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Strikingly higher interleukin (IL)-1α, IL-1β and soluble interleukin-1 receptor antagonist (sIL-1RA) but similar IL-2, sIL-2R, IL-3, IL-4, IL-6, sIL-6R, IL-10, tumour necrosis factor (TNF)-α, transforming growth factor (TGF)-β_2 and interferon IFN-γ urine levels in healthy females compared to healthy males: protection against urinary tract injury?

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Summary

The aim of this prospective study was to examine gender-related differences of cytokines in the plasma and urine of healthy individuals that might provide a clue concerning the lower rate of chronic renal diseases in females. Soluble interleukin-1 receptor antagonist (sIL-1RA), interleukin (IL)-1α, IL-1β, IL-2, sIL-2R, IL-3, IL-4, IL-6, sIL-6R, IL-10, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β_2 and interferon (IFN)-γ were determined using standard enzyme-linked immunosorbent assay (ELISA). Cytokine levels were determined in simultaneously obtained plasma and urine samples of 18 male and 28 female healthy members of our laboratory staff. Urine cytokine levels were studied three times at 1-month intervals. All individuals had a negative urine nitrite test and showed no symptoms of urinary tract infection (UTI). Plasma levels of all studied cytokines were similar in males and females (P = n.s.). However, females had significantly higher urine IL-1α ($P < 0{\cdot}0001$; $P < 0{\cdot}0001$; $P < 0{\cdot}0001$) and sIL-1RA ($P = 0{\cdot}0001$; $P = 0{\cdot}0003$; $P = 0{\cdot}0002$) than males at three and higher IL-1β at one of the three investigations ($P = 0{\cdot}098$; $P = 0{\cdot}003$; $P = 0{\cdot}073$). Urine levels of the other cytokines were similar in males and females. Higher urine levels of IL-1α, IL-1β and sIL-1RA in females may result from stimulation of cells in the urinary tract. Increased sIL-1RA might block T lymphocyte activation. The elevated cytokines may play a role in the protection of the female urinary tract from certain renal diseases, such as pyelonephritis and other inflammatory and sclerotic kidney diseases.

Keywords: gender-related differences, protection, scarring, urine sIL-1RA, urine IL-1α, urine IL-1β, urinary tract infection

Introduction

It is well known that men are more prone to develop membranous nephropathy, immunoglobulin A nephropathy or polycystic kidney disease than women [1,2], and that women experience urinary tract infection and slower progression of chronic renal diseases more often than men [1,3]. It has been hypothesized that the underlying mechanisms for this gender disparity might be related to gender-specific differences in glomerular structure, glomerular hemodynamics, diet, variations in the production and activity of local cytokines and hormones, and/or the effect of sex hormones on kidney cells [1,2].

In this prospective study we investigated a series of 13 different cytokines, soluble cytokine receptors and soluble cytokine receptor antagonists in simultaneously obtained plasma and urine samples of healthy females and males. We investigated gender-related differences of monocyte- and lymphocyte-derived mediators of immune responses that might be protective against urinary tract infection (UTI) and certain renal diseases, such as pyelonephritis and other inflammatory and sclerotic kidney diseases.

Methods and subjects

Female and male healthy individuals

Cytokine levels were determined in simultaneously obtained plasma and urine samples of 18 male and 28 female healthy members of our laboratory staff. Because gender-related

differences were found only in the urine, we studied urine cytokine levels in 18 male and 28 female staff members two times after a 1-month interval, and in a subgroup of 18 males and 24 females a third time after another month. The age of male and female staff members was similar (36·9 ± 10·8 years *versus* 36·9 ± 7·7 years: P = n.s.) and ranged from 21 to 63 years. All subjects were free of acute or chronic disease and urinary tract infection, and none was on any medication. The women had no menstrual bleeding at the time of investigation. Anamnestic data were obtained using a questionnaire. To exclude bacterial contamination and undiagnosed infection, all urine samples were tested for nitrite using urine sticks (Medi-Test, Macherey-Nagel, Düren, Germany). All individuals had negative test results at the three determinations. Urine cultures for the detection of asymptomatic bacteriuria were not performed. The study was conducted in accordance with local ethical guidelines and all individuals gave informed consent for analysis of their plasma and urine samples.

