PAPER

Gender Differences in Human Sepsis

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Background: In animal studies, gender differences were related to hormonal and immunologic changes that were associated with an increased susceptibility to sepsis in males.

Objective: In a prospective study, gender differences in patients with surgical sepsis were evaluated in terms of survival, sex hormones, and proinflammatory as well as anti-inflammatory mediators.

Setting: Surgical intensive care unit of a university hospital.

Patients: Fifty-two patients (19 women and 33 men) with surgical sepsis.

Measurements and Main Results: In a prospective study, tumor necrosis factor α and interleukin 6 bioactivity and plasma levels of interleukin 10 (using enzyme-linked immunosorbent assay), total testosterone, and 17-β estradiol (using radioimmunoassay) were determined on days 1, 3, 5, 7, 10, and 14 after diagnosis of sepsis. There were no differences in characteristics of patients in age (mean age, 55.4 years for women and 53.1 years for men) or cause and severity of sepsis (Acute Physiology and Chronic Health Evaluation II score, 17.3 for women and 18.5 for men; multiple organ dysfunction score, 9.9 vs 10.8, respectively). Although no difference could be found in the multiple organ dysfunction score from day 1 to day 28, the prognosis of sepsis was significantly different in women compared with men. Hospital mortality rate was 70% (23 of 33 patients) in male and 26% (5 of 19) in female patients ($P<.008$, log-rank test). Bioactivity of tumor necrosis factor continuously increased in men after diagnosis of sepsis, with significantly elevated levels on day 10 ($P<.05$, Mann-Whitney *U* test with Bonferroni correction), whereas no difference was found for interleukin 6 bioactivity. Women displayed enhanced interleukin 10 levels compared with men from day 1 to day 10 that reached a significant difference on days 3 and 5 ($P<.05$). Total testosterone levels were below the normal range for men, and estradiol levels were initially increased in both men and postmenopausal women, with higher levels for women.

Conclusions: In this prospective study, gender differences were confirmed in human sepsis, with a significantly better prognosis for women, which may be related to increased levels of anti-inflammatory mediators. The hypothetical different ratio of proinflammatory and anti-inflammatory mediators may be important for further therapeutic interventions in sepsis.

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DESPITE IMPROVEMENT in surgical and critical care management, the prognosis of sepsis and subsequent multiple organ dysfunction remained unchanged during the past decades.[1] The common pathway of multiple organ dysfunction is a severe inflammatory reaction resulting from systemic cytokine release.[2] In response to the initiating proinflammatory reaction, with tumor necrosis factor (TNF-α), interleukin (IL) 1 and IL-6 playing the predominant role, the body also mounts an immediate anti-inflammatory response. Among the diverse agents, different interleukins, such as IL-10, have profound anti-inflammatory effects that are suggested to control the proinflammatory reaction.[3]

Despite identical surgical and intensive care management, some surgical patients die of overwhelming sepsis, predominantly because of severe peritonitis and necrotizing pancreatitis, while others recover uneventfully. Why is it that some patients recover, whereas others progress to multiple organ dysfunction and death? In addition to the interaction in the complex cytokine network, biological variations[4] in terms of genetic determination,[5] age,[6] and gender[7] may influence the outcome.

Experimental studies demonstrated improved cell-mediated immune response in females compared with males.[8] In female mice after cecal ligation and puncture, the improved cell-mediated immune response

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PATIENTS AND METHODS

PATIENT SELECTION

Patients eligible for this study were those with severe sepsis or septic shock according to the definition of Bone et al.[14] *Septic shock* was defined as a sustained decrease in systolic blood pressure to less than 90 mm Hg, or a decrease of 40 mm Hg from baseline in the absence of antihypertensive agents despite adequate fluid resuscitation. Written informed consent was obtained from all patients or their relatives to draw blood for determination of cytokines and sex hormones. Patients received full intensive care management for sepsis, including fluid resuscitation, vasopressors, ventilatory support, hemofiltration, antibiotics, and surgical procedures as required.

Exclusion criteria were age younger than 18 years or older than 75 years; suspected pregnancy; uncontrolled hemorrhage; cardiogenic shock; burns; severe, preexisting parenchymal liver disease with clinically significant portal hypertension; former therapy with glucocorticoids; former irradiation or chemotherapy; and participation in ongoing or previous clinical trials using anti-inflammatory agents. Organ transplant recipients and patients with hematological malignant neoplasms as acute underlying conditions were not enrolled.

