European Review for Medical and Pharmacological Sciences 2022; 26: 8342-8350

Effect of Benson's relaxation therapy alone or combined with aerobic exercise on cortisol, sleeping quality, estrogen, and severity of dyspeptic symptoms in perimenopausal women with functional dyspepsia

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Abstract. – OBJECTIVE: Besides repeated stress exposure, a sedentary lifestyle and low estrogen levels are risk factors for the development of functional dyspepsia (FD). The aim of this study was to find out the effect of adding aerobic exercise (5 sessions per week) to the daily application of a 40-minute Benson's relaxation therapy (BRT) (diaphragmatic breathing and progressive muscle relaxation applied for 20 minutes in the morning and evening) on Glasgow dyspepsia severity score (GDSS), cortisol, visual analogue scale (VAS) (for abdominal symptoms), estradiol (one of the endogenous estrogens), Pittsburgh sleep quality index (PSQI), and 42-item depression, anxiety, and stress scales (DASS-42) in 60 perimenopausal women with FD.

PATIENTS AND METHODS: Women who consumed a daily dose of pantoprazole (40 mg tablet administered as a proton pump inhibitor drug) were randomly assigned to an 8-week study group (this group received aerobic exercise plus BRT, N=30) or an 8-week control group (this group received BRT only, N=30).

RESULTS: Significant improvements were reported in all measured variables within women groups (except estradiol of the control group). Compared to the control group, the reported within-group significant improvements in GDSS, cortisol, VAS, PSQI, and DASS-42 were higher in the study group.

CONCLUSIONS: Significant improvements in GDSS, cortisol, VAS, PSQI, and DASS-42 could be achieved after adding adjunctive therapies – aerobic exercise and BRT – to the medications of FD in perimenopausal women. Compared to BRT alone, physical exercise plus BRT significantly increases the levels of estradiol in perimenopausal women with FD.

Key Words:
Exercise, Relaxation technique, Cortisol, Sleeping, Estrogen, Functional dyspepsia.

Introduction

Functional dyspepsia (FD) is one of the most common gastrointestinal illnesses that can develop during the perimenopausal period. The perimenopause-related FD (PRFD) accounts for 30% of gastroenterologist counseling. In the absence of known organic and/or metabolic diseases, the main symptoms/complaints of PRFD include discomfort and/or burning in the epigastric area, postprandial fullness, and early satiety[1].

Estrogen (E) levels highly fluctuate during the perimenopausal period. Through the stimulation of different neurogenic, immune, and endocrinal pathways, fluctuations of E levels are frequently associated with episodes of visceral pain. This pain is highly associated with the development of psychological disturbances such as anxiety, emotional disturbance, depression, and stress[2,3]. Long-term exposure to perimenopause-associated stress and psychological disturbances alter or suppress vagal activity[1]. Besides the development

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of sensory abnormalities (gastroduodenal hypersensitivity), stress-associated low vagal activity impairs the relaxation of gastric wall musculature, impairs the gastric accommodation to a meal, and delays the gastric motility and emptying, hence the PRFD develops[4].

To improve the symptoms, a wide variety of FD medications are frequently prescribed such as psychotropic and/or prokinetic agents, proton pump inhibitor drugs (PPID), or anti-*Helicobacter pylori* agents (*Helicobacter pylori* is a widespread human pathogen that describes the main cause of different gastrointestinal diseases, including FD). Despite the wide variety of the reported medicines, reports confirm the failure of FD drugs due to disappointing outcomes, adverse effects, and adherence issues[5].

Recently, alternative or complementary therapies have taken an important path in the treatment of FD and its associated problems such as psychological disturbances and sleep disorders which presents in 68% of FD sufferers[6]. It is reported that adherence to energy-expenditure programs such as aerobic exercise may improve dyspeptic symptoms and discomfort, digestive malfunctions, gastrointestinal immotility, sleeping quality, and FD-associated psychological disturbances[7]. Also, relaxation therapy – a meditation technique - is used to improve symptoms of psychological disturbances - anxiety, stress, and depression (SAD) trilogy – via lowering the activity of the autonomic nervous system in different chronic disorders including functional gastrointestinal disorders (FGD)[8].