Determination of plasma and urine cytokines, soluble cytokine receptors and soluble cytokine receptor antagonists

Plasma and urine levels of soluble interleukin-1 receptor antagonist (sIL-1RA), IL-1α, IL-1β, IL-2, sIL-2R, IL-3, IL-4, IL-6, sIL-6R, IL-10, tumour necrosis factor (TNF)-α, transforming growth factor (TGF)-β_2 and interferon (IFN)-γ were determined using standard enzyme-linked immunosorbent assay (ELISA). IL-1α, IL-1β, sIL-1RA, IL-2, sIL-2R, IL-3, IL-4, IL-6, sIL-6R, IL-10, TGF-β_2, and TNF-α were measured using Quantikine kits (R&D Systems, Wiesbaden, Germany), and IFN-γ using HBT kits (Holland Biotechnology BV, Firma Biermann, Bad Nauheim, Germany). Plasma was snap-frozen within 2 h after the blood was drawn. The urine samples were freshly obtained in the morning, snap-frozen within 2 h and stored at −30°C until testing.

Statistical analysis

The Mann–Whitney U-test was applied using the Statistical Package for the Social Sciences (SPSS, Chicago, USA). Adjustment for multiple testing (n = 13) was performed according to Bonferroni's method. P-values of < 0·01 were considered significant and are shown in Tables 1 and 2.

Results

Cytokine levels in simultaneously obtained plasma and urine samples

Plasma levels of IL-1α, IL-1β, sIL-1RA, IL-2, sIL-2R, IL-3, IL-4, IL-6, sIL-6R, IL-10, TNF-α, TGF-β_2 and IFN-γ were similar in males and females (P = n.s.) (Table 1). In contrast, IL-1α and sIL-1RA levels in simultaneously obtained urine samples were significantly higher in females than males (IL-1α: P < 0·0001; sIL-1RA: P = 0·0001), whereas the other cytokines were similar in females and males and apparently not affected by gender (P = n.s.) (Tables 2; first investigation).

Table 1. Plasma cytokine levels of male and female healthy staff members.

Parameter	Males (n = 18)	Females (n = 28)	P
P_IL-1α (pg/ml)	1·7 ± 2·7	2·3 ± 3·0	0·044
P_IL-1β (pg/ml)	1·0 ± 2·8	0·5 ± 0·7	0·738
P_sIL-1RA (pg/ml)	205 ± 88	334 ± 480	0·964
P_IL-2 (pg/ml)	0·6 ± 2·7	1·8 ± 4·2	0·122
P_sIL-2R (pg(ml)	559 ± 191	566 ± 198	0·848
P_IL-3 (pg/ml)	16·8 ± 24·7	4·2 ± 7·1	0·133
P_IL-4 (pg/ml)	2·6 ± 7·5	0·2 ± 0·7	0·298
P_IL-6 (pg/ml)	1·8 ± 3·2	0·5 ± 0·9	0·136
P_sIL-6R (pg/ml)	34 536 ± 9871	29 298 ± 9802	0·068
P_IL-10 (pg/ml)	8·1 ± 17·5	3·9 ± 10·2	0·124
P_TNF-α (pg/ml)	1·4 ± 3·3	0·8 ± 1·5	0·719
P_TGF-β2 (pg/ml)	3·6 ± 15·3	0·8 ± 2·8	0·596
P_IFN-γ (pg/ml)	1194 ± 1737	489 ± 624	0·653

P_ = plasma level. All data are given as mean ± 1 s.d. P-values were calculated using the Mann–Whitney U-test. Adjustment for multiple testing (n = 13) was performed according to Bonferroni's method. Only P-values of < 0·01 were considered to be significant.