CLINICAL EVALUATION

All patients were followed up throughout their hospital stay. Vital signs were monitored at the time of diagnosis of sepsis and until patients were discharged from the intensive care unit or died. Variables for calculation of the Acute Physiology and Chronic Health Evaluation (APACHE) II score[15] were recorded at the time of diagnosis of sepsis, and variables for the calculation of multiple organ dysfunction score according to Marshall et al[16] were recorded throughout the intensive care therapy. In addition, the following data were determined daily at 8 AM on days 1, 3, 5, 7, 10, and 14 after diagnosis of sepsis: plasma levels of TNF-α, IL-6, IL-10, total testosterone, and 17β-estradiol.

PROINFLAMMATORY CYTOKINES

Biological activity of TNF-α was determined by its cytotoxic effect on the fibrosarcoma cell line WEHI 164 subclone 13.[17] The detection limit of the assay was 2 pg/mL. The IL-6 bioactivity was measured by means of the specific IL-6–dependent murine hybridoma cell line B 13-29 subclone 9,[18] with a detection limit of 1.25 pg/mL. All cytokine samples were tested in duplicate.

INTERLEUKIN 10

Human IL-10 plasma concentrations were determined with a commercially available solid-phase sandwich enzyme-linked immunosorbent assay kit (BioSource International, Menlo Park, Calif) according to the manufacturer's instructions. The detection limit of the IL-10 enzyme-linked immunosorbent assay was 5 pg/mL. All samples were tested in duplicate.

RADIOIMMUNOASSAYS

Serum estradiol levels were measured by radioimmunoassay (^{125}I Estradiol-RIA, Biermann Inc, Bad Nauheim, Germany). Minimal detection limit was 18 pmol/L (5 pg/mL). Normal values in our laboratory are less than 128 pmol/L (35 pg/mL) in men and less than 70 pmol/L (19 pg/mL) in postmenopausal women. All samples were tested in duplicate. The percentage of cross-reactivity of the antiserum with other steroids at the maximum concentration is as follows: 17β-estradiol, 100%; estrone, 12.5%; estriol, 0.24%; and all other tested steroids (including male and female sex steroids and their metabolites), less than 2%. The intra-assay variation is 4% to 16%, and interassay variation is 4.9% to 5.5%.

The concentration of serum total testosterone was estimated by radioimmunoassay (^{125}I Testosteron-RIA, Biermann Inc). Minimal detection limit was 0.14 nmol/L (4 ng/dL). Normal values in our laboratory are 10.4 to 31.2 nmol/L (300-900 ng/dL) in men and 0.7 to 3.5 nmol/L (20-100 ng/dL) in women. All samples were tested in duplicate. The percentage of cross-reactivity of the antiserum with other steroids at the maximum concentration is as follows: testosterone, 100%; 5α-androstane-3β, 17β diol, 0.04%; 5β-androstane-3β, 17β diol, 0.4%; androstendione, 0.5%; 5β-dihydrotestosterone, 3.3%; 11β-dihydrotestosterone, 0.8%; 11-oxotestosterone, 16%; methyltestosterone, 1.7%; and all other tested steroids (including male and female sex steroids and their metabolites), less than 0.1%. The intra-assay variation is 5% to 18% and interassay variation is 7.3% to 11.0%.

STATISTICAL ANALYSIS

Data are expressed as mean ± SEM. Statistical analysis for normally distributed data was performed with unpaired Student *t* test to test differences between the groups. Nonparametric comparisons were evaluated with the Mann-Whitney *U* test and Bonferroni correction for multiple comparisons. The χ^2 test was used to compare patient characteristics at enrollment of the study. The hospital survival rate was estimated in female and male patients by the Kaplan-Meier method, and these estimates were compared with the log-rank test. Differences were considered significant at $P<.05$.

resulted in the ability to tolerate sepsis significantly better than male animals.[9] Sex steroids are known to contribute to the observed sexual dimorphism.[10,11] The enhanced immune response in females may be related to the absence of immunosuppressive androgenic hormones or caused by the immunostimulating properties of female sex steroids.[12,13]

Sexual dimorphism in the immune response demonstrated in experimental studies, however, has not been taken into consideration in sepsis therapy. Therefore, the aim of this prospective study was to evaluate the prognostic role of gender differences in patients with surgical sepsis. In addition, sex hormones and the relation of proinflammatory (TNF-α, IL-6) and anti-inflammatory (IL-10) mediators were determined to study possible underlying mechanisms of sexual dimorphism.

