristics of the lipodystrophy syndrome. Weight was 91.7±3.5% of ideal. Weight loss was on average 14.6±2.5% from pre-illness baseline. At baseline, % IBW was significantly correlated with the AUC for DHEA:cortisol (r= 0.64, P=0.01, Figure 1), suggesting that lower weight was associated with a decreased ratio of adrenal androgens to cortisol.
Effects of Metyrapone on Basal Hormone Concentrations and Other Endpoints

Total testosterone (84±54 vs. –0.4±2 ng/dL, P=0.024), free testosterone (6.5±2.8 vs. 0.1±0.1 pg/mL, P=0.024), DHEA (5.0±3.2 vs. –0.6±0.5 (µg/L, P=0.024) and 11-deoxycortisol (2145±820 vs. –14±22 ng/dL, P=0.024) levels increased in response to metyrapone compared to placebo treatment over 14 days. Metyrapone normalized low total and free testosterone levels. Urine free cortisol and fasting AM cortisol levels did not change (Table 3). Weight did not change (Table 3) and changes in body composition between the groups were not detected (data not shown).

Responses to ACTH Stimulation

In response to ACTH, significant increases in androstenedione and the DHEA:cortisol ratio were seen over time in the metyrapone group compared to placebo. In contrast, the cortisol response to ACTH decreased in the metyrapone group compared to placebo (Figure 2).

Adverse Events and Safety

No adverse events occurred related to the study drug administration. One subject in the placebo group developed bronchitis on Day 4 of the study. This event was felt to be unrelated to the study protocol. Blood pressure, potassium, sodium and hematocrit (HCT) did not change between the groups. No patients developed clinical signs of adrenal insufficiency during careful monitoring.

Discussion
In this study we demonstrate that use of an adrenal enzyme blocker, metyrapone, can shift adrenal metabolism toward androgen production, thus reversing a potentially maladaptive stress response that may contribute to reduced lean body mass and decreased functional status.

HIV disease is a catabolic illness, characterized by sarcopenia (16) and significant changes in hormonal metabolism (9). Weight loss in HIV-infected men and women is associated with androgen deficiency, and increased risk of death (12) (26). Androgen deficiency is common and occurs in 66% of HIV-infected women with wasting (10). Androgen levels in HIV-infected women correlate with lean body mass and functional status, as measured by exercise performance on isometric testing (5, 10). The mechanisms of androgen deficiency in HIV-infected women are not known, but may relate to reduced ovarian or adrenal androgen production. We measured free testosterone by equilibrium dialysis, as an SHBG independent measure of bioavailable testosterone to assess the effects of metyrapone on overall androgen status. In addition, we assessed adrenal specific androgen responses.

We have previously shown that serum levels of DHEAS, an adrenal androgen, are decreased and highly correlated with serum free testosterone levels in women with the AIDS wasting syndrome, suggesting the importance of adrenal androgen production to the overall circulating testosterone level in this population (8). In prior studies, we investigated the mechanism of androgen deficiency in women with AIDS wasting using ACTH stimulation testing of adrenal steroids. Our prior data demonstrated a significantly decreased DHEA:cortisol ratio after ACTH stimulation in HIV-infected patients compared to age and BMI-matched control subjects (11). Furthermore, we showed that the DHEA:cortisol ratio correlated with
CD4 count and was reduced in association with low CD4 count in HIV-infected women. These data suggested significant shunting of adrenal steroid metabolism toward cortisol production and away from androgen production in women with AIDS wasting, a phenomenon that correlates with decreased immune function and disease severity.

In the current study, we investigated the use of metyrapone, an inhibitor of 11-beta hydroxylase, an enzyme that converts 11-deoxycortisol to cortisol in the final step of glucocorticoid production and deoxycorticosterone to corticosterone in mineralocorticoid production. We postulated that by inhibiting this enzyme, we would increase ACTH stimulation of adrenal androgen and mineralocorticoid pathways. We administered metyrapone over 2 weeks at a dose of 500 mg QID. Our data demonstrate increased androgen concentrations, e.g. of DHEA, total and free testosterone as well as 11-deoxycortisol, the precursor hormone to the point of the enzymatic blockade. In addition, the DHEA and androstenedione responses to ACTH increased whereas stimulated aldosterone and cortisol responses decreased more in the metyrapone group, resulting in a significant increase in the ratio of stimulated DHEA: cortisol in the metyrapone group relative to the placebo group. We pretreated with dexamethasone on the evening prior to ACTH testing, as we did in our prior study, to reduce variability in ACTH response and better compare changes between the treatment groups. ACTH levels were not investigated as an endpoint due to known variability in secretion.

