

Effects of Functional Relaxation and Guided Imagery on IgE in Dust-Mite Allergic Adult Asthmatics

A Randomized, Controlled Clinical Trial

Claas Lahmann, MD,*† Peter Henningsen, MD,* Christian Schulz, MD,‡ Tibor Schuster, Dipl.-Stat,§
Nina Sauer, MD,¶ Michael Noll-Hussong, MD,* Joram Ronel, MD,* Karin Tritt, PhD,†
and Thomas Loew, MD†

Abstract: Although relaxation and imagination techniques have repeatedly proven their effectiveness in asthma, nothing is known about the immunological effects of these complementary interventions. Therefore, the aim of this study is to investigate the effects of the brief relaxation technique of functional relaxation (FR) with guided imagery (GI) on serum IgE in adult patients with dust mite allergic asthma in a randomized, controlled trial. Sixty-four patients were treated over a 4-week period and assessed at baseline, after treatment and after 4 months for follow-up. Due to its significant role in the pathophysiology of allergic asthma, the serum IgE was employed as outcome measure in this investigation. Participation in FR, GI, and FR/GI led to decreases in serum IgE (IU/mL) of -54.7 ± 67.1 , -49.5 ± 93.4 , and -28.4 ± 93.9 compared with an increase of 27.7 ± 43.2 in CI. Our study confirmed a positive and clinically relevant effect of FR and GI on total serum IgE levels.

Key Words: Allergic asthma, immunoglobulin E, relaxation techniques, imagery, randomized controlled trial.

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Asthma is a serious global health problem with an estimated 300 million affected individuals (Masoli et al., 2004). The prevalence ranges between 2% and 8% in adults (ECRHS, 1996) and up to 21% in children (ISAAC, 1998). When uncontrolled this chronic airway disorder can place severe limits on everyday life. Asthma is a significant burden, not only in terms of health care costs but also of lost productivity and reduced participation in family life (GINA, 2006).

From today's perspective, asthma is a disease of multiple-factor etiology in which environmental, genetic, infectious, allergic, and psychological elements all play a respective part (Lahmann et al., 2005; Lehrer, 1998).

The development of asthma can be considered to consist of several distinct but probably related processes. First, exposure of the genetically predisposed individual to a critical level of allergen may result in sensitization; then, further exposure of the sensitized individual leads to the development of airway inflammation and

bronchial hyper responsiveness (Sporik et al., 1992). Today atopic diseases such as asthma can be divided into 2 variants: First, the intrinsic nonallergic variant, with no detectable sensitization and with low IgE serum levels, and second the extrinsic allergic variant, which occurs in the context of sensitization towards environmental allergens and usually elevated IgE serum levels. Among the wide variety of allergen sources in human dwellings are domestic mites, furred animals, and fungi. Exposure and sensitization to house dust mite allergens has been established as an important risk factor for the development of asthma (Custovic et al., 1998) and 45% to 85% of patients with asthma in the United Kingdom show skin test reactivity to mites, as compared with 5% to 30% in the general population (Smith et al., 1969). Allergen-specific IgE antibodies have been considered to play an important role in the pathogenesis of exogen-allergic asthma (Platts-Mills, 1994). A tendency to produce an elevated level of total serum IgE is coinherited with airway hyper responsiveness (Postma et al., 1995). In almost all studies, patients with asthma have total serum IgE levels that are elevated compared with both controls and patients with hay fever (Wittig et al., 1980; Burrows et al., 1989). Furthermore, there is a strong association between acute episodes of asthma measured by emergency department visits or hospital admissions and elevation of total IgE in children as well as in adult patients (Gelber et al., 1993; Rasmussen et al., 2002). Contrarily, cutoff values for IgE that consistently distinguish between allergic and nonallergic individuals are difficult to define (Klink et al., 1990).

Adequate management of asthmatic complaints relies heavily on the patient's ability to detect changes in breathing, to assess these changes accurately, and to respond to them appropriately (Vamos and Kolbe, 1999). These considerations have lead to the use of complementary relaxation techniques and body-psychotherapeutic methods for improving body awareness and better regulation of the autonomic nervous system.