RESULTS

The study included 52 patients, 19 women and 33 men. There were no significant differences between women and

Demographic Characteristics of Female and Male Patients With Severe Sepsis at Diagnosis*

	Women	Men	*P*
Age, y	55.4 ± 4.4	53.1 ± 2.0	.55
APACHE II score	17.3 ± 5.5	18.5 ± 3.6	.35
MOD score	9.9 ± 0.9	10.8 ± 0.5	.44
Patients with shock/ total No. of patients	14/19	27/33	.49
Cause of sepsis, No. (%)			
Peritonitis	12 (63)	21 (64)	.97
Necrotizing pancreatitis	4 (21)	8 (24)	.79
Other	3 (16)	4 (12)	.71

**Values are mean ± SEM unless otherwise specified. APACHE II[15] indicates Acute Physiology and Chronic Health Evaluation; MOD, multiple organ dysfunction.[16]*

men in age (mean age, 55.4 years for women and 53.1 years for men) or severity of sepsis. At diagnosis of sepsis, APACHE II score was 17.3 for women and 18.5 for men. Initial multiple organ dysfunction score was 9.9 for women and 10.8 for men. Fourteen women (74%) and 27 men (82%) had septic shock. Twelve women (63%) had peritonitis, compared with 21 men (64%). Four women (21%) and 8 men (24%) had necrotizing pancreatitis (**Table**). Multiple organ dysfunction score was not significantly different between women and men from day 1 to day 28 after diagnosis of severe sepsis (**Figure 1**). Despite this comparable clinical course, hospital mortality rate (**Figure 2**) was significantly different: 70% (23 of 33 patients) in men and 26% (5 of 19) in women ($P<.008$, log-rank test).

The TNF-α levels increased continuously in men after diagnosis of sepsis (**Figure 3**, top), which was significantly different on day 10 compared with women ($P<.05$, Mann-Whitney *U* test with Bonferroni correction). In contrast to TNF-α bioactivity, no gender differences were found for IL-6 bioactivity during the observation period (data not shown). Median initial IL-6 bioactivity was 6543 pg/mL in women compared with 4263 pg/mL in men. Levels remained elevated until the end of the observation period (357 pg/mL in women and 1144 pg/mL in men). Interleukin 10 levels were elevated in women with severe sepsis from day 1 to day 10, which was significantly different on days 3 and 5 ($P<.05$) compared with men (Figure 3, bottom). Total testosterone levels (**Figure 4**) were below the normal range for men and within the normal range for women. During the observation period, estradiol levels in both women (only postmenopausal women [n = 16] were considered) and men were increased. Women displayed higher, but not significantly different, levels compared with men.

COMMENT

Gender differences in terms of infection and sepsis have been observed in several clinical and epidemiological studies with a preponderance of male patients.[7,19] An effect of gender on mortality, however, could only be demonstrated in children after severe thermal injury, with a significantly higher mortality rate in boys compared with girls.[20]

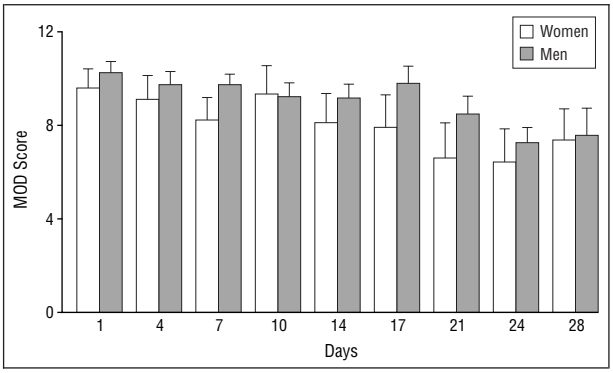

Figure 1. *Serial multiple organ dysfunction (MOD) score according to Marshall et al[16] in female and male surgical patients with severe sepsis. Values are mean ± SEM.*