The aim of this study was to examine the effect of Benson's relaxation therapy (BRT) - a combination of diaphragmatic breathing exercise with progressive relaxation technique[9] – alone or combined with aerobic exercise on cortisol (one of the common stress hormones), sleeping quality, SAD trilogy, dyspeptic symptoms, and estradiol (one of three naturally produced endogenous estrogens) in women with PRFD.

Patients and Methods

Study Design and Ethics of this FD Study

The four authors of this study followed the randomized controlled design during the conceptualization of the FD interventions. Besides following the ethics of Helsinki, FD interventions in this study were accredited by the ''Local Ethical Committee of Cairo University'' (Physical Therapy Faculty Approval No. P.T.REC/012/003657).

Settings

Women with PRFD were recruited from Shibin El-Qanatr General Hospital (outpatient clinic of internal medicine). This FD study was conducted from 1st March to 15th June 2022.

Functional Dyspepsia Patients

Sixty FD women – aged 41 to 52 years old - were included in this study. According to Rome criteria III[10], FD diagnosis is accredited if the patient complained of one of the following symptoms within the last six months: pain and/or burning sensation in the epigastric region, a sensation of postprandial gastric fullness/heaviness, or early satiety.

A physician excluded women with autoimmune diseases, gastric and/or duodenal ulcers, hypertension, esophagitis, cardiopulmonary disorders, diabetes mellitus, *Helicobacter pylori* infection, renal or hepatic disorders, rumination syndrome, neurological/musculoskeletal disorders, structural gastrointestinal disorders, or mental disorders were excluded. Obese, pregnant, or lactating women with PRFD were excluded. Women with PRFD who showed a regular adherence to contraceptive pills, sleeping pills, anti-depressants, hormonal replacement agents, analgesic agents, or complementary therapies (yoga, acupuncture, herbal therapies *etc.*) were also excluded.

Randomization

The randomization of women with PRFD was done through the random-block list (a computer-generated randomization technique). Women with PRFD who consumed a daily dose of pantoprazole (40 mg tablet administered as a proton pump inhibitor drug that was prescribed by an internal medicine physician) were randomly assigned to an 8-week study group (this group received aerobic exercise plus BRT, N=30) or 8-week control group (this group received BRT only, N=30) (Figure 1).

Interventions

Aerobic exercise

This training included walking on a treadmill for 30 minutes in the first month. During the second month, the time of training was increased to 40 minutes. The patients were trained at 60-65% of the maximum reserve of heart rate (MRHR) in the first month. In the second month, the training

