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Administration of testosterone to elderly hypogonadal men with Crohn's disease improves their Crohn's Disease Activity Index: a pilot study

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Abstract

Background: Both elevated and depressed testosterone (T) levels have been reported in Crohn's disease (CD). In this pilot study, effects of T administration on CD were assessed.
Materials and methods: A total of 13 men with CD, aged 45–67 years, had subnormal plasma T (mean ± SD = 9.0 ± 1.4 nmol/L) (reference >12.0); they were compared to a group of 110 men of similar age with sexual and urological problems whose plasma T was also subnormal: 10.4 ± 1.4 nmol/L ($p = 0.02$). All received treatment with parenteral T undecanoate for 24 months. The Crohn's Disease Activity Index (CDAI) was assessed as an indicator of the severity of the disease every 3 months. Levels of T and C-reactive protein (CRP) were compared between the 13 men with CD and the other men in this study. Values of CDAI and CRP were followed-up.
Results: CRP levels were 22.7 mg/dL (95% confidence interval of the mean: 14.9–34.3) in the 13 men with CD vs. 3.5 (2.9–4.1) in 107 control men ($p = 0.001$). Upon normalization of serum T, there was a significant decline of CDAI (from 243 ± 19 to 89 ± 9), CRP levels from 22.7 ± 8.1 to 6.9 ± 2.9 mg/dL, and white blood cell count. Hemoglobin/hematocrit increased significantly.
Conclusions: Upon normalization of plasma T the CDAI and CRP levels decreased in hypogonadal patients with CD. The mechanism of this improvement could be through immunosuppressive effects of T, reducing chronic inflammation of the intestinal wall in CD.

Keywords: crohn's disease; testosterone; C-reactive protein; inflammation.

Introduction

Crohn's disease (CD) is a chronic inflammatory disease of the intestine of unknown etiology. It is characterized by focal or segmental transmural inflammation which can occur in any part of the digestive tract, with occasional granuloma formation. This transmural inflammation disrupts intestinal mucosal integrity (1).

Men with celiac disease or CD quite often suffer from infertility, sexual dysfunction and loss of bone mineral density whose pathogenesis remains unclear. It has been suggested that factors such as endocrine dysfunction (2–4) or other specific nutritional deficiency could be involved.

Several studies have been conducted to explore hormonal abnormalities in patients with CD and the results have been inconsistent and conflicting. In a study of 48 men with CD, 6% of men had a low free androgen index and normal gonadotrophins consistent with secondary hypogonadism, two of whom had osteopenia of the hip and spine. Age and small bowel CD were the only independent predictors of serum testosterone. Another study found an altered sex hormonal status – a deficiency of 17β-estradiol and, to a lesser extent, a deficiency of testosterone – in male patients with CD (3). In children with CD, a mild suppression of the hypothalamic-pituitary axis has been found resulting in slightly diminished secretion of growth hormone, luteinizing hormone and follicle stimulating hormone (5).

Associations with dehydroepiandrosterone sulfate (DHEAS) with chronic inflammatory bowel disease have been established with greater certainty. Several studies have concluded that low blood DHEAS is a feature of chronic inflammatory bowel disease in a majority of patients (6–8). In the latter study there was a correlation with bone loss (8). No independent effect of testosterone was detected on bone parameters (8).

The secretion of proinflammatory cytokines, such as interleukin-6 (7) and interleukin-12, and the activation of nuclear factor kappa B is increased in patients with inflammatory bowel disease (9). CD is characterized by an exaggerated and poorly controlled T helper (Th) type 1 or Th2 cell response, respectively, characterized by a sustained produc-

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tion of cytokines made by a distinct lineage of Th17 cells (1).

In an intervention study of 20 patients with chronic active inflammatory bowel disease [seven CD (Crohn's Disease Activity Index (CDAI), 242±51; mean±SD); 13 ulcerative colitis (clinical activity index, 7.8±2.1)] who took 200 mg dehydroepiandrosterone per day orally for 56 days, a remarkable improvement of the CDAI was noted: six of the seven patients with CD and eight of the 13 patients with ulcerative colitis responded to treatment, with a decrease in the CDAI of >70 points and a decrease in the clinical activity index of >4 points, respectively. Six CD patients and six ulcerative colitis patients went into remission (CDAI <150; clinical activity index >4). The decrease in C-reactive protein (CRP) levels (from 20.3±25.1 mg/dL to 9.7±11.4 mg/dL) was not statistically significant (11).