A large body of literature (Huntley et al., 2002) exists regarding the complementary use of relaxation techniques in the treatment of symptoms of asthma. Promising results have also been shown in several studies using the technique of functional relaxation (FR), a brief relaxation technique based on principles of psychodynamic body-psychotherapy. In 2 trials (Loew et al., 1996, 2001) FR lead to significant short-term improvements in pulmonary function in asthma patients with effect sizes comparable to inhaled β_2 -sympathomimetics, and Lahmann et al. (2009) could prove the long-term effectiveness of FR and Guided Imagery in a trial including a 4-month follow-up.

However, the psychophysiological mechanisms and psychoneuroendocrinological effects of FR still remain unclear (Lahmann et al., 2008).

We therefore analyzed changes in serum IgE aiming to compare the brief relaxation technique of FR with guided imagery (GI) in adult asthmatics. The changes in forced expiratory volume in

*Department of Psychosomatic Medicine, Technische Universität München, Germany; †Department of Psychosomatic Medicine, University of Regensburg Medical Center, Germany; ‡Department of Internal Medicine II, University of Regensburg Medical Center, Germany; §Institute for Medical Statistics and Epidemiology, Technische Universität München, Germany; and ¶Department of Psychosomatic Medicine, Henriettenstiftung Hannover, Germany.

Sent reprint requests to Claas Lahmann, MD, Department of Psychosomatic Medicine and Psychotherapy, Klinikum rechts der Isar, Technische Universität München, Langerstrasse 3, 81675 Munich, Germany. E-mail: lahmann@tum.de.

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the first second (FEV₁), as well as specific airway resistance (sR_{aw}) in the same sample, were recently published by Lahmann et al. (2009).

METHODS

Participants

Patients with mild to moderate allergic asthma participated in this study. Patients were recruited using a local newspaper advertisement, which was answered by 291 patients. Allergic testing consisted of prick testing to aeroallergens including indoor and outdoor allergens. Patients with proven sensitization to dust-mite based on skin testing and/or increased levels of specific IgE to house dust mite were randomized to one of the treatment strata. To be eligible, patients had to have controlled asthma on the current treatment level. To assess the level of asthma control daytime symptoms, limitations of activity, nocturnal symptoms, need for reliever and/or rescue medications as well as lung function testing were considered. Exclusion criteria were age under 18 years; severe psychiatric or somatic disease other than the allergic asthma; current use of any psychoactive medication or psychotherapy including regular relaxation training; and use of medication, anything other than the usual types of asthma medication prescribed by a chest physician or modification of asthma medication during the previous 4 weeks, or within the course of the trial. During the trial patients continued on their usual dose of asthma treatment. In addition no drugs with potential modulation of serum IgE such as antihistamines or oral corticosteroids were allowed. Current mental illness was excluded using a clinical face-to-face interview.

Due to the fact that patients were recruited by newspaper advertisement, the primary sample was unselected, and a high proportion did not fulfill the strict inclusion criteria given above. Seventy-five potential participants were identified and received a comprehensive description of the study specifics. Sixty-four patients gave their written informed consent to participate and were randomized to FR, GI, a combination of FR and GI (FR/GI) or a placebo relaxation technique as control intervention (CI). Randomization was carried out in confidence by a study nurse, with allocation concealment using a randomization list created before the study. Of the 64 patients included 17 patients were lost to follow-up due to invalid or missing laboratory values.

The sample size of 14 patients per group was calculated regarding the assumed effects of the interventions on pulmonary function as reported by Lahmann et al. (2009). Considering the changes of serum IgE given below, the sample size was also adequate to detect differences in IgE change between control and intervention groups of 45 IU/mL with 80% power, assuming a common standard deviation of 40 IU/mL, and considering an explorative type I error level of 0.05 in each comparison.

Assessment

Total IgE-levels were measured using the ImmunoCAP System (Pharmacia, Freiburg, Germany), in accordance with instructions of the manufacturer. In all patients blood was drawn by peripheral vein puncture always between 8 am and 10 am. Immediately after collection, samples were centrifuged and serum was deep-frozen at -80°C until testing. All analyses were carried out by the Department for Clinical Chemistry and Laboratory Medicine of a university hospital.