Short-term metyrapone administration was generally well tolerated. All subjects passed a standard cosyntropin stimulation test at screening and symptoms of adrenal insufficiency did not develop. Moreover, blood pressure and electrolyte measurements did not change between the groups. Cortisol responses to ACTH decreased in the metyrapone group relative to placebo, as anticipated. However, 24 hour urine free cortisol levels and fasting AM levels prior to
dexamethasone did not change significantly between the groups, suggesting that relatively normal adrenal glucocorticoid production persisted. Basal aldosterone levels tended to decrease and ACTH stimulated aldosterone levels decreased significantly in response to metyrapone compared to placebo. However, there was no change in blood pressure or electrolyte values during very careful monitoring. It is possible that relative increases in mineralocorticoid precursors, such as DOC, resulted in preservation of normal blood pressure and electrolytes, despite a relative reduction in aldosterone production. Use of metyrapone at the dose chosen may be associated with adrenal insufficiency, and it possible that subjects had mild insufficiency, not detected by clinical exam and blood work. Future studies will need to assess adrenal function using more frequent morning cortisol and cortrosyn simulation testing. This study was not undertaken to prove the clinical utility of metyrapone for HIV-infected patients, rather to investigate the physiologic effects of 11-Beta hydroxylase inhibition on adrenal androgen secretion in a population with chronic illness, stress, and reduced adrenal androgen secretion. Another alternative, would be to administer DHEA, which has had limited efficacy in studies to date (25) and would not be expected to alter the potentially maladaptive relative imbalance of cortisol and DHEA.

Alterations in adrenal androgens are known to occur in severe stress (24) and among HIV-infected patients. The mechanism of this effect is not well understood, but may involve reduced 17,20 lyase activity of the cytochrome P450c17 system, which converts androgen precursors to DHEA and androstenedione. 17-20 lyase activity may be reduced by cytokines, NADPH or other factors during inflammation or severe illness (1, 13, 14, 21). In turn, a relative reduction in the ratio of DHEA to cortisol production might result in altered immunological response, and worsen susceptibility to infection, and even potentially contribute to viral
progression, whereas increases in DHEA or its metabolites may reduce susceptibility to infection
(17, 23). Furthermore, the altered hormonal responses of stress may be maladaptive, and
contribute to reduced lean body mass and functional status, as androgens are anabolic and
cortisol catabolic to muscle. In severe HIV infection, marked sarcopenia is seen, and the altered
adrenal responses to stress may contribute to reduction in muscle mass and even bone density. In
this study, CD4 count increased by 47±36 in the metyrapone group and decreased by 55±43 in
the control group, potentially suggestive of positive immunomodulation by metyrapone.
However, the small sample size limited our ability to detect statistically significant changes in
CD4. Furthermore, our study was too short to expect clinically significant changes in body
composition. However, our data suggest the need for additional studies of longer duration to
study immune function, body composition and other potential clinical responses

These data suggest that inhibition of 11-beta hydroxylase increases androgen levels
among HIV-infected women with low weight. At baseline, the decreased DHEA:cortisol ratio
correlated tightly with weight, suggesting a biologically related stress response. Further studies
will be necessary to determine if increasing adrenal androgen secretion by this method improves
lean body mass, functional status and even immunological function in HIV-infected patients
and/or other patients with severe illness and adrenal shunting, and whether such a strategy can be
accomplished without causing untoward side effects of glucocorticoid deficiency.
Acknowledgements

The investigators would like to thank the nursing staffs of the Massachusetts General Hospital General Clinical Research Center for their dedicated patient care.
Figure Legends

Figure 1.
Correlation between %IBW and the ACTH stimulated DHEA:cortisol ratio at study entry.

Figure 2. Changes from baseline in cortisol, androstenedione, DHEA, and DHEA:cortisol responses to ACTH. * P<0.05 for comparison between metyrapone and placebo at each time point and †<0.05 for overall AUC between metyrapone and placebo. Results are mean±SEM
References


Table I. Demographics and Clinical Characteristics at Study Entry

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<tr>
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<th>Placebo (N=5)</th>
<th>Metyrapone (N=5)</th>
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<td><strong>Age (yrs)</strong></td>
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<td><strong>HIV Characteristics</strong></td>
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<td>Duration of HIV (months)</td>
<td>164.8 ± 21.3</td>
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<td>PI usage (months)</td>
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<td>NNRTI usage (months)</td>
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<td>NtRTI usage (months)</td>
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<td><strong>Body Composition</strong></td>
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<td>Weight (kg)</td>
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<td>BMI (kg/m²)</td>
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<td>IBW (%)</td>
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<td><strong>Hormone Levels</strong></td>
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<td>Total Testosterone (ng/dL)</td>
<td>14 ± 3</td>
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<td>Free Testosterone (pg/mL)</td>
<td>1.5 ± 0.4</td>
<td>2.0 ± 0.3</td>
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<td><strong>Cortisol Stimulation Test</strong></td>
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<td>Cortisol-0min (µg/dL)</td>
<td>7.9 ± 2.8</td>
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<td>Cortisol-60min (µg/dL)</td>
<td>26.5 ± 1.6</td>
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Results are mean ± SEM. PI= protease inhibitor. NRTI= nucleoside reverse transcriptase inhibitor. NNRTI= nonnucleoside reverse transcriptase inhibitor. NtRTI=nucleotide analog.
Table II. Study Procedures