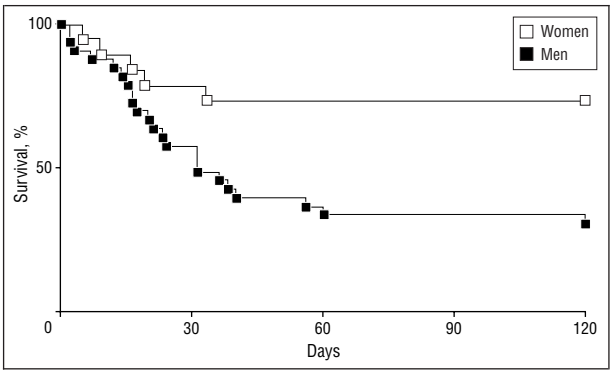

Figure 2. *Kaplan-Meier hospital survival analysis for female and male patients. Survival was significantly different between men and women with severe sepsis (P<.008 for hospital survival, log-rank test).*

To the best of our knowledge, no prospective data are available on the prognosis of human sepsis with respect to sexual dimorphism. Therefore, the present study is the first clinical investigation that reports a significantly improved survival rate in women with severe sepsis.

Bone[7] noted that the predominance of male patients (60%-65% of all patients) may be because clinical studies underestimate the frequency of severe sepsis in women. The percentages of septic women (36%) and septic men (64%) in the present study reflect the overall ratio of patients admitted to our intensive care unit (40.5% women and 59.5% men of a total of 6828 patients) during the study period (data not shown), which may exclude an underestimation of women with sepsis.

The groups of women and men in our study were well matched in terms of age and cause of sepsis, which was predominently peritonitis and necrotizing pancreatitis. To define the severity of sepsis, the APACHE II score[15] and the multiple organ dysfunction score[16] were used, indicating no differences between men and women at diagnosis. Despite a comparable cause of sepsis and no differences in the severity at study entry as well as during the clinical course, the present study demonstrated a significantly enhanced survival of women with severe sepsis compared with men.

Gender differences in the patients observed in this study may confirm experimental data showing a significantly higher survival rate in female mice after a polymicrobial septic challenge.[9] Nevertheless, the question

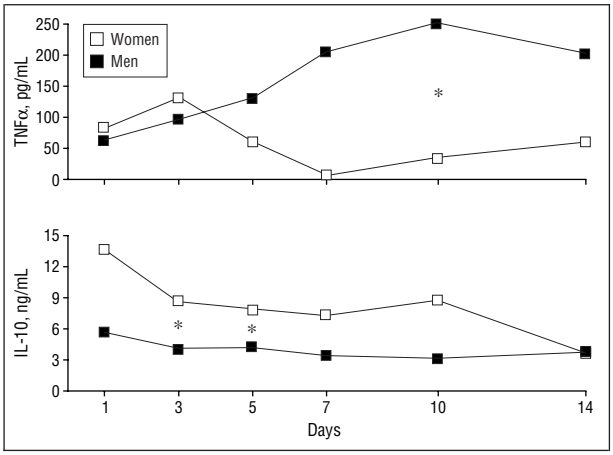

Figure 3. *Changes in median tumor necrosis factor α (TNF-α) bioactivity (top) and interleukin 10 (IL-10) plasma levels (bottom) in women compared with men from day 1 to day 14 after diagnosis of severe sepsis. Asterisk indicates P<.05, women vs men (Mann-Whitney U test with Bonferroni correction).*

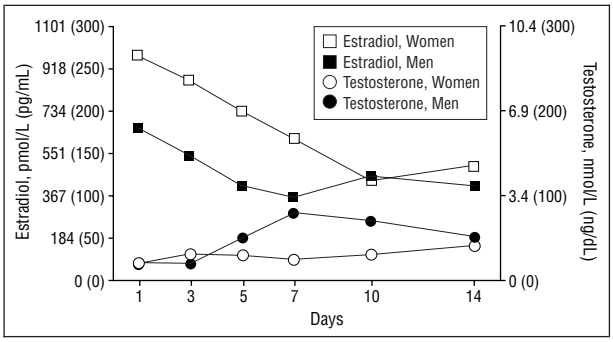

Figure 4. *Changes in mean estradiol and total testosterone levels from day 1 to day 14 after diagnosis of severe sepsis. Reference range values of estradiol are less than 128 pmol/L (35 pg/mL) in men and less than 70 pmol/L (19 pg/mL) in postmenopausal women. Reference range values of testosterone are 10.4 to 31.2 nmol/L (300-900 ng/dL) in men and 0.7 to 3.5 nmol/L (20-100 ng/dL) in women.*