In addition, sex hormones are associated with inflammation (12). Low testosterone levels have been found in men with chronic inflammatory diseases. But studies investigating the effects of administration of sex steroids on the course of CD have not been reported. Proinflammatory cytokines suppress the hypothalamic-pituitary-gonadal axis (12), and low testosterone levels might be expected if inflammation is active. There is an inverse relationship between plasma testosterone and inflammatory markers in elderly men (12–14). The acute withdrawal of testosterone in young, otherwise healthy hypogonadal male patients caused significant increases in interleukin-6 and tumor necrosis factor-α 2 weeks after the suspension of treatment (15). Administration of testosterone to androgen-deficient men has a suppressive effect on circulating levels of certain proinflammatory cytokines, usually studied in the context of the role of testosterone in the metabolic syndrome (12, 16, 17). Testosterone has immunosuppressive properties concerning macrophages, T cells and B cells (18). Reduced testosterone concentrations thus affect the anti-inflammatory ability of the immune system and a chronic inflammatory state can develop.

In the present pilot study, we monitored the effects of administration of testosterone in 13 patients with lower-than-normal testosterone levels suffering from CD.

Subjects and methods

Plasma testosterone levels were determined in 13 patients, 59.6±8.0 years (SD), with CD: their baseline testosterone concentrations were between 5.8 and 12.1 nmol/L (mean±SD=9.0±1.4) (reference >12.0 nmol/L). Because of their subnormal plasma testosterone levels, they were referred to the department of urology. They had other complaints which were consistent with hypogonadism, such as sexual dysfunction and urological problems. A group of 110 men, of similar age, served as a comparison group. Their baseline plasma testosterone was 10.4±1.4 nmol/L. The etiology of their hypogonadism was thought to be late onset hypogonadism (19). They had sought urological consultation for several reasons: erectile dysfunction, questions about their testosterone status or a variety of urological complaints. Both the patients with CD and the men in the comparison group received treatment with parenteral testosterone undecanoate (TU, administration at 0 and 6 weeks and thereafter every 12 weeks; Nebido®; Bayer Schering Pharma, Berlin, Germany). Plasma testosterone returned to the physiological range. They were followed for at least 24 months after the beginning of treatment. This study was not specifically designed to study the effects of normalization of serum testosterone levels on the disease course of CD but rather the administration of testosterone to these men for their hypogonadism, and provided an opportunity to monitor effects of testosterone administration on CD. The CDAI has been developed to assess the severity of the disease and to monitor the effects of interventions on the course of the disease. The CADI consists of eight factors, each summed after adjustment with a weighting factor. Index values of 150 and below are associated with quiescent disease, values above that indicate active disease, and values above 450 are seen with extremely severe disease (20). The CDAI (20) was assessed to monitor the effects of testosterone on the clinical course of CD.

CRP was measured to monitor the effects of testosterone administration on a biological activity marker of bowel disease (21).

Ethical guidelines as formulated by the German ''Ärztekammer'' (the German Medical Association) for observational studies in patients receiving standard treatment were followed. After receiving an explanation regarding the nature and the purpose of the study, all subjects consented to be included in the research of their treatment protocol.

Statistical analysis

Variables with strongly positively skewed distributions (i.e., white blood cell count and CRP) were logarithmically transformed before analyses to approach a normal distribution. T-tests for independent samples and Pearson χ^2 tests were used to test for differences between the randomized groups. Back-transformed geometric mean values [with 95% confidence intervals of the means (CI)] are presented for transformed variables.

Multilevel regression analysis (i.e., mixed models) was used to study changes over time in the CD group as compared to the hypogonadal controls without CD. Participants were measured 9 times, so a two-level structure consists of the 9 observations (i.e., lower level) and the participant (i.e., higher level). As multiple tests were done, a two-tailed $p<0.01$ was considered statistically significant. Analyses were done using SPSS version 16.0 (SPSS, Chicago, IL, USA).

Results

At baseline (Table 1) men with CD had a lower body weight and a lower waist circumference than men in the comparison group. Hemoglobin and hematocrit levels were lower in men with CD.