Design

The time structure of the trial was identical for all conditions. Recruitment was carried out between June and September, interventions took place in October, and follow-up period was November till February for minimizing the influence of other exogenous allergens

than dust mites. After giving informed consent, the patients were randomized to FR, GI, FR/GI, or CI. The interventions were carried out over a period of 4 weeks in small groups of 3 to 5 persons with one group session per week. Directly before (t0) and after finishing the therapies (t1), and again 4 months later (t2), blood samples were taken and the participants also underwent lung function tests, the results of which are reported by Lahmann et al. (2009). The study was completed according to plan.

Interventions

All interventions were carried out by a physician specialized in psychosomatic medicine and certified in FR and hypnotherapy, assisted by a PhD student.

FR is a somatopsychotherapeutic intervention technique commonly used in Germany, Austria, and Switzerland for the treatment of various psychosomatic disorders (Lahmann et al., 2008). Its therapeutic effects are delivered through the assumed mechanism of positive stimulation of the autonomic nervous system as well as facilitation of proprioceptive awareness (Arnim, 1994). Patients perform minute movements of small joints during relaxed expiration while focusing on perceived changes in bodily feelings triggered by the movements. In this way, the focus of attention is directed towards the subjects relationship to the floor or to some other external foundation (that is, outer support), to the bony skeleton (referred to in FR as inner support) and to the interior regions of the body and skin (the latter being the outer border separating the body from one's environment).

In the FR treatment group, the group-therapy setting is guided by a manual which was generated during previous investigations (Lahmann et al., 2009; Loew et al., 2000), and has been adapted to special features of asthmatic patients.

The GI consists of a set of standardized imageries targeting the airways (Rietveld et al., 2000). Participants are instructed in positive imagery of a situation with deep "free" breathing and are encouraged to implement this positive imagination in their daydreams. A more detailed description is given by Lahmann et al. (2009).

In the combined FR and GI group the FR units are combined with elements of imagery in each session. In contrast the CI consists of isotonic exercises of one hand, which requires—in comparison to FR—an equivalent amount of movement, but does not involve chest, shoulders, neck or head. To enhance its credibility, the patients are told that this new technique is called focused body awareness training.

In all groups the patients are encouraged to practice the interventions learned in the session during the week and also throughout the follow-up period. They were instructed not to practice in a schematic manner, but to try to integrate elements of the interventions into daily live.

In the interest of minimizing potential therapist bias, all 3 forms of intervention were conducted by the same therapeutic team. The time structure was the same in every group, with one 60-minute session weekly.

Statistical Analysis

Statistical analyses were performed using SPSS software v. 15.0 (SPSS Inc., Chicago, IL) and the statistical software package R version 2.7.1 (R Foundation for Statistical Computing, Vienna, Austria) with function "qr" (quantreg package) (Koenker, 2005). Patients' basic data were characterized by descriptive statistics. *Chi square* test and analysis of variance (ANOVA) were used for exploratory comparisons of social demographic data between intervention groups. Due to skewed distribution of the considered outcome parameter IgE and presents of considerable outliers quantile regression analysis (Koenker, 2005) was employed for analyzing

differences in median change of total IgE between control group (CI) and intervention groups FR, GI, and FR/GI. In this analysis, to correct for impact of initial value level, baseline IgE was considered as adjustment covariate. In contrast to ordinary parametric analyses like ANOVA and/or ANCOVA inference by quantile regression approach is based on conditional quantile (in particular median) estimation and allows therefore a robust inference independently from normality assumption. For estimation of quantile group contrasts 95% confidence intervals were computed by the rank inversion method described by Koenker (2005). All statistical analyses were performed 2-sided at a 0.05 level of significance. To reduce multiple test issue, Bonferroni correction of *P*-values was conducted in each many-one group comparison (intervention groups vs. control). There were no imputations of missing data values. Since the primary

objective was change in IgE, patients without any follow-up measurement could not be considered in the analysis.