remains which possible underlying mechanisms determine the observed sexual dimorphism in the immune response. Experimental studies clearly indicate that sex hormones appear to be involved in the determination of sexual dimorphism.[10,13] The enhanced immune function in females is known to be associated with a higher prevalence of autoimmune disorders, which may be caused by the absence of immunosuppressive androgenic hormones.[21] Significant depression of macrophage and lymphocyte function after hemorrhagic shock has been reported in male mice compared with enhanced immunity in females. Enhancement of immune function in females was associated with a significantly increased in vitro immune responsiveness, as opposed to significantly decreased levels of different interleukins in male animals.[12]

However, it remains unknown whether the absence of testosterone or the presence of estrogen contributes to the improved survival in critically ill women. Testosterone has been shown to play a key role in immune depression after trauma and hemorrhage and subsequent sepsis.[12] Testosterone depletion in male animals had salutary effects, prevented cell-mediated immune depression after trauma and hemorrhage, and improved survival after polymicrobial sepsis.[11] In addition, the administration of testosterone in female mice led to a significant immune depression, comparable to that in male mice.[11] Experimental studies demonstrated that the effect of sex hormones on the immune system were mediated through their own receptors. Estrogen and androgen receptors have been found on thymocytes as well as on peripheral T cells. Nevertheless, the evidence for such receptors on other important immune-competent cells, such as macrophages, is still missing.[13]

Low testosterone levels in the present study were in accordance with studies showing decreased testosterone secretion after burns, shock, and sepsis. Persistently depressed testosterone levels have been demonstrated in experimental or clinical sepsis, which may be caused by stress-induced decreased adrenal and testicular androgen secretion.[22-24]

In contrast, increased estradiol levels were shown in both men and postmenopausal women with sepsis in this study. The major source of enhanced estradiol production in men and postmenopausal women is suggested to be the conversion by aromatization of testosterone to estradiol.[22] Increased aromatase activity may be the main mechanism, which was supported by experimental studies in male rats challenged with endotoxin.[25] Another possible source of elevated estrogen levels could be decreased hepatic estrogen catabolism caused by hepatic dysfunction, which is common in sepsis and subsequent multiple organ dysfunction syndrome.[16] Decreased serum follicle-stimulating and luteinizing hormone levels in septic patients may be consistent with a negative feedback of high estrogen concentrations on the pituitary gonadotropin release.[22] The question, however, of whether low testosterone or increased estradiol levels may produce the better prognosis in females with sepsis cannot be answered on the basis of the present results. Further studies will be necessary to evaluate the pathophysiological and prognostic role of sex hormones in humans with severe sepsis.

Sustained elevation of IL-6 level was shown to be associated with multiple organ dysfunction and a high mortality rate[26] but did not demonstrate any difference between women and men in the present study. In contrast to IL-6, bioactivity of TNF-α as the central mediator in sepsis[27,28] increased continuously in men, whereas levels remained low in women.

During the observation period, high TNF-α levels were associated with significantly lower levels of IL-10 in men. Interestingly, a different pattern of proinflammatory and anti-inflammatory mediators was demonstrated in women, with lower bioactivity of TNF-α and significantly increased levels of IL-10. Interleukin 10 is known as a potent anti-inflammatory cytokine that inhibits the production of other cytokines from activated macrophages and T-helper cells.[29] Increased production of IL-10 may be an important regulatory mechanism in the control of cytokine-producing cells,[30] which was protective and increased survival rates in experimentally induced sepsis.[31]

In view of the complex interaction between the immune and the endocrine systems, sexual dimorphism may

Statement of Clinical Relevance

Sepsis and subsequent multiple organ dysfunction are the most common causes of death in surgical intensive care units. In the pathogenesis of sepsis and septic shock, proinflammatory cytokines have been implicated as central mediators. While the efficacy of cytokine blockade has been shown in animal models of sepsis, this therapeutic strategy demonstrated only marginal benefits or failed to show improved survival in humans. The discrepancy in human clinical trials may result from difficulties in defining a potential study population that may benefit from adjuvant sepsis therapy.

