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Original Investigation

Humor in systemic lupus erythematosus

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Abstract

Objective: Humor has neurophysiological effects influencing the release of cortisol, which may have a direct impact on the immune system. Laughter is associated with a decreased production of inflammatory cytokines both in the general population and in rheumatoid arthritis (RA). Our objective was to explore the effects of humor on serum cytokines [particularly interleukin-6 (IL-6)] and cortisol levels in systemic lupus erythematosus (SLE), after a standard intervention (120 min of visual comedy).

Material and Methods: We enrolled 58 females with SLE from consecutive patients assessed in the Montreal General Hospital lupus clinic. The subjects who consented to participate were randomized in a 1:1 ratio to the intervention (watching 120 min of comedy) or control group (watching a 120 min documentary). Measurements of cytokine and serum cortisol levels as well as 24-h urine cortisol were taken before, during, and after the interventions. We compared serum cytokine levels and serum and 24-h urine cortisol levels in the humor and control groups and performed regression analyses of these outcomes, adjusting for demographics and the current use of prednisone.

Results: There were no significant differences between the control and humor groups in demographics or clinical variables. Baseline serum levels of IL-6, IL-10, tumor necrosis factor-alpha, and B-cell activating factor were also similar in both groups. There was no evidence of a humor effect in terms of decreasing cytokine levels, although there was some suggestion of lowered cortisol secretion in the humor group based the 24-h urinary cortisol levels in a subgroup.

Conclusion: In contrast to what has been published for RA, we saw no clear effects of humor in altering cytokine levels in SLE, although interesting trends were seen for lower cortisol levels after humor intervention compared with the control group.

Keywords: Epidemiology, cytokine, rheumatoid arthritis, humor, systemic lupus erythematosus

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Introduction

Humor that induces laughter has been associated with decreased inflammatory cytokines such as serum interleukin (IL-6) and serum tumor necrosis factor (TNF)-alpha, both in the general population and in rheumatoid arthritis (RA) (1). Our objective was to explore the effects of humor on cytokines (particularly IL-6) and cortisol levels in systemic lupus erythematosus (SLE) after a standard intervention (120 min of visual comedy). Our hypothesis was that cytokines that are associated with SLE activity [primarily IL-6, but also possibly IL-10, anti-TNF-alpha, and B-cell activating factor (BAFF)] would decreased after the humor (but not the control) intervention. In addition, humor has neurophysiological effects influencing the release of cortisol, which may have a direct impact on the immune system (2, 3). Thus, we also assessed cortisol levels in the subjects.

Material and Methods

The study was approved by the McGill University Health Centre's research ethics board. SLE female patients were recruited for this study from the Montreal General Hospital lupus clinic registry. Our work was limited to females because the SLE population is >90% female; in addition, the effects of humor on cytokines may be modified by sex/gender (4). This research registry currently has over 300 SLE patients in active follow-up. To be eligible, patients had to meet the 1982 SLE criteria (updated 1997 updated) of the American College of Rheumatology (ACR) and had to communicate in either French or English. Pregnant women were excluded because neuroendocrine and immune parameters are altered during pregnancy; subjects with a current active infection were rescheduled as inflammatory markers may be influenced by inter-current infections. The recruitment occurred at the time when patients attended the clinic for their annual evaluation of longitudinal outcomes in SLE. Based on previous studies (1), we estimated that the planned sample size would provide an 85% power to detect a difference ≥0.4 pg/mL in serum IL-6 between the groups after the humor intervention. All participating patients signed an informed consent form detailing the procedures and potential risks.

The subjects were randomized to either the intervention or control group, using a set of randomly generated numbers. The intervention group watched 120 min of comedy from the *Just for Laughs*: Gags col-

lection, which features non-offensive practical jokes that are visual and that tend to appeal to a universal audience. This exposure is similar to interventions used in previous studies on the effects of humor (5, 6). The comparator group consisted of patients who watched a 120 min international award-winning science documentary (on endangered ocean species) (7, 8). The investigators a priori expected the control exposure to be engaging and emotionally neutral or possibly evoking mild mixed emotions (e.g., admiration, sadness, anger, and hope).