Urine cytokine levels studied three times at 1-month intervals

When the urine samples of the 18 male and 28 female staff members were investigated a second time after a 1-month interval, and in a subgroup of 18 males and 24 females a third time after another month, females had consistently higher urine IL-1α (P < 0·0001 at first, second and third investigations) and urine sIL-1RA (P = 0·0001 at firsst, P = 0·0003 at second and P = 0·0002 at third investigations) (Table 2) than male individuals. In addition, urine IL-1β was increased significantly in females at one and slightly increased at the other two investigations (P = 0·098 at first, P = 0·003 at second and P = 0·073 at third investigations). In contrast to cytokines of the IL-1 family, urine levels of IL-2, sIL-2R, IL-3, IL-4, IL-6, sIL-6R, IL-10, TNF-α, TGF-β_2 and IFN-γ were consistently similar in females and males at all measurements (P > 0·01) (Table 2). The data suggest that only cytokines of the IL-1 family are increased in the urine of females, whereas the urine levels of other cytokines are not gender-related. Figure 1 shows the IL-1α, IL-1β and sIL-1RA urine levels of males and females.

Discussion

The aim of this study was to examine gender-related differences in mono- and lymphokine levels in plasma and urine

Table 2. Urine cytokine levels in males and females measured in 1-month intervals at three different investigations.

	1st investigation*			2nd investigation			3rd investigation		
Parameter	Male ($n = 18$)	Female ($n = 28$)	P	Male ($n = 18$)	Female ($n = 28$)	P	Male ($n = 18$)	Female ($n = 24$)	P
U_IL-1α (pg/ml)	0·7 ±1·1	12·6 ±14·3	**< 0·0001**	0·6 ±1·2	17·9 ±18·7	**< 0·0001**	1·9 ±1·5	8·1 ±7·5	**< 0·0001**
U_IL-1β (pg/ml)	0·4 ±0·8	5·2 ±11·9	0·098	0·8 ±1·0	5·1 ±7·9	**0·003**	0·4 ±0·5	1·8 ±3·6	0·073
U_sIL-1RA (pg/ml)	1727 ±801	2686 ±573	**0·0001**	2010 ±790	2859 ±662	**0·0003**	1414 ±805	2452 ±877	**0·0002**
U_IL-2 (pg/ml)	1·8 ±5·1	1·4 ±2·9	0·082	4·8 ±16·5	4·3 ±0·10·8	0·543	2·0 ±4·0	3·8 ±9·4	0·432
U_sIL-2R (pg/ml)	750 ±540	535 ±520	0·163	695 ±561	685 ±623	0·644	753 ±566	448 ±407	0·049
U_IL-3 (pg/ml)	5·7 ±11·3	3·1 ±6·9	0·928	3·1 ±4·2	2·6 ±5·0	0·363	1·2 ±2·2	1·8 ±3·1	0·587
U_IL-4 (pg/ml)	0·7 ±1·7	0·4 ±0·8	0·904	0·7 ±1·5	0·8 ±4·0	0·280	0·5 ±0·9	0·4 ±1·2	0·266
U_IL-6 (pg/ml)	0·9 ±1·5	1·3 ±2·9	0·620	2·1 ±3·2	1·5 ±1·8	0·731	1·3 ±2·4	0·4 ±1·1	0·111
U_sIL-6R (pg/ml)	814 ±500	1142 ±2285	0·558	1478 ±1867	743 ±482	0·115	673 ±502	700 ±566	0·990
U_IL-10 (pg/ml)	2·7 ±4·53	7·3 ±10·2	0·136	4·4 ±8·0	7·1 ±13·6	0·246	1·4 ±2·1	3·5 ±6·5	0·366
U_TNF-α (pg/ml)	4·0 ±7·0	3·4 ±4·1	0·583	3·8 ±2·7	3·6 ±3·3	0·569	2·3 ±2·4	1·9 ±2·1	0·575
U_TGF-β2 (pg/ml)	1·5 ±4·4	3·2 ±7·8	0·904	0·8 ±2·2	2·5 ±5·4	0·115	2·3 ±5·4	3·4 ±6·1	0·473
U_IFN-γ (pg/ml)	11·8 ±19·4	26·7 ±44·5	0·551	16·1 ±23·5	39·4 ±74·8	0·147	102·5 ±125·8	71·3 ±87·5	0·990