Source of Funding and Ethical Considerations

The study was planned and conducted in accordance with the Declaration of Helsinki and ethical laws pertaining to the medical professions. The design was approved by the ethics committee of the responsible university medical center. This study was conducted independently of any institutional influence and was not funded externally.

RESULTS

The study sample consists of 64 patients at time of randomization; the basic data is given in Table 1. Due to invalid or missing

TABLE 1. Basic Data at Time of Randomization

	Age (yr) (SD)	Gender (Female)	Smokers	Living in a Partnership	Profession		
					Blue-Collar Worker	White-Collar Worker	Homemaker
FR (<i>n</i> = 16)	41.9 ^a (14.5)	10 (62.5%)	3 (18.8%)	12 (75.0%)	2 (12.5%)	7 (43.8%)	7 (43.8%)
GI (<i>n</i> = 16)	45.5 ^a (13.4)	12 (75.0%)	2 (12.5%)	11 (68.8%)	1 (6.3%)	9 (56.3%)	6 (37.5%)
FR/GI (<i>n</i> = 16)	39.0 ^a (9.7)	8 (50.0%)	3 (18.8%)	11 (68.8%)	4 (25.0%)	8 (50.0%)	4 (25.0%)
CI (<i>n</i> = 16)	45.1 ^a (10.4)	11 (68.8%)	4 (25.0%)	14 (87.5%)	1 (6.3%)	6 (37.5%)	9 (56.3%)
<i>P</i>	0.40	0.50	0.85	0.58		0.46	

^aMean value; FR indicates group with functional relaxation; GI, group with guided imagery; FR/GI, group with combination of functional relaxation and guided imagery; CI, group with control intervention.