Levels of CRP were geometric mean 22.7 mg/dL (95% CI: 14.9–34.3) in 13 men with CD vs. 3.5 (2.9–4.1) in 107 control men ($p=0.001$). Levels of testosterone also tended to be lower in men with CD vs. controls (9.0±1.4 nmol/L; 95% CI: 8.0–10.8; vs. 10.4±1.4 nmol/L; 95% CI: 10.1–12.4; $p=0.02$). White blood cell counts were significantly higher in the men with CD ($p<0.01$). Hemoglobin and hematocrit values were significantly lower in men with CD ($p<0.01$).

Upon normalization of serum testosterone (Table 2), there were significant changes in several mean scores of body composition and metabolic components. There was a decline in the CDAI scores over the first 15 months, with stabili-

Table 1 Demographic and baseline clinical characteristics of the two groups.

Variable	n	Hypogonadal patients with Crohn's disease	n	Hypogonadal patients without Crohn's disease	p-Value
Age, years	13	57.9±4.3	110	68.3±6.9	0.24
Total testosterone level, nmol/L	13	9.0±1.4	108	10.0±1.4	0.02
Body mass index, kg/m^2	13	26.1±4.0	109	34.7±4.6	<0.001
Waist circumference, cm	13	94.1±5.3	110	108.4±9.7	<0.001
Current smoking, %	12	5 (42%)	107	87 (81%)	0.005
Current alcohol users, %	12	6 (50%)	107	88 (82%)	0.02
Total cholesterol level, mmol/L	13	270±38	110	293±38	0.04
LDL cholesterol level, mmol/L	13	150±48	110	149±43	0.75
HDL cholesterol level, mmol/L	13	55.9±27.8	110	58.5±28.8	0.92
Triglycerides level, mmol/L	13	249±67	110	286±53	0.03
Glucose level, mmol/L	12	108.4±11.9	110	103.3±18.9	0.37
Hemoglobin level, g/dL	13	13.0±0.8	110	14.3±0.7	<0.001
Hematocrit, %	13	37.3±1.8	109	42.2±2.6	<0.001
White blood cell count, $\times 10^3$ cells/μL	13	14.8 (12.7–17.3)	109	6.8 (6.4–7.2)	<0.001
C-reactive protein, mg/dL	13	22.7 (14.9–34.3)	107	3.5 (2.9–4.1)	<0.001
Total prostate specific antigen, μg/L	12	2.2±0.7	109	1.6±1.2	0.09

HDL, high-density lipoprotein; LDL, low-density lipoprotein. Data are means (±SD), means (95% confidence interval between parentheses) for white blood cell count and C-reactive protein levels, or number (percentage) for smoking and alcohol use.

zation of the improvement over the next 9 months. Levels of CRP declined continuously over the study period of 24 months (Figure 1). Also, the white blood cell count decreased significantly, whereas the hemoglobin level and hematocrit increased more strongly than the control group of hypogonadal men without CD. Remarkably, the metabolic profile improved: body mass index and waist circumference modestly decreased, whereas fasting glucose levels and the lipid profile strongly improved. Hemoglobin levels and the hematocrit increased significantly, whereas there was no change in prostate specific antigen levels. Values of CRP levels during testosterone administration in 13 patients with CD were compared to 110 hypogonadal patients without CD. In both groups, a decline of CRP levels was noted but quantitatively the decline was larger in the men with CD (Table 2) but, calculated as percentage, the declines were of similar magnitude.

Discussion

Our pilot study found that CRP was elevated in patients with CD compared to the other patients, which is in agreement with other studies (9, 10). Also, baseline serum testosterone tended to be lower than in other men consistent with the theory that proinflammatory cytokines have a suppressive effect on the hypothalamo-pituitary-gonadal axis (12), which was also reported in several epidemiological studies (14, 22).

To the best of our knowledge this is the first study reporting that upon normalization of plasma testosterone an improvement of the CDAI was noted, which paralleled a strong decline in serum levels of CRP and in the white blood cell count (1). An improvement occurred over the first 15 months. Thereafter, values of CDAI and CRP stabilized. Upon testosterone administration, the metabolic profile of the men with CD improved, and so did hemoglobin levels and the hematocrit. Anemia often complicates inflammatory bowel diseases and is associated with disease activity (24, 25).