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<td>Cosyntropin stimulation testing with measurement of Cortisol, DHEA, and Androstenedione</td>
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<td>0900</td>
<td>End of study hormonal measurements (Free testosterone, DHEA, 11-desoxycortisol, 24 hour urine free cortisol)</td>
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<td></td>
<td>2400</td>
<td>Dexamethasone 1 mg PO</td>
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<td>Cosyntropin stimulation testing with measurement of Cortisol, DHEA, and Androstenedione</td>
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### Table III. Changes in Response to Metyrapone vs. Placebo

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<td>Change from baseline</td>
<td>Baseline</td>
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<td><strong>Weight (kg)</strong></td>
<td>58.4 ± 4.1</td>
<td>54.4 ± 1.5</td>
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<td>51.6 ± 4.0</td>
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<td><strong>BMI (kg/m²)</strong></td>
<td>21.9 ± 1.3</td>
<td>20.6 ± 0.6</td>
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<td><strong>Hormonal Indices</strong></td>
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<tr>
<td>Total Testosterone</td>
<td>11 ± 2</td>
<td>10 ± 1</td>
<td>-0.4 ± 2</td>
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<tr>
<td>Free Testosterone</td>
<td>0.6 ± 0.1</td>
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<td>0.1 ± 0.1</td>
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<td>SHBG (nmol/L)</td>
<td>178 ± 42</td>
<td>190 ± 56</td>
<td>-14 ± 13</td>
<td>129 ± 32</td>
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<td>Estradiol (pg/mL)</td>
<td>34 ± 12</td>
<td>46 ± 16</td>
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<td>46 ± 14</td>
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<td>Cortisol (µg/dL)</td>
<td>8.0 ± 1.7</td>
<td>6.5 ± 1.1</td>
<td>-2.8 ± 0.7</td>
<td>14.3 ± 2.4</td>
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<td>DHEA (µg/L)</td>
<td>3.9 ± 0.6</td>
<td>3.1 ± 0.5</td>
<td>-0.6 ± 0.5</td>
<td>6.7 ± 0.9</td>
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<td>Aldosterone (ng/L)</td>
<td>89 ± 20</td>
<td>126 ± 27</td>
<td>26 ± 14</td>
<td>220 ± 111</td>
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<td>11-deoxycortisol (ng/dL)</td>
<td>79 ± 20</td>
<td>77 ± 14</td>
<td>-14 ± 22</td>
<td>123 ± 14</td>
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<td>Urine free cortisol (µg/24h)</td>
<td>26 ± 8</td>
<td>29 ± 10</td>
<td>6 ± 8</td>
<td>26 ± 5</td>
</tr>
<tr>
<td><strong>Immune Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (thou/cm³)</td>
<td>5.9 ± 0.9</td>
<td>5.4 ± 0.8</td>
<td>-0.2 ± 0.6</td>
<td>5.8 ± 1.1</td>
</tr>
<tr>
<td>CD4 count (cells/mm³)</td>
<td>342 ± 111</td>
<td>307 ± 106</td>
<td>-55 ± 43</td>
<td>492 ± 232</td>
</tr>
<tr>
<td>Viral Load (copies/mm³)</td>
<td>13912 ± 8832</td>
<td>6515 ± 6133</td>
<td>-0.5 ± 122</td>
<td>24710 ± 19358</td>
</tr>
<tr>
<td><strong>Safety Parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.8 ± 0.2</td>
<td>3.8 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>3.7 ± 0.1</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>139 ± 1</td>
<td>139 ± 1</td>
<td>-1 ± 1</td>
<td>137 ± 1</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>111 ± 4</td>
<td>108 ± 3</td>
<td>-3 ± 5</td>
<td>111 ± 2</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>70 ± 2</td>
<td>74 ± 3</td>
<td>2 ± 2</td>
<td>73 ± 2</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>38.0 ± 1.3</td>
<td>36.8 ± 2.1</td>
<td>-1.6 ± 1.5</td>
<td>35.6 ± 2.0</td>
</tr>
</tbody>
</table>

Results are mean ± SEM
Figure 1

The graph illustrates the relationship between % IBW and DHEA:Cortisol AUC. The correlation coefficient (r) is 0.64, and the significance level (P) is 0.01.
Figure 2

**Change in Cortisol**

![Graph showing the change in cortisol levels over time with Metyrapone and Placebo treatments.](image)

**Change in Androstenedione**

![Graph showing the change in androstenedione levels over time with Metyrapone and Placebo treatments.](image)

**Change in DHEA**

![Graph showing the change in DHEA levels over time with Metyrapone and Placebo treatments.](image)

**Change in DHEA: Cortisol**

![Graph showing the change in DHEA: Cortisol levels over time with Metyrapone and Placebo treatments.](image)