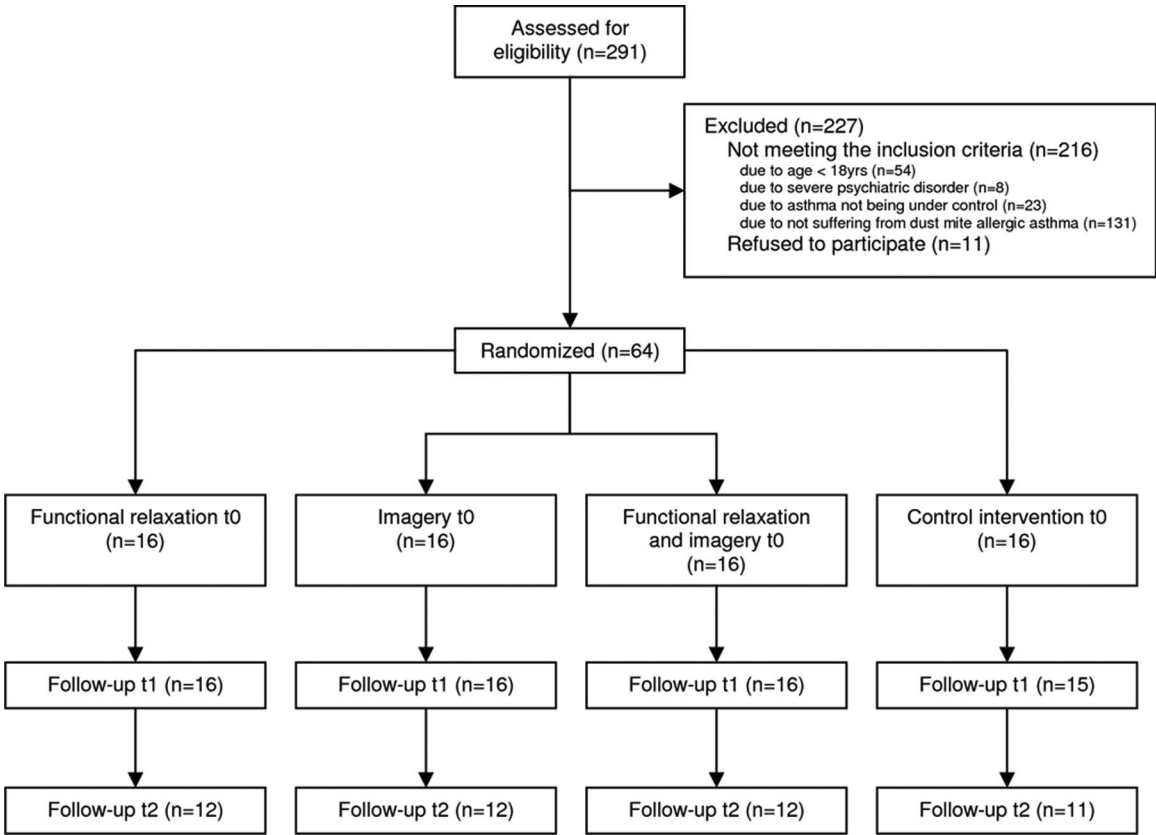


FIGURE 1. Flow diagram of trial process.

data, blood samples of 62 patients could be analyzed at t0, 62 samples at t1, and 47 at follow-up (t2) as given in Figure 1. The patient's basic data at the time of randomization are presented in Table 1. No statistically significant group differences were obvious between the 3 treatment groups regarding sociodemographic parameters, lung function tests as well as IgE at t0. Also, no statistically significant differences could be revealed in patients' attendance of the intervention sessions: an average of 3.81 ± 0.54 sessions were attended in FR, 3.75 ± 0.58 sessions in GI, 3.81 ± 0.54 sessions in FR/GI, and 3.62 ± 0.72 sessions in CI. Table 2 shows the explorative analysis of the total serum IgE over the course of the trial. No statistically significant differences were found in mean baseline values. Nevertheless, there were some positive correlation between baseline IgE and decrease of IgE by therapy ($\rho = 0.387$, $P < 0.001$). Thus, investigation of change of IgE was carried out considering adjustment for baseline values in a quantile regression approach.

Change of IgE about time is shown in Figure 2. All P -values reported below result from Bonferroni adjusted group comparisons with CI as reference group in the multivariable quantile regression model. In addition the adjusted group contrasts in median change of IGE are reported with 95% confidence intervals.

Participation in FR, GI, and FR/GI revealed differences in median change of IgE (IU/mL) compared with CI of -36.4 (95% CI: -54.1 to -23.6 , $P = 0.017$), -34.1 (95% CI: -57.9 to -23.6 , $P = 0.024$) and -23.8 (95% CI: -58.1 to -10.1 , $P = 0.59$). Up to t2 the differences in median increases in serum IgE were -76.9 (FR vs. CI, 95% CI: -99.7 to -29.3 , $P = 0.017$), -74.6 (GI vs. CI, 95% CI: -112.1 to -27.6 , $P = 0.023$), and -47.5 (FR/GI vs. CI, 95% CI: -95.0 to 1.11 , $P = 0.39$).

In an adjusted ANOVA relating to FEV₁ only the FR-group reached a level of statistical significance when compared with CI. A detailed analysis of FEV₁ and sRaw as clinically relevant outcome parameters is published by Lahmann et al. (2009).

No side effects to the interventions were reported by any of the patients, nor did any patients report difficulties with implementation of the body-psychotherapeutic technique of FR.

DISCUSSION

In the present study we were able to demonstrate for the first time that body-oriented interventions are not only leading to clinically relevant improvements in patients with allergic asthma (Lahmann, 2009), but are also accompanied by a distinct decrease of total serum IgE. IgE acts as part of a protein network and is playing a central role in allergic asthma (Gould and Sutton, 2008). The success of the IgE-specific antibody, Omalizumab, in the treatment of asthma and other allergic diseases demonstrates the virtues of targeting IgE for therapy (Holgate et al., 2005). In the present trial total serum IgE decreased in all intervention groups. The decrease of IgE was correlated significantly with the improvement of FEV₁ as the leading clinical outcome parameter as reported by Lahmann et al. (2009).

IgE is considered to be a key mediator in the pathogenesis of asthma and other allergic diseases (Gould and Sutton, 2008). Several studies have demonstrated that elevated levels of total IgE are associated with allergic asthma (Barnes, 2008; Postma et al., 1995; Rasmussen et al., 2002). IgE synthesis and regulation is complex and presents manifold opportunities for interventions (Gould and Sutton, 2008). It is conceivable that FE has sustainable psychoneuroimmunological effects on IgE synthesis via rebalancing the autonomous nervous system. However, it was beyond the aim of the present study to address these aspects of the complex IgE network more precisely.