Interpretation of the mechanism of this improvement is speculative. First, CD is characterized by an exaggerated and poorly controlled Th1 or Th2 cell response, respectively, characterized by a sustained production of cytokines made by a distinct lineage of Th17 cells (1). There is an inverse relationship between plasma testosterone and levels of some inflammatory markers (14, 23). There could be a parallel with another autoimmune disease; treatment with testosterone could suppress inflammation in patients with rheumatoid arthritis, as shown by Cutolo et al. (24, 25). Such interventions have not been undertaken in men with CD.

Second, endogenous cortisol is regarded as physiological compound to combat inflammation. The local activation of glucocorticoids is mediated by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) which increases cortisol and 11β-HSD2 which decreases cortisol concentrations. Expression of 11β-HSD1 was significantly elevated in inflamed tissue compared to non-inflamed colonic tissue in CD, whereas 11β-HSD2 expression was decreased in the same samples. Male patients showed a more pronounced upregulation of 11β-HSD1 compared to females, which could be due to the higher levels of circulating anti-inflammatory estrogens in women (10). Normalizing serum testosterone in our patients could have added to the upregulation of 11β-HSD1, but that is speculative. Little is known about the effects of testosterone on local activation/deactivation of cortisol in the gut.

This is a pilot study and it has a number of methodological limitations. It was not designed to specifically measure the effects of testosterone on the course of CD. It is not placebo-

Table 2 Changes during 2 years testosterone administration in hypogonadal men with and without Crohn's disease.