Measurements of serum cytokine concentrations, cortisol levels, and C-reactive protein were taken before, during, and after the interventions in the study and control patients. Angiocatheters attached to a needleless saline luer lock adapter were placed in the antecubital vein. After 15 min of resting, a baseline sample (T1) was drawn, followed by two other samples drawn after the first 60 min of the video and again immediately at the end (T2 and T3, respectively). These intervals were based time points suggested in literature when an effect can be determined for various behavioral interventions on cytokine levels (9). Additionally, a sample was drawn 24 h later (T4) to explore the durability of any cytokine and/or cortisol response. For the cytokine reagents, we used an ultrasensitive kit (allowing measurement of IL-6, IL-10, TNF-alpha, and BAFF with a high sensitivity) that was validated to ensure no interactions between cytokines. Individual cytokines were quantified using R&D systems' (Minnesota, United States) high-sensitivity Quantikine enzyme-linked immunosorbent assay kits for Human IL-4 (Cat# SS400), Human IL-6 (Cat# SS600B), Human IL-10 (Cat# SS100C), and Human TNF-alpha (Cat# SSTA00D). Human BAFF/BLyS/TNFSF13B was quantified using the R&D systems' Quantikine kit (Cat# SBLYS0B).

Because cortisol levels vary diurnally, all subjects began their assessment at the same time of day. Patient blood samples were processed immediately after being taken from the patient; the sera arrived in the laboratory at room temperature, were processed (spun and aliquoted) within 30 min, and were stored at -80°C. They were stored for up to six months (in order to accumulate enough samples for batch analysis) and were subsequently thawed in batch for analysis. The subjects were also asked to collect a 24-h urine sample (brought in the following day) to measure cortisol production.

At the clinic visit where recruitment took place, the SLE Disease Activity Index (SLEDAI-2K) (10) and the Systemic Lupus International Collaborating Clinics/American College of rheumatology damage index (11) were scored by the assessing physician and were used to ensure comparability of these two variables in the control and intervention groups at baseline. In order to compare the humor and control groups for mood and psychosocial status (which could alter cortisol and cytokines, as well as response to the intervention) and to control the analyses for these variables if necessary, SLE patients completed several scales: the Center for Epidemiologic Studies Depression Scale (CES-D, where scores >16 are often associated with significant depression), Perceived Stress Scale (12), and Coping with Health Injuries and Problems (13). The Humor Response Scale (HRS) was used to measure sense of humor. HRS is a validated observer rating scale that allows humor responses (e.g., smiling, laughter) to be recorded and quantified in a systematic fashion (5). Records were made of SLE duration, demographics, and current immunosuppressive drug use [particularly glucocorticosteroids, which have important direct effects on mood and cytokines (14)]. All these assessments were recorded prior to randomization.

Descriptive statistics were used to illustrate the baseline characteristics of the study population and to examine whether randomization successfully balanced the subjects in terms of demographic and clinical factors. Our analyses focused on the effects of humor on IL-6, IL-10, TNF-alpha, and BAFF levels. Out-of-range cytokine values were excluded from the analysis and were defined by the following accepted ranges: IL-6 values, <0.156pg/mL or >10 pg/mL; IL-10 values, <0.781 pg/mL or >50 pg/mL; TNF-alpha values, <0.5 pg/mL or >32 pg/mL; and BAFF values, <62.5 pg/mL or >403,00 pg/mL. These are out-of-range not only according to established laboratory norms (15) but also according to published studies of cytokine levels in SLE (16).

We provide descriptive analyses for changes in each cytokine level at each assessment from T1 (baseline) to T3 (completion of the intervention) as well as for the subgroup that provided a serum sample the following day (T4). Adjusted logistic regression models estimated odds ratios (ORs) and 95% confidence intervals (CIs) for changes in cytokine levels from baseline to T3. We ran four models, considering each cytokine as a unique outcome. In all models, we used dichotomous variables to adjust for current prednisone (categorically as <10 mg per day or ≥10 mg because this variable was not normally distributed) and for depression (based on a CES-D score ≥16). Sensitivity analyses were performed with these continuous variables (mg of prednisone per day and actual CES-D score). We also excluded patients using prednisone in the sensitivity analyses. Because patients were studied over the course of a year, we included dummy variables to adjust for whether the analyses were done in spring (March-May), summer (June-August), fall (September-November), or winter (December-February). Finally, a sensitivity analysis was also performed including the HRS values in our regression. All regression analyses were performed using the software R for Windows® version 2.11.1 (The R Foundation for Statistical Computing, Vienna, Austria). We also described the results of the 24-h urinary cortisol assay in a subgroup of participants who were able to provide their urine sample.