U_ = urine level. All data are given as mean ± 1s.d. *Urine samples of the first investigation were obtained simultaneously with plasma samples (see Table 1). P-values were calculated using the Mann–Whitney U-test. Adjustment for multiple testing ($n = 13$) was performed according to Bonferroni's method. P-values of < 0·01 were considered to be significant and are shown in bold type.

Fig. 1. Interleukin (IL)-1α, IL-1β and sIL-1RA levels in urine samples of 18 male and 28 female healthy individuals. Female individuals had significantly higher urine IL-1α ($P < 0·0001$), IL-β ($P = 0·003$) and soluble interleukin-1 receptor antagonist (sIL-1RA) ($P = 0·0003$) levels than male individuals. Means are represented by horizontal bars.

under physiological conditions in order to obtain information concerning the pathogenesis of gender-related differences in the rate of infectious diseases and certain renal diseases, such as pyelonephritis and other inflammatory and sclerotic kidney diseases.

Our data agree with the findings of Lynch *et al.* and Rauta *et al.* who reported a higher urinary excretion of IL-1RA and IL-1β in healthy females than males [4,5]. Moreover, Lynch *et al.* described a 5–10× higher secretion of IL-1α, IL-1β and sIL-1RA from mononuclear cells (MNC) obtained from the blood of healthy female controls during the luteal phase, and a 13–28× higher secretion of these cytokines from MNC obtained during the follicular phase compared to the secretion obtained with cells from healthy males [4]. The finding

of a consistently higher spontaneous release of IL-1α, IL-1β and sIL-1RA *in vitro* from MNC of females stands in contrast to our results, which showed similar cytokine levels in the plasma of females and males. Dilution of *in-vivo* secreted cytokines with plasma to undetectable levels can be ruled out as a source of error for IL-α and sIL-1RA because only two of 18 male and two of 28 female individuals had undetectable plasma IL-1α, and none of the male and only one female individual had undetectable plasma sIL-1RA. IL-1β levels were generally low, and 11 of 18 males and 16 of 28 females had undetectable levels. That the mean concentrations of IL-1α and IL-1β in plasma samples of males were higher than those in simultaneously obtained urine samples also argues against an influence of a limited sensitivity of the detection method. Unfortunately, we did not measure urine creatinine levels in our healthy controls. However, the reproducibility of increased IL-1α, IL-1β and sIL-1RA concentrations in female urine samples and the similar levels of lymphocyte-derived cytokines in male and female urine samples indicate that intra- and interindividual differences in urine volumes as well as urine creatinine levels did not markedly distort our results. As shown in Fig. 1, gender-related differences of the three cytokines were so profound that small dilution effects caused by varying urine volumes were most probably irrelevant.