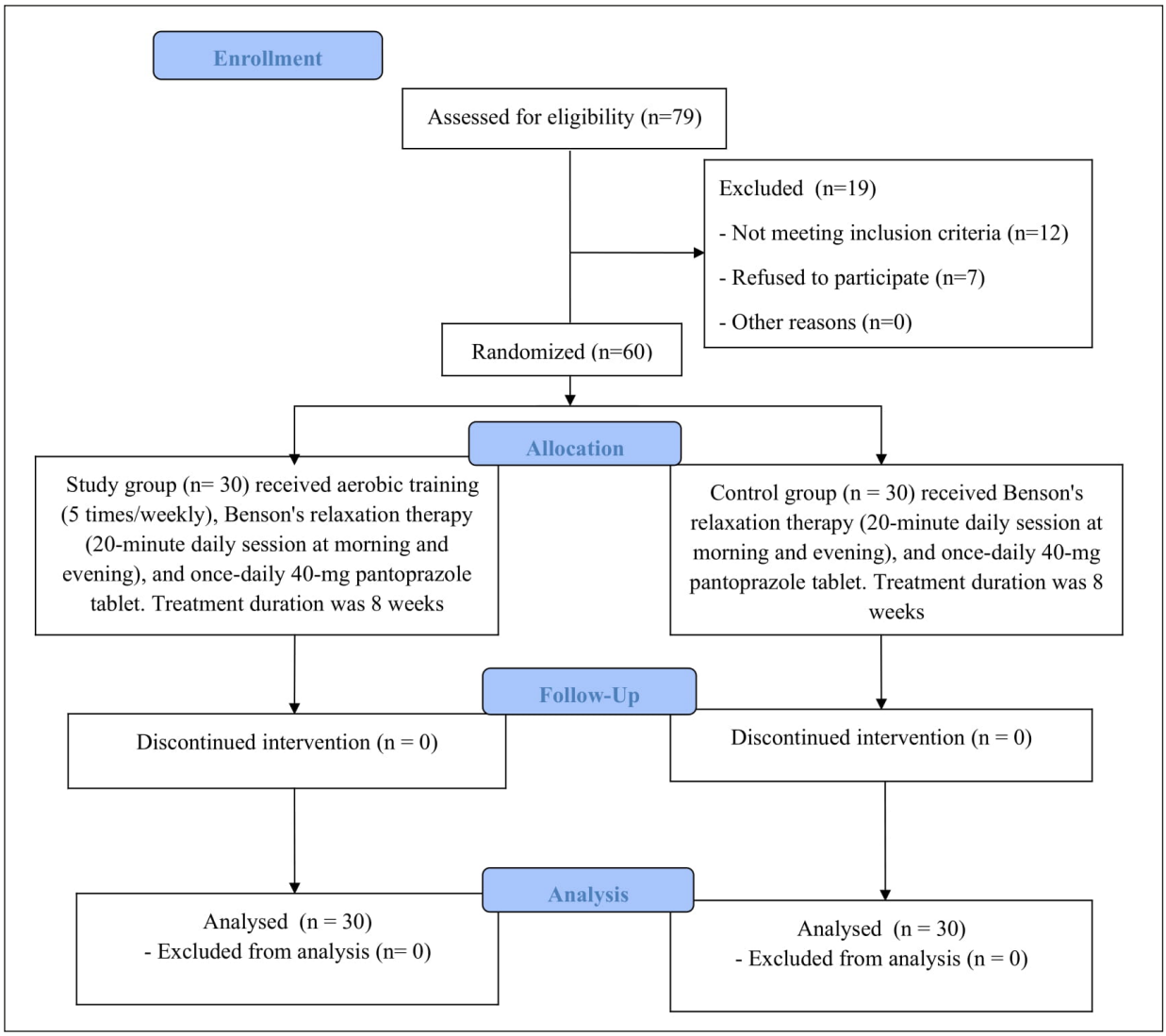

Figure 1. Functional dyspepsia interventional flow chart.

reached 70-75% of MRHR. Every training session was opened with a warming-up period and ended with a cooling-down period (both periods continued for 5 minutes at 50% of MRHR). Except for Sundays and Mondays, the exercise was conducted daily.

Benson's relaxation therapy

Women with PRFD executed twenty-minute morning and evening BRT in their homes. Daily for 8 weeks, women were contacted by a telephone call to remind them of the timed practice of BRT sessions.

On the first date, one author taught and explained BRT steps to every woman in a quiet room. For the home-based BRT, session instructions were recorded with relaxing music in the background of the record by one of the authors. The record was shared through WhatsApp on the phone of every woman to be played during the application of home sessions. At the start of the recorded audio file, the patient was told that the time of the audio file was twenty minutes, so it was not important to set an alarm clock to determine the duration of the BRT session. According to previous studies[8,9], the steps of BRT sessions in the recorded audiotape were as follow:

- Lie in a comfortable position without restricting clothes.
- Now, close both eyes slowly.
- Start to deeply relax your body muscles from the toes to the top of the head.
- While keeping your awareness, take a breath from your nose. Be aware that our inspiration

must move your abdomen up to focus on your diaphragm muscle. and keep your awareness. Expire quietly from your mouth while saying one Arabic word on your lips.
- Repeat the breathing exercise for the resting 20 minutes.
- While repeating breathing exercises, keep your body muscles relaxed. When annoying thoughts happen, ignore them. Do not worry or think about whether or not you are at a deep relaxation level.
- Now, you are at the last minute of the session, open your closed eyes for a few seconds while you are lying down. It is finished. If you want to move, you can.