Results

Fifty-eight women were enrolled in the study, of which 32 were randomized to the humor group and 26 to the control group. Baseline characteristics of the study population as well as baseline serum cytokine concentrations are shown in Table 1. Most (72.4%) participants were Caucasian, and the median age was 45.2 years (range 20-74 years). Twenty per cent of the subjects were on prednisone; four of these (3 in the humor group, 1 in the control group) were on doses of 10 mg or more per day. Because these doses of steroids affect the results of the cortisol measurements, data on these patients were excluded in the analyses of cortisol levels. There were no significant differences between the control and humor groups in baseline variables. Scores on HRS taken during the intervention were significantly higher for subjects in the humor group (mean, 54.6; standard deviation, SD 15.4 versus 13.9; SD 3.1 for control group).

For cytokine levels, we excluded 59 readings (similar numbers between the humor and control groups in 24 patients) with out-of-range values from the analysis: 18 at baseline (T1), 20 at T2, 18 at 2-h (T3), and 3 at 24 h (T4). The out-of-range values were almost all low IL-10 (35) or high BAFF (13) levels with 9 high IL-6 levels and two low out-of-range TNF-alpha levels. Table 2 shows baseline and follow-up measures (after intervention) for IL-6, IL-10, TNF-alpha, and BAFF levels. There was an unexpected trend for increasing IL-6 levels over time in the humor group. In contrast, IL-6 tended to decrease (non-significantly) from baseline in the control group. No consistent changes were seen in the humor and control groups for serum levels of IL-10, TNF-alpha, or BAFF.

Table 3 shows ORs for four logistic regressions where the outcome modeled in each case was different (decreased) in cytokine level from T1 to T3. OR, adjusted for prednisone use, depres-

Table 1. Baseline SLE participant characteristics, humor group versus controls

Variable	Groups Humor (N=32)	Control (N=26)	Difference (Humor group versus Control group) 95% CI
Mean age in years (95% CI)	47.7 (42.9-52.5)	42.0 (35.7-48.3)	5.7 (-2.0, 13.4)
Race/ethnicity: Caucasian % (N)	81.3 (26)	61.5% (16)	20% (-3, 41)
Mean SLE duration, years (95% CI)	14.6 (10.9-18.3)	10.7 (7.2-14.2)	3.9 (-1.1, 8.9)
Corticosteroid use, % (N)	21.9 (7)	15.4 (4)	6.9% (-14.7, 25.7)
SLEDAI mean (95% CI)	3.7 (2.4-4.9)	4.5 (2.7-6.3)	-0.8 (-2.9-1.3)
CES-D score> 16, %*	34.4	34.6	-
CHIP: emotional** median	17	18	
Perceived Stress Scale median	15	16	-
Serum cortisol median nmol/L	251.0	251.5	-
IL-6, median (N)[ff]	0.58 (30)	0.66 (25)	-
IL-10, median (N)[ff]	1.00 (26)	1.00 (21)	-
TNF-alpha, median (N)[ff]	1.83 (32)	1.58 (26)	-
BAFF, median (N)[ff]	894.5 (29)	907.2 (25)	-

SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; CES-D: center for epidemiologic studies depression scale; CHIP: coping with health ınjuries and problems; IL: interleukin; TNF: tumor necrosis factor; BAFF: B-Cell activating factor

*CES-D scores>16 are often associated with significant depression

**; Median scores for other CHIP subscales were also similar in humor and control groups

[ff]. N represents the number of baseline samples assessed for each cytokine, once out-of-range values were excluded (hence, N differs for each)

Table 2. Mean cytokine serum levels at baseline (T1), 2 h (T3), and 24-h (T4) after the intervention (humor and control group SLE patients). Mean differences over time (for T3-T1 and T4-T1) are shown with 95% confidence intervals (CIs); a negative number for the difference indicates a decrease in cytokine levels over time, whereas a positive number suggests an increase