Cytokines have a low molecular weight and can therefore easily undergo glomerular filtration followed by reabsorption in the tubuli [6]. However, reabsorption should strongly decrease the urine levels and should increase the plasma levels of the corresponding cytokines. Because cytokines of the IL-1 family were increased only in urine but not in plasma samples of females we favour the hypothesis that the increased urine levels reflect an increased production of these cytokines in the female urinary tract. Continuous stimulation in the urinary tract of females, inducing the production of these cytokines, could be the reason for the high urine levels of IL-1α, IL-1β and sIL-1RA. Production of IL-1 by activated infiltrating mononuclear cells as well as activated resident cells, including glomerular endothelial cells, capsular epithelial cells, smooth muscle cells of vessel walls, fibroblasts and some tubular epithelial cells, has been reported previously [7–11]. IL-1 is a profibrogenic cytokine capable of inducing epithelial–myofibroblast transdifferentiation, and thereby renal fibrosis through a TGF-β1-dependent mechanism that can be inhibited completely by IL-1RA [12]. Increased sIL-1RA production of glomerular cells might protect the female kidney against glomerular diseases, resulting in renal fibrosis [12,13]. Female gonadal steroids at normal physiological levels can induce expression of sIL-1RA [14]. A protective role of oestrogen and female gender in non-diabetic chronic renal disease, such as polycystic kidney disease, chronic glomerulonephritis, hypertensive angionephrosclerosis, chronic tubulointerstitial nephritis, IgA nephropathy and membranous nephropathy, has been established in a meta-analysis by Neugarten *et al.* [15]. Oestrogen suppresses TGF-β, α1 type IV collagen gene expression and the synthesis of type I collagen, preventing renal injury [16–20]. Androgens, the natural opponent of oestrogens, inhibit Th1 cytokines such as IL-2 and IFN-γ and induce IL-10. Androgens represent natural anti-inflammatory hormones [21,22]. One might speculate that the higher oestrogen levels in females induce a consistent prophylactic anti-inflammatory response of monocytes and endothelial cells in the urinary tract, intensified by low anti-inflammatory androgen levels, and that this might block Th1 activation and the development of inflammation and scarring in the female urinary tract.

We hypothesize that IL-1α, IL-1β and sIL-1RA, produced by activated resident cells of the urinary tract as well as activated infiltrating mononuclear cells within the urinary tract, protect the kidney against acute and chronic inflammation induced by bacterial infection ascending from the urethra via the bladder to the kidney. The bactericidal milieu, including activated monocytes, prevents or at least decreases the antigenic stimulation of the female urinary tract by bacteria that otherwise would have resulted in chronic inflammation and fibrosis [23,24]. Tullus *et al.*, studying IL-1α and sIL-1RA in the urine of children with acute pyelonephritis, suggested that persisting high urine levels of IL-1α may protect the urinary tract from inflammation and scarring [25]. Interestingly, they reported that urine sIL-1RA levels were higher in healthy controls than in children with recurrent pyelonephritis or children convalescent after acute pyelonephritis, but they did not differentiate between males and females [25]. Because sIL-1RA has been shown to function as an anti-inflammatory cytokine, it seems reasonable to suggest that higher levels of IL-1 and its receptor antagonist may play a role in the protection of female kidneys from T lymphocyte-mediated immune responses and/or certain infections and renal diseases, such as pyelonephritis. Differences in cytokine responses may be a result of gender-related differences in the response to bacteria in the urinary tract, and a consequence of the body's defence mechanism against increased urinary tract infections in females.

We did not find literature reports on gender-related differences in the cytokine production of renal cells in cell culture experiments. However, several studies have described the influence of gender on cytokine production [26–30]. Further, there are no reports on the effect of sex hormones on the production of IL-1 and sIL-1RA in tubular cells. However, we found three citations in the literature on an effect of oestrogen on TGF-β production in renal cells [18–20].

The described cytokine increases might have a prophylactic effect because they were observed in healthy individuals. All individuals in our study had a negative urine nitrite test and were asymptomatic. As shown in Fig. 1, nearly all females had higher sIL-1RA and higher IL-1α urine levels than males (minimal overlap), suggesting that increased cytokine urine levels in our healthy female controls did not originate from undiagnosed UTI. In a previous study, we

showed that female transplant recipients with or without bacteriuria had significantly higher sIL-1RA urine levels than male transplant recipients with or without bacteriuria [31]. We believe that pro- and anti-inflammatory cytokines in females regulate each other at a higher level than in males, thus establishing a balance with higher IL-1α, IL-1β and sIL-1RA urine levels. sIL-1RA produced by stimulated cells in the female urinary tract suppresses T lymphocytes that would otherwise initiate a T cell-mediated immune response. The results of many studies in humans and animals establish the importance of endogenous sIL-1RA as part of the host's response against infection and in limiting organ damage [32]. New potential approaches to modify glomerular inflammation using anti-inflammatory cytokines have been highlighted recently by Kluth and Rees [33].

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