Outcomes

Primary outcome

ELISA assay kits were used to assess the morning serum cortisol (the primary outcome which is often called a stress hormone).

Secondary outcomes

- Glasgow dyspepsia severity score (GDSS): with scores ranging from 0-20, GDSS monitors symptomatic frequencies of FD, routine activities affection by FD symptoms, absence from work, frequency of medical consoling, performed dyspepsia tests, and the used drugs with or without prescription.
- Visual analogue scale (VAS): To assess the severity of abdominal symptoms, every woman was ordered to mark her perception of FD-related abdominal symptoms on a 10-cm straight-line VAS.
- The 42-Item Depression, Anxiety, Stress Scales (DASS-42): with a separate subscale for depression, anxiety, and stress, DASS-42 is a valid and reliable questionnaire used in clinical settings and research. It contains 14 questions for every subscale. The score of each question is evaluated from 0 to 3. The total score of every subscale is scored from 0 to 42. The total DASS-42 score of all subscales ranges from 0-126.
- Pittsburgh sleep quality index (PSQI): Pittsburgh sleep quality index is a valid tool used to assess sleeping quality in clinical trials. The score of each item within the PSQI was evaluated from 0 to 3. The results of the self-rating 19-item PSQI were summed to give the Global Score of PSQI (GS-PSQI). Higher GS-PSQI was an indicator of poorer sleep.
- Estradiol: Estradiol, estrone, and estriol are three endogenous estrogens that are produced naturally in the normal body of any living woman. In this study, we measured serum estradiol using estradiol-ELISA kits.

Blinding

The authors and participating women did not explain any data about the quality/type of FD interventions to the laboratory technicians who assessed estradiol and cortisol levels or outcomes evaluators who assessed DASS-42, GS-PSQI, GDSS, and VAS.

Sample Size

By defining cortisol as the primary result of this FD study, the process of by-G*Power sample size estimation indicated d equal to 0.72 (d is the estimated effect size calculated at 80%). The extracted minimum number from this estimation was 50 PRFD women (25 women in each group). Considering a 20% drop during the study course, the number was augmented with an additional ten PRFD women.

Statistical Analysis

The statistics of this study were managed on SPSS 18 (SPSS Inc., Chicago, IL, USA) which showed a Kolmogorov-Smirnov normal distribution of all PRFD women's data before conducting further tests. For judging data significance ($p < 0.05$) within and between dyspeptic women groups, paired and unpaired tests were respectively practiced.

Results

Age and body mass index – as pretreatment demographic data of the participating women – showed a non-statistically significant difference between FD groups (Table I). Also, between-group non-significant differences were recorded regarding the pretreatment outcomes (VAS, cortisol, DASS-42, estradiol, GDSS, and GS-PSQI) (Table II).

In both FD groups, the results of within-group parity showed significant improvements in all outcomes (except estradiol of the control group). These improvements were relatively high in the study group (group of aerobic exercise plus BRT). Except for cortisol and estradiol, after-treatment parity between the dyspeptic groups showed significantly improved differences in VAS, DASS-42, GS-PSQI, and GDSS in favor of the study group (Table II).

Table I. Demographic data of functional dyspepsia groups.