TABLE 2. Measurement of IgE Over the Course of the Trial

Group	t0				t1				t2			
	FR	GI	FR/GI	CI	FR	GI	FR/GI	CI	FR	GI	FR/GI	CI
N	15	16	16	15	15	16	16	15	12	12	12	11
IgE ± SD	209.5 ± 220.7	165.5 ± 169.5	232.5 ± 180.3	256.8 ± 204.5	173.6 ± 180.5	134.8 ± 149.9	188 ± 135.3	266.8 ± 200.6	166.9 ± 162.4	118.8 ± 116.7	225.1 ± 167.2	240.8 ± 164.5
IgE Min	17.2	11.8	50.2	4.3	15.4	2.0	6.0	9.2	23.8	9.5	45.4	51.0
IgE Max	678.0	708.0	656.0	601.0	599.0	609.0	564.0	650.0	485.0	374.0	582.0	622.0
IgE 25th percentile	34.9	52.3	111.3	114.0	35.2	38.2	115.0	128.0	46.5	32.7	96.5	135.0
IgE 50th percentile	113.0	137.0	195.0	176.0	91.6	91.4	161.5	195.0	98.1	66.8	181.5	197.0
IgE 75th percentile	375.0	201.8	288.0	446.0	254.0	166.3	229.3	399.0	262.8	185.0	325.0	280.0

IgE indicates total serum IgE (IU/mL); SD, standard deviation; Min, minimum; Max, maximum; FR, group with functional relaxation; GI, group with guided imagery; FR/GI, group with combination of functional relaxation and guided imagery; CI, group with control intervention.