The present study confirmed the importance of gender differences in human sepsis, which may be related to hormonal and immunologic changes as shown in experimental studies. The majority of animal models of sepsis that demonstrated beneficial anticytokine effects were performed in males while, a mixed population was included in clinical trials. A different effect in these human studies with respect to gender may be suggested, but this has to be proved retrospectively. On the basis of the hypothesis of different hormonal and immunologic changes in men and women with sepsis, different therapy for male and female patients may improve survival, which would be of important clinical relevance.

be influenced by the effects of sex steroids and a different ratio of proinflammatory and anti-inflammatory mediators in women. Considering the relationship of TNF-α and IL-6 as proinflammatory mediators, as well as IL-10 as an anti-inflammatory mediator, the hypothesis can be drawn that a predominance of anti-inflammatory mediators may be protective in women. The potential role of this interaction, however, cannot be estimated on the basis of phenomenological data and must be evaluated in further studies.

Sexual and immunologic dimorphism, as well as the observation that women tolerate sepsis better than men, suggest differentiated adjuvant therapy for severe sepsis. Modulation of the hormonal response may be more effective in the prevention of septic complications, as demonstrated in experimental studies,[11] while different modulation of the cytokine network in men and women may be important for further therapeutic interventions in sepsis.

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DISCUSSION

Irshad H. Chaudry, MD, Providence, RI: Your results clearly indicated that, although there were no differences in the characteristics of patients with respect to age, cause, and severity of sepsis as well as multiple organ dysfunction score, the prognosis of sepsis was significantly higher in males compared to

females. Moreover, significantly higher plasma IL-10 levels early after the onset of sepsis in females was observed compared to higher TNF levels in males. You concluded that the slightly higher plasma estradiol levels contribute to the observed differences in plasma IL-10 and TNF levels. This is a very unique study, since it confirms several epidemiological studies as well as experimental studies, including our own, that females are better positioned to tolerate the deleterious consequences of sepsis. I do have a couple of questions, however. These include the following:

Number one, since the female patients you used were postmenopausal, could you please tell us how many of these women were on estrogen replacement therapy?

Secondly, you concluded that IL-10 played a key role in controlling the proinflammatory cytokine release and also in decreasing the mortality from sepsis. However, higher plasma IL-10 levels in females were observed only up to day 5 after the diagnosis of sepsis. In contrast, no differences in the plasma TNF levels were observed before day 10. In view of this, one can argue whether the higher plasma IL-10 levels in females were not associated with a decrease of TNF levels.

Thirdly, plasma cytokine levels and hormone levels were determined only for the first 14 days after the onset of sepsis. The survival rate, however, was monitored over a period of 120 days. Clearly, there was no difference in the survival within the first 20 days, and, therefore, how could you relate the improved survival with the higher levels of estradiol or higher IL-10 levels?

Lastly, your results clearly indicated that plasma TNF levels were highest at day 10 after this onset of sepsis in males, but at the same time there was no difference in the plasma estradiol levels between males and females. Are you therefore suggesting that the initially higher estradiol levels are the important factors responsible for the enhanced survival in female septic patients?

Dr Schröder: Thank you, Dr Chaudry, for the comments and the questions. It is difficult to evaluate the number of those patients who received estrogen replacement, but as far as it was evaluable, about one fourth of the female patients. But even if you consider estrogen therapy, levels of female patients during the first 2 weeks were increased above the normal range. Higher levels of TNF increased from day 3 to day 10, and they decreased in female patients from day 3 and remained low in these patients. However, the plasma levels of IL-10 increased from day 3, day 5, until day 10, but were only significantly different on days 3 and 5. So there is an association between increasing levels of TNF, an increase in males, and increased levels of IL-10 in women.

However, you are right that if we are talking about a septic cause, we cannot talk about 2 weeks, we have to talk about 4 weeks. Most of the female patients died within 4 weeks, and most of the male patients died within 8 weeks. But up to now we did not measure cytokines or hormone levels after the observation period of 14 days. But further studies are necessary to evaluate the role of hormones and cytokines for a longer period of time, and it may be the question if measuring of plasma levels may be sufficient to get more insight into the relationship between the immune and endocrine systems, and it will be probably more effective to investigate the effects on hormones and cytokines on the immune-competent cells.

These levels I demonstrated here are only phenomenological, but they cannot answer the question of the interaction between hormones and cytokines.