		Study group (Aerobic exercise plus BRT interventions)	Control group (BRT intervention)	*p* Unpaired *t*-test value
Age (year) (Mean ± SD)		44.26±2.62	46.06±2.97	0.051
BMI (kg/m^2) (Mean ± SD)		27.65±1.49	27.61±1.37	0.914
Education-al level (N)	Low	21	19	
	high	9	11	

SD = Standard deviation. BRT = Benson's relaxation therapy. BMI = Body mass index. N = Number. Because p is > 0.05, it is a non-significant value.

Discussion

Exercise, Cortisol, and SAD Trilogy

Perimenopause-induced stress, depression, and anxiety evoke physiological malfunctions in different body systems, including the gastrointestinal tract[3]. Mindful exercises (body relaxation plus breathing exercises) send signals to the limbic system. This system inhibits the within-brain axes, including the hypothalamic-pituitary-adrenal axis. This axis is responsible for the production of stress hormones. Consequently, the production

Table II. Outcomes analysis before and after exercise-plus-BRT or BRT alone.

Outcome measure	Study group (Exercise plus BRT)	Control group (BRT)	*p* (among FD groups)
VAS for severity of abdominal symptoms	**Mean ± SD**	**Mean ± SD**	
Pre	7.22±2.60	6.04±2.64	0.086
Post	2.14±1.62	3.36±2.17	0.016*
p (within FD groups)	< 0.001*	< 0.001*	
GDSS	**Mean ± SD**	**Mean ± SD**	
Pre	14.43±5.06	11.93±4.98	0.058
Post	5.33±3.31	7.86±3.78	0.007*
p (within FD groups)	< 0.001*	< 0.001*	
Total score of DASS/42 (mg/dL)	**Mean ± SD**	**Mean ± SD**	
Pre	42.20±22.13	38.60±18.48	0.496
Post	18.33±15.32	26.73±17.02	0.049*
p (within FD groups)	< 0.001*	< 0.001*	
PSQIgs	**Mean ± SD**	**Mean ± SD**	
Pre	9.70±4.79	9.56±5.48	0.916
Post	4.93±3.67	7.35±5.32	0.044*
p (within FD groups)	< 0.001*	< 0.001*	
Cortisol (μg/dl)	**Mean ± SD**	**Mean ± SD**	
Pre	15.76±8.32	14.80±8.53	0.660
Post	12.70±7.55	13.63±7.97	0.644
value (within FD groups)	< 0.001*	< 0.001*	
Estradiol (pg/ml)	**Mean ± SD**	**Mean ± SD**	
Pre	54.80±22.03	55.26±23.78	0.938
Post	55.84±21.37	55.10±23.70	0.899
p-value (within FD groups)	0.036*	0.169	

GDSS = Glasgow dyspepsia severity score. PSQIgs = Global score of Pittsburgh sleep quality index. SD = Standard deviation. FD = Functional dyspepsia = VAS = Visual analogue scale. *: Means a significant *p*-value ($p < 0.05$). BRT = Benson's relaxation therapy. DASS = Depression, Anxiety, Stress Scales.

of stress hormones - including cortisol - decreases[11]. Thus, the decrease in cortisol production may lower the perception of perimenopause-associated stress in our studied women.

The increase in aerobic-exercise-induced endorphin secretion can positively alter the presentation of disease-associated symptoms, including mood disturbances, stress, and low quality-of-life (QoL) aspects[12]. Also, exercise can improve mood disturbances and episodes of depression and anxiety which are highly reported in functional gastrointestinal disorders[7] due to increased secretion of dopamine and serotonin hormones[12].

Consistent with us, in obsessive-compulsive disorder, patients can significantly improve their cortisol, mood, and depression after regular adherence to moderate amplitude aerobic exercises[13]. Opposing us, a non-significant cortisol decrease was reported in perimenopausal women who participated in a 4-week aerobic exercise due to the small number of women (N=11)[14].