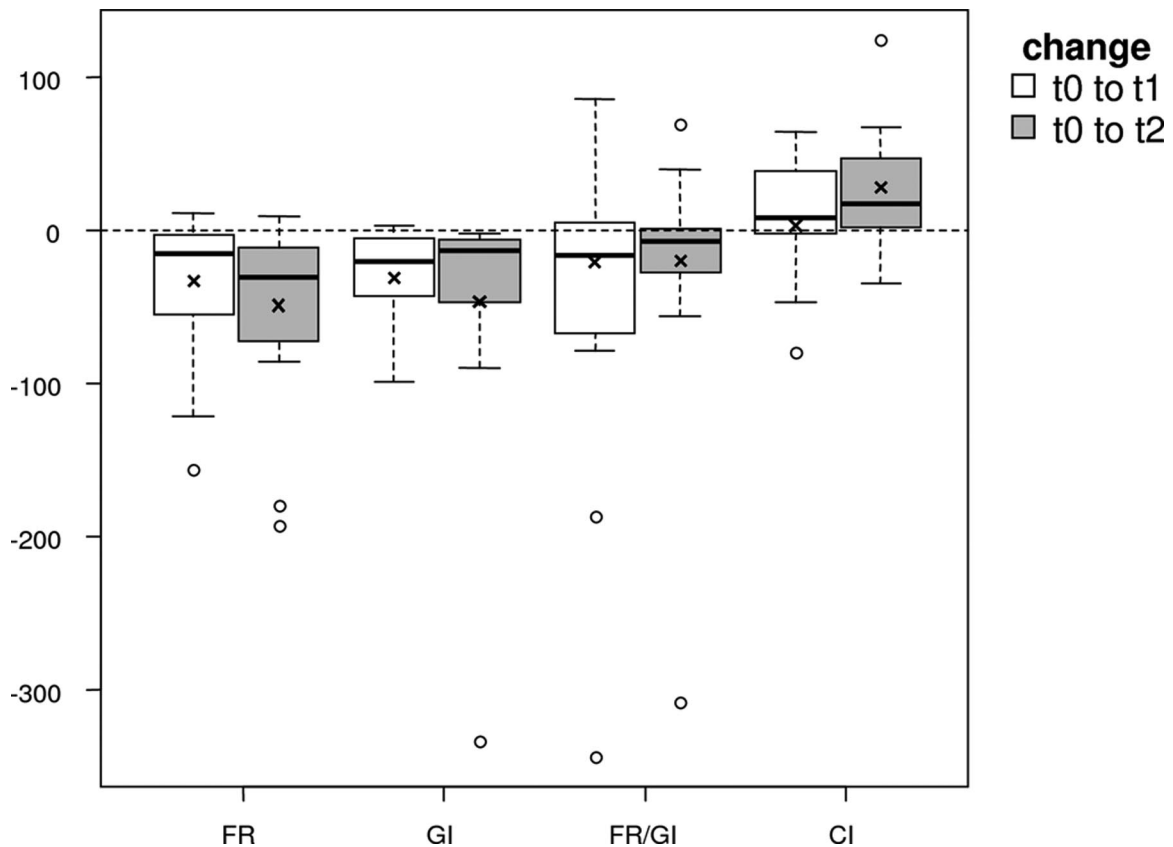


FIGURE 2. Changes in total IgE (IU/mL) t1 minus t0 and t2 minus t0. ○ indicates more than 1.5 times the interquartile range (IQR) from the first and third quartile; ×, conditional estimation of media from the multivariable quantile regression model.

Nevertheless, this study has several methodological limitations. First, the sample size was relatively small due to a considerably dropout rate, resulting in a sample of $n = 62$ at t1 but only $n = 47$ at t2 compared with $n = 62$ patients at t0. Since differences in IGE values showed a skewed distribution with considerable outliers a nonparametric quantile regression approach was used instead of common analysis of covariance. By the quantile regression method interpretability remains on a base of median values and additionally inflating baseline values can be considered.

Furthermore, the trial was conducted in a group of patients with relatively stable asthma. There is no evidence yet suggesting that FR or FR/GI will have similar effects during an acute asthma exacerbation, which is frequently accompanied by considerably higher IgE-levels (Rasmussen et al., 2002). In addition, since the follow-up period of this trial was only 4 months, the long-term stability of the achieved decreases of IgE remains slightly unclear.

Given that the body-oriented therapy sessions were carefully designed and matched for possible nonspecific effects (e.g. attention given by the trainer or learning effects), it is difficult to claim that outcome variables were influenced by nonspecific ingredients of FR. However, one possible influence may be seen in the fact that the study was not, and cannot be, conducted in an entirely double-blind setting, since it is not feasible that an experienced therapist does not know what kind of technique she/he is applying. Although adherence of therapists to the treatment manual was controlled by continuous supervision, the adherence of patients to the given instructions was not measured in the trial. The latter was due to the fact that the patients were strongly encouraged to further apply individually

modified exercise elements to various everyday situations over the course of the therapy phase and catamnesis, but were at the same time instructed to avoid schematic training sessions. Therefore, no precise information about the treatment dose is available. However, a reasonable hypothesis would be that the interventions FR and GI are self-effective, and therefore practiced more frequently by the participants than CI.

The present trial focused on the influence of FR, GI, and FR/GI on IgE as the major immunological parameter in patients with allergic asthma, and therefore no subjective outcome parameters were measured. As a matter of course, it must be considered that improved physiological outcomes are not necessarily reflected in improved asthma-related quality of life (Carranza et al., 2004).

CONCLUSIONS

Even considering the above limitations, the results of our study are promising, because they show for the first time that body oriented therapy is not only effective in achieving clinical improvements in patients with chronic asthma as reported by Lahmann et al.(2009), but also leads to clinically relevant changes of immunological parameters. This is an important confirmation of psychoneuroendocrinological effects of FR as a body psychotherapeutic technique; furthermore, these effects were shown as maintained over a period of 4 months. These benefits of treatment are the result of only 4 sessions of complementary body-oriented therapy. Additional research is needed to ascertain if these results can be replicated, how long-lasting the

benefits are beyond a 4-month follow-up, and whether the regular complementary use of FR also leads to clinically relevant improvements of further clinical relevant neuroendocrinological parameters.

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