Cytokine	Baseline, T1 value (N)*	2 h, T3 value (N)*	Mean difference T3-T1 (95% CI)*	24 h, T4 value (N)*	Mean difference T4-T1 (95% CI*)
IL-6	0.92 (30)	1.60 (31)	0.41 (0.07, 0.90)	0.70 (11)	-0.27 (-0.94, 0.38)
IL-10	1.42 (26)	1.51 (26)	0.11 (-0.39, 0.61)	1.08 (10)	-0.01 (-0.24, 0.22)
TNF-alpha	2.56 (32)	2.57 (32)	0.01 (-0.18, 0.20)	2.34 (11)	-0.40 (-1.27, 0.47)
BAFF	1187.8 (29)	1159.3 (29)	-28.5 (-109.9, 53.0)	878.6 (10)	72.9 (-34.7,180.5)
			Control Group		
IL-6	1.08 (25)	0.92 (24)	0.04 (-0.08, 0.16)	0.89 (12)	-0.09 (-0.52, 0.34)
IL-10	1.68 (21)	1.72 (21)	0.06 (-0.09, 0.21)	2.44 (12)	0.35 (-0.34, 1.05)
TNF-alpha	1.88 (26)	1.77 (26)	-0.12 (-0.26, 0.03)	2.07 (11)	-0.10 (-0.34, 0.13)
BAFF	1056.2 (25)	1032.0 (25)	-24.2 (-101.1, 52.6)	1078.8 (12)	63.5 (-4.24,131.2)

IL: interleukin; TNF: tumor necrosis factor; BAFF: B-Cell activating factor

*Samples with out-of-range values were excluded, resulting in N samples (shown for each time point for each cytokine). Differences are calculated on the subjects that had both values available (e.g., to calculate difference between T3 and T1, both T3 and T1 were needed)

Table 3. Adjusted odds ratio (OR) and 95% confidence interval (CI) estimates for cytokine level changes in the humor group versus control group SLE patients. The logistic regression modeled the outcomes as 1 if the cytokine level increased from baseline to T3, and 0 otherwise

Outcome*	OR increase** (95% CI)
IL-6	4.02 (1.17-15.8)
IL-10	1.89 (0.44-9.24)
TNF-alpha	4.35 (1.29-17.05)
BAFF	2.13 (0.68-7.07)

IL: interleukin; TNF: tumor necrosis factor; BAFF: B-Cell activating factor

*Out-of-range values were excluded

**Adjusted for depression (CES-D score>16), prednisone use, and season of the year

sion, and season, indicates that the subjects exposed to humor were actually more likely than controls to show increased IL-6 and TNF-alpha cytokine levels after the intervention. Including HRS reduced the magnitude of the association and led to widened CIs, so that in all cases, the 95% CI included the possibility of no difference between the humor and control groups for changes in cytokine levels from T1 to T3.

For serum and 24-h urinary cortisol levels (Table 4), assessments were performed excluding the four individuals with daily prednisone

Table 4. Cortisol values for humor and control groups* SLE patients

	Humor (N=39)	Control (N=25)	Difference between means of humor and control groups (95% CI for differences)
Average (SD) baseline serum cortisol nmol/L	257.62±96.14	261.52±94	3.9 (-57.41, 49.61)
Median (range) baseline serum cortisol	270 (437)	263 (407)	-
Average (SD) second serum cortisol	231±90.5	216.2±101.96	15.2 (-39.71, 69.30)
Average (SD) third serum cortisol	190.29±69.11	171.52±69.25	18.77 (-20.20, 57.74)
Average (SD) change (between baseline and third sample)	93.86±74.55	94.16±73.26	-0.3(-41.90, 41.30)
Average (SD) 24-h urine cortisol level**	47±23.92	75±17.45	-28 (-39.66, -16.34)
Median (range) 24-h urine cortisol level**	43 (72)	76 (56)	-

*Cortisol levels were assessed excluding the four individuals who had a daily prednisone dose >10 mg because such exposures have very pronounced effects on cortisol excretion.