Variable	Baseline	6 months	12 months	18 months	24 months	p-Value*
Total testosterone level, nmol/L						
Crohn's disease (mean, SE)	9.0±0.7	16.3±0.7	18.0±0.7	17.0±0.7	18.4±0.7	0.34
Crohn's disease (percent change)	–	83.5%	102.1%	91.6%	107.2%	
Controls (mean, SE)	10.1±0.3	17.0±0.3	19.1±0.3	18.7±0.3	18.4±0.3	
Controls (percent change)	–	70.2%	93.5%	86.8%	83.6%	
Body mass index, kg/m^2						
Crohn's disease (mean, SE)	26.1±1.2	26.4±1.2	26.7±1.2	26.9±1.2	26.2±1.2	<0.001
Crohn's disease (percent change)	–	1.2%	2.6%	3.2%	0.4%	
Controls (mean, SE)	34.7±0.4	34.1±0.4	33.2±0.4	32.5±0.4	31.8±0.4	
Controls (percent change)	–	–1.7%	–4.4%	–6.4%	–8.4%	
Waist circumference, cm						
Crohn's disease (mean, SE)	94.1±2.4	94.2±2.4	94.3±2.4	94.4±2.4	92.6±2.4	<0.001
Crohn's disease (percent change)	–	0.2%	0.2%	0.3%	–1.6%	
Controls (mean, SE)	108.4±0.8	106.9±0.8	104.5±0.8	103.2±0.8	102.3±0.8	
Controls (percent change)	–	–1.3%	–3.6%	–4.8%	–5.7%	
Total cholesterol level, mmol/L						
Crohn's disease (mean, SE)	269.5±8.9	217.9±8.9	202.1±8.9	193.7±8.9	188.5±8.9	0.001
Crohn's disease (percent change)	–	–19.1%	–25.0%	–28.1%	–30.1%	
Controls (mean, SE)	292.6±3.1	241.0±3.1	206.3±3.1	198.7±3.1	194.7±3.1	
Controls (percent change)	–	–17.6%	–29.5%	–32.1%	–33.5%	
LDL cholesterol level, mmol/L						
Crohn's disease (mean, SE)	150.2±10.7	141.4±10.7	130.2±10.7	122.5±10.7	115.3±10.7	0.88
Crohn's disease (percent change)	–	–5.8%	–13.3%	–18.4%	–23.2%	
Controls (mean, SE)	148.8±3.7	134.5±3.7	123.6±3.7	115.1±3.7	113.9±3.7	
Controls (percent change)	–	–9.6%	–16.9%	–22.7%	–23.4%	
HDL cholesterol level, mmol/L						
Crohn's disease (mean, SE)	55.8±7.2	59.5±7.2	64.0±7.2	67.0±7.2	72.5±7.2	0.81
Crohn's disease (percent change)	–	6.5%	14.6%	20.0%	29.8%	
Controls (mean, SE)	58.5±2.5	60.4±2.5	64.8±2.5	68.6±2.5	72.9±2.5	
Controls (percent change)	–	3.2%	10.8%	17.3%	24.6%	
Triglycerides level, mmol/L						
Crohn's disease (mean, SE)	249.4±11.2	217.8±11.2	196.1±11.2	188.2±11.2	183.5±11.2	0.007
Crohn's disease (percent change)	–	–12.7%	–21.4%	–24.6%	–26.4%	
Controls (mean, SE)	285.7±3.8	233.8±3.8	203.9±3.8	199.6±3.8	194.5±3.8	
Controls (percent change)	–	–18.1%	–28.6%	–30.1%	–31.9%	
Glucose level, mmol/L						
Crohn's disease (mean, SE)	108.0±4.7	97.7±4.6	101.9±4.6	96.3±4.6	90.9±4.6	0.25
Crohn's disease (percent change)	–	–9.5%	–5.6%	–10.8%	–15.8%	
Controls (mean, SE)	103.3±1.6	102.2±1.6	98.7±1.6	95.8±1.6	95.6±1.6	
Controls (percent change)	–	–1.1%	–4.5%	–7.3%	–7.5%	
Hemoglobin level, g/dL						
Crohn's disease (mean, SE)	13.0±0.2	13.6±0.2	14.2±0.2	14.2±0.2	14.5±0.2	<0.001
Crohn's disease (percent change)	–	4.8%	9.7%	9.5%	11.6%	
Controls (mean, SE)	14.3±0.1	14.6±0.1	15.1±0.1	15.1±0.1	15.2±0.1	
Controls (percent change)	–	2.6%	5.5%	6.1%	6.4%	
Hematocrit, %						
Crohn's disease (mean, SE)	37.3±0.8	40.2±0.8	43.2±0.8	44.8±0.8	46.2±0.8	0.001
Crohn's disease (percent change)	–	7.8%	15.9%	20.0%	23.9%	
Controls (mean, SE)	42.2±0.3	44.8±0.3	48.1±0.3	48.8±0.3	49.0±0.3	
Controls (percent change)	–	6.3%	14.1%	15.7%	16.3%	
White blood cell count, $\times 10^3/\mu$L						
Crohn's disease (mean, SE)	14.8 (12.8–17.2)	8.4 (7.2–9.8)	6.4 (5.4–7.5)	9.1 (7.8–10.6)	8.3 (7.1–9.7)	<0.001
Crohn's disease (percent change)	–	–43.2%	–56.8%	–38.5%	–43.9%	
Controls (mean, SE)	6.8 (6.4–7.1)	6.1 (5.8–6.5)	6.2 (5.8–6.5)	6.3 (6.0–6.7)	6.2 (5.9–6.6)	
Controls (percent change)	–	–10.3%	–8.8%	–7.4%	–8.8%	
C-reactive protein, mg/dL						
Crohn's disease (mean, 95% CI)	22.7 (15.7–32.6)	13.4 (9.2–19.5)	8.9 (5.9–13.0)	7.8 (5.2–11.5)	6.9 (4.6–10.3)	<0.001
Crohn's disease (percent change)	–	–41.0%	–60.8%	–65.6%	–69.6%	
Controls (mean, 95% CI)	3.5 (2.9–4.0)	2.6 (2.2–3.1)	2.2 (1.8–2.6)	1.7 (1.4–2.1)	1.4 (1.1–1.7)	
Controls (percent change)	–	–25.7%	–37.1%	–51.4%	–60.0%	–

(Table 2 continued)

Variable	Baseline	6 months	12 months	18 months	24 months	p-Value*
Total PSA, μg/L						
Crohn's disease (mean, SE)	2.2±0.3	2.3±0.3	2.3±0.3	2.4±0.3	2.6±0.3	0.40
Crohn's disease (percent change)	–	1.4%	2.0%	9.1%	14.7%	
Controls (mean, SE)	1.6±0.1	1.6±0.1	1.7±0.1	1.7±0.1	1.7±0.1	
Controls (percent change)	–	–1.2%	2.0%	3.8%	6.5%	
Crohn's Disease Activity Index						
Crohn's disease (mean, SE)	242.9±9.1	154.2±8.6	103.1±8.6	92.9±8.8	88.8±8.8	–
Crohn's disease (percent change)	–	–36.5%	–57.6%	–61.7%	–63.4%	

HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSA, prostate specific antigen. Data are means (±SD) or geometric means (95% confidence interval between parentheses) for white blood cell count and C-reactive protein levels. *p-Value by multilevel regression analysis (i.e., MIXED) for the comparison of the change over time (i.e., for the time×group interaction term) in 13 hypogonadal patients with Crohn's disease as compared to 108 hypogonadal control patients during 2 years of follow-up.

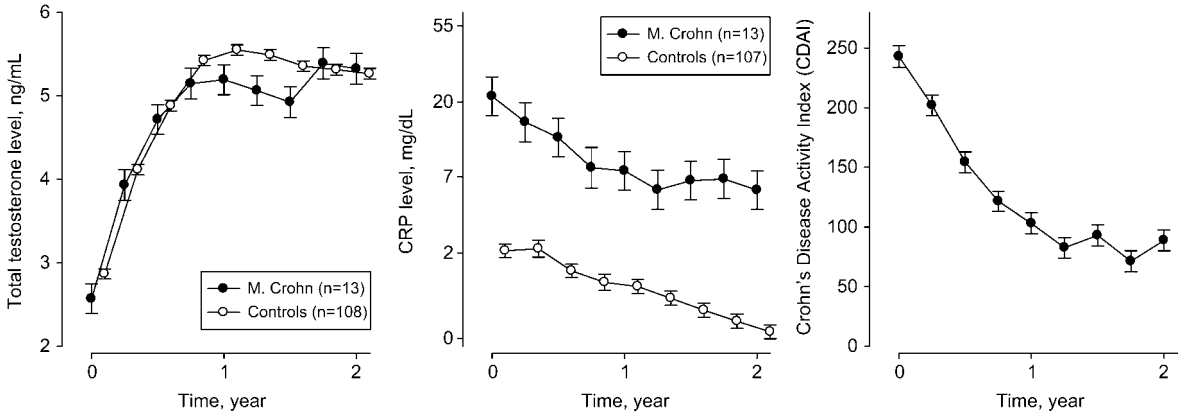

Figure 1 Changes in total testosterone levels, C-reactive protein (CRP) levels and Crohn's Disease Activity Index (CDAI) in 13 hypogonadal patients with Crohn's disease as compared to 108 hypogonadal control patients during 2 years of follow-up.

controlled. But the results are encouraging: not only the clinical scores of disease activity improved but there was also a remarkable improvement in laboratory parameters of disease activity, such as CRP. Randomized controlled trials are needed to confirm these promising results.

Declaration of interest, funding, author contributions

Farid Saad is an employee of Bayer Schering Pharma AG, which produces the intramuscular depot formulation of testosterone undecanoate. The other authors declare no conflict of interests. This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

1. Abraham C, Cho JH. Inflammatory bowel disease [Review]. N Engl J Med 2009;361:2066–78.
2. Szarvas F. [Andrological abnormalities in internal diseases and following drug therapy]. Andrologia 1987;19(Spec No):284–9.
3. Klaus J, Reinshagen M, Adler G, Boehm B, von Tirpitz C. Bones and Crohn's: estradiol deficiency in men with Crohn's disease is not associated with reduced bone mineral density. BMC Gastroenterol 2008;8:48.
4. Robinson RJ, Iqbal SJ, Al-Azzawi F, Abrams K, Mayberry JF. Sex hormone status and bone metabolism in men with Crohn's disease. Aliment Pharmacol Ther 1998;12:21–5.
5. Farthing MJ, Campbell CA, Walker-Smith J, Edwards CR, Rees LH, Dawson AM. Nocturnal growth hormone and gonadotrophin secretion in growth retarded children with Crohn's disease. Gut 1981;22:933–8.
6. de la Torre B, Hedman M, Befrits R. Blood and tissue dehydroepiandrosterone sulphate levels and their relationship to chronic inflammatory bowel disease. Clin Exp Rheumatol 1998;16:579–82.
7. Straub RH, Konecna L, Hrach S, Rothe G, Kreutz M, Scholmerich J, Falk W, Lang B. Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin-6 (IL-6), and DHEA inhibits IL-6 secretion from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence. J Clin Endocrinol Metab 1998;83:2012–7.
8. Szathmari M, Vasarhelyi B, Treszl A, Tulassay T, Tulassay Z. Association of dehydroepiandrosterone sulfate and testosterone deficiency with bone turnover in men with inflammatory bowel disease. Int J Colorectal Dis 2002;17:63–6.
9. Poynter ME, Daynes RA. Peroxisome proliferator-activated receptor alpha activation modulates cellular redox status,