Exercise and FD

The mechanism of exercise-induced improvement in dyspeptic symptoms, abdominal discomfort, and visceral pain in FD was not fully explained in the literature. Improved antral contraction, opiate and endorphin secretion, intestinal motility, the action of beneficial intestinal bacteria (bacteria flora), immune activities in the small intestine[15], and rate of gastric emptying (the rate of emptying solid and/or liquid nutrients from the stomach)[16] may explain the exercise-induced improvements in FD-associated symptoms.

Supporting our FD results, previous internet-based[17] and email-based surveys[7] reported that a sedentary lifestyle and lack of exercise are usually associated with the exacerbation of FD symptoms. Also, the results of a recent Indian study revealed that adding aerobic exercise - applied in moderate intensity for 6 weeks - to proton pump inhibitors significantly magnified the improvements in GDSS, functional dyspepsia VAS, and DASS-42 in FD sufferers[18].

Benson's Relaxation Therapy and FD

Relaxation techniques are widely recommended complementary treatments for FGD-associated symptoms. Relaxation is designed to modulate some physiological processes in the human body. One of these processes is FD-associated autonomic arousal which may aggravate the symptoms of FD. Yoga practices (breathing exercises and relaxation techniques) not only improve depression and mood disturbances but also improve autonomic regulation and vagal activity in chronic disorders[19]. Elimination of anxiety- or stress-induced suppression of vagal activity via breathing exercises[4] and relaxation techniques[8] not only improves patients' coping with symptoms of chronic diseases[4,8] but also improves bowel dysfunction[19], gastric/visceral hypersensitivity, visceral pain[8] which may be reported in some FGD.

The role of anxiety in the inhibition of gastric accommodation after a meal administration test was documented experimentally. Respiratory control via breathing exercises can reverse this inhibition by developing a state of peacefulness and relaxation. Physiological self-control over previously uncontrolled symptoms or future unpredicted symptoms is an earned gain from the progressive muscle relaxation technique. Background music emitted by the recorder during the application of the relaxation exercise, BRT, may be the cause of less-reported anxiety and stress[4] in FD women.

As a support to our results, but this time in irritable bowel syndrome sufferers, diaphragmatic breathing exercise and relaxation therapy approved their significant roles in improving anxiety, QoL, VAS of pain, mood disturbances, and stress[20]. Supporting the course of our findings, adding four-week breathing exercises to vagal biofeedback training can improve FD-related QoL, anxiety, and drinking capacity[4].

Sleeping Quality

Aerobic-exercise-induced stimulation of multiple pathways that produce harmony between the body's different systems (thermoregulatory, immune, endocrine, and vascular systems), metabolism, mood, and circadian rhythm is the main suggested mechanism[21] that may explain the reported improvement of FD-associated low sleeping quality in this study.

Disturbance of autonomic functions is highly documented in chronic FGD. This disturbance is closely associated with sleep difficulties[17]. BRT-induced improvement in the autonomic functions - mainly the parasympathetic autonomic functions - may enhance the episodes of sleep difficulties. Stimulation of the parasympathetic system decreases the release of stress hormones, enhances the feeling of subjective wellbeing, aids the ignorance of bad thoughts, lowers anxiety and pain levels, and enhances self-control and self-esteem, hence sleeping difficulties may be controlled in patients with chronic diseases[22].

Supporting us, in an internet-based survey, high stress, low exercise levels, and sleeping difficulties exacerbate the FGD-reported symptoms[17]. The reported improvement of women's GS-PSQI in our FD study was supported previously by a study that reported a significant improvement of GS-PSQI in women involved in a 12-week pedometer-based walking[23]. The results of recent research approved our findings because it found that an 8-week diaphragmatic breathing and progressive muscle relaxation significantly improved DASS and GS-PSQI in perimenopausal women[24]. On the opposite side, another study reported no improvement in sleeping quality - measured by PSQI - after a 16-week walking program may be due to the inclusion of premenopausal and postmenopausal obese women[25].