**24-h cortisol excretion was based on 17 subjects, 7 from the humor group and 10 from the control group, who brought in a 24-h urine sample the day following the intervention

dose ≥10 mg because such exposures have very pronounced effects on cortisol excretion. As can be seen in the table, the mean values of serum cortisol at baseline were very similar [258 nmol/L (SD 96.1) in the humor group versus 262 nmol/L (SD 94) in the control group]. In both groups, there was a similar decrease in serum cortisol levels over time with both groups averaging 94 nmol/L at the end of the intervention.

There was a trend toward lower 24-h urinary cortisol levels in the humor (average 47 nmol/L, SD 23.8) group compared with the control group (average 75 nmol/L, SD 17.45), indicating that the average values for the 24-h cortisol collection from the humor group participants were almost 40% lower than those of the control group. Unfortunately, the strong trend of decreased 24-h cortisol excretion in the humor group (which would be expected, given our hypothesis of humor decreasing cortisol levels over this period) was based on a small number (only 17 subjects, seven from the humor group and 10 from the control group, brought in a 24-h urine sample the following day).

Discussion

Laughter has been shown to decrease the levels of inflammatory cytokines both in the general population (1) and in RA (17, 18). In contrast to what has been published for RA, we saw no clear effects of humor on altering cytokine levels in SLE. In a study by Matsuzaki T et al. (18) on RA subjects and healthy controls, after experiencing a humor intervention, the levels of serum IL-6 and serum IL-4 decreased significantly in the RA group but not in the healthy subjects. Our results did not significantly change in our sensitivity analyses after excluding patients using steroids (data not shown).

A limitation of our study was the small number of subjects and the number of out-of-range values that were not included in the analysis. Using the pre-defined criteria, a relatively large number of IL-10 results were discarded, which limited meaningful conclusions about differences between the groups for this cytokine. Nevertheless, based on the published literature related to the effects of humor in RA, we would have expected that if humor had the same effects in SLE that had been shown in RA, same results would have been seen in our SLE sample, which exceeded the number of patients enrolled than the previous RA studies. Additionally, the trend we established was actually the reverse of what was shown in RA.

We did note interesting trends toward lower cortisol levels (in 24-h urinary samples) after the humor intervention compared with the control group. This is noteworthy because serum cytokine levels can vary greatly in an SLE population and even within the same SLE subject over short periods of time. Assessing cortisol secretion in our study was important because laughter is known to cause the release of cortisol, which can directly influence the immune system, potentially improving excess inflammation that characterizes autoimmune diseases such as RA and SLE. Another limitation of our novel and interesting finding was that the urinary cortisol assessments were based on a small number of subjects. The most reliable index of cortisol secretion is the 24-h urine sample collection, but only 17 subjects (seven from the humor group and 10 from the control group), were able to bring in a 24-h urine sample the following day.

An additional limitation was that we had to enroll subjects over the course of an entire year, which meant that seasonal variations (in cytokine or especially cortisol levels) could have hampered our attempts to show a difference between the humor and control groups. However, we did attempt to control this by including a value for season. Finally, the subjects studied were of relatively long duration (averaging more than 10 years of SLE) with a moderate disease activity (median SLEDAI-2k score being 4), which may have resulted in overall cytokine levels leaning toward low values. Thus, we cannot comment on what the effects of humor intervention may be in patients of shorter SLE duration or higher disease activity.

Finally, it is possible that the humorous films selected did not appeal to everyone's sense of humor; in complex ways, different aspects of our personality affect how we experience humor (19). Still, we applied HRS to both groups and found that humor response was indeed significantly higher for the subjects in the humor group. Future studies may also measure other patient-oriented outcomes, including self-perceived state of health and stress after the intervention.

In summary, we provided a well-designed, rigorous assessment of the effects of humor on SLE. Though our intervention did not decrease inflammatory cytokine profiles, there was a suggestion of a trend for decrease in cortisol levels. We hope that our novel study may inform other researchers planning studies on similar interventions in connective tissue diseases such SLE and RA.

Ethics Committee Approval: Ethics committee approval was received for this study from McGill University Heralth Center.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.B.O., D.D.C., D.B., S.B., C.A.P.; Design - A.B.O., D.D.C., D.B., S.B., C.A.P.; Supervision - A.B.O., D.D.C., D.B., S.B., C.A.P.; Materials - A.B.O., D.D.C., D.B., S.B., C.A.P.; Data Collection and/

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