represses nuclear factor-kappaB signaling, and reduces inflammatory cytokine production in aging. J Biol Chem 1998;273: 32833–41.
10. Stegk JP, Ebert B, Martin HJ, Maser E. Expression profiles of human 11beta-hydroxysteroid dehydrogenases type 1 and type 2 in inflammatory bowel diseases. Mol Cell Endocrinol 2009; 301:104–8.
11. Andus T, Klebl F, Rogler G, Bregenzer N, Scholmerich J, Straub RH. Patients with refractory Crohn's disease or ulcerative colitis respond to dehydroepiandrosterone: a pilot study. Aliment Pharmacol Ther 2003;17:409–14.
12. Maggio M, Basaria S, Ceda GP, Ble A, Ling SM, Bandinelli S, Valenti G, Ferrucci L. The relationship between testosterone and molecular markers of inflammation in older men. J Endocrinol Invest 2005;28:116–9.
13. Maggio M, Basaria S, Ble A, Lauretani F, Bandinelli S, Ceda GP, Valenti G, Ling SM, Ferrucci L. Correlation between testosterone and the inflammatory marker soluble interleukin-6 receptor in older men. J Clin Endocrinol Metab 2006;91:345–7.
14. Nettleship JE, Pugh PJ, Channer KS, Jones T, Jones RD. Inverse relationship between serum levels of interleukin-1beta and testosterone in men with stable coronary artery disease. Horm Metab Res 2007;39:366–71.
15. Yialamas MA, Dwyer AA, Hanley E, Lee H, Pitteloud N, Hayes FJ. Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2007;92:4254–9.
16. Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J Clin Endocrinol Metab 2004;89:3313–8.
17. Corrales JJ, Almeida M, Burgo R, Mories MT, Miralles JM, Orfao A. Androgen-replacement therapy depresses the ex vivo production of inflammatory cytokines by circulating antigen-presenting cells in aging type-2 diabetic men with partial androgen deficiency. J Endocrinol 2006;189:595–604.
18. Masi AT, Bijlsma JW, Chikanza IC, Pitzalis C, Cutolo M. Neuroendocrine, immunologic, and microvascular systems interactions in rheumatoid arthritis: physiopathogenetic and therapeutic perspectives. Semin Arthritis Rheum 1999;29:65–81.
19. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morales A, Morley JE, Schulman C, Thompson IM, Weidner W, Wu FC. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol 2008;159:507–14.
20. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70:439–44.
21. Desai D, Faubion WA, Sandborn WJ. Review article: biological activity markers in inflammatory bowel disease. Aliment Pharmacol Ther 2007;25:247–55.
22. Kupelian V, Chiu GR, Araujo AB, Williams RE, Clark RV, McKinlay JB. Association of sex hormones and C-reactive protein levels in men. Clin Endocrinol (Oxf) 2010;72:527–33.
23. Kupelian V, McVary KT, Barry MJ, Link CL, Rosen RC, Aiyer LP, Mollon P, McKinlay JB. Association of C-reactive protein and lower urinary tract symptoms in men and women: results from Boston Area Community Health Survey. Urology 2009; 73:950–7.
24. Cutolo M, Balleari E, Giusti M, Intra E, Accardo S. Androgen replacement therapy in male patients with rheumatoid arthritis. Arthritis Rheum 1991;34:1–5.
25. Cutolo M, Seriolo B, Villaggio B, Pizzorni C, Craviotto C, Sulli A. Androgens and estrogens modulate the immune and inflammatory responses in rheumatoid arthritis. Ann NY Acad Sci 2002;966:131–42.