Estradiol and FD

Massive perimenopause-associated physiological changes are highly reported. Low levels of women's sex hormones – including estrogen and its endogenous subcomponents such as estradiol, estrone, and estriol – are one of the perimenopause-associated hormonal changes. Due to the presence of estrogen receptors in different body parts including the gastrointestinal tract, the low levels of estradiol – the most active endogenous subcomponent of estrogen – negatively affect its regulating gastrointestinal functions such as modulation of visceral pain and dysmotility of the upper and lower gastrointestinal tract[26].

A previous study showed a strong relationship between the regularity of normal bowel functions and the normal estrogen levels in women. Perimenopause- and postmenopause-associated massive estrogen fluctuations may be related to the higher percentage (38%) of irritable bowel syndrome in perimenopausal and postmenopausal women compared to the lower percentage (14%) of the same disease in premenopausal women[27].

Our study is the first randomized-controlled complementary treatment trial that approved a significant role of aerobic exercise in improving estradiol levels in PRFD. Exercise-induced elevation of estradiol levels may be the cause of the reported improvement of dyspeptic symptoms, especially with the documented role of estradiol in modulating visceral pain and dysmotility of the upper and lower gastrointestinal tract[26].

The mechanism of the exercise-induced increase in estradiol levels is not fully explained. Exercise-induced repeated stimulation of the central nervous system is documented to improve the secretion of sex hormones, including estrogen[28]. The presence of estrogen receptors on pain neuronal afferents regulates the expression of messenger-RNA coding receptors. This regulation stimulates pain-relieving pathways within the central nervous system in patients with chronic disorders, including FGD[29]. Improvement of estrogen-induced modulation of nociception may be the suggested cause of improved FD-associated abdominal pain and discomfort after the 8-week aerobic exercise in this study.

The selection of moderate amplitude exercise in our study may be another suggested explanation for the exercised-induced increase in estradiol levels. As reported previously, vigorous or high-intensity physical activity inhibits the production of female sex hormones (progesterone and estrogen), and sometimes it can induce the occurrence of amenorrhea[30], so the choice of moderate amplitude aerobic activity in this study may be avoided the authors to obtain these results. Exercise-induced hydroxylation and methylation of estrogen via controlling the enzyme-regulating P450-cytochrome action is another suggested mechanism of exercise-induced increase of estradiol levels[31]. Consistent with us, a study revealed that estrogen levels are significantly increased after 60-day aquatic aerobics in obese or non-obese women[31]. Opposite to our results, maybe due to the inclusion of postmenopausal women, estradiol did not show a significant increase after the adherence of women to a long-term physical activity program[32]. From our point of view, the failure of BRT to improve estradiol is very difficult to be explained. Regular and repetitive physical exercise may be the strongest influencer to induce a change in estrogen levels compared to effortless interventions such as BRT.

Limitations

The inclusion of premenopausal and postmenopausal women was the main limitation of this study. The authors recommend researching this limitation in future FD studies.

Conclusions

SAD trilogy, cortisol, sleeping quality, estradiol, and dyspeptic symptoms could be significantly improved after adding adjunctive lifestyle therapies such as aerobic exercise to BRT in perimenopause-associated FD.

Conflict of Interest
The authors declare that they have no conflict of interest.

Ethical Statements
The study was concived following the ethics of the Declaration of Helsinki. FD interventions in this study were accredited by the Local Ethical Committee of Cairo University (Physical Therapy Faculty Approval No. P.T.REC/012/003657).

Informed Consent
All FD women in this study signed the consent form.

Acknowledgments
The authors thank all functional dyspepsia women who participated in this study. The registration identifier of this functional-dyspepsia study is NCT05378009.

Funding
This FD research did not receive national/international funds.

Authors' Contributions
All four authors contributed equally to the development of this FD research concept. In addition, all authors contributed equally to raw data collection, analysis/interpretation, as well as scientific writing of the presented FD paper. All authors acknowledged responsibility for the whole content of this FD manuscript and approved its submission, as indicated in European Review for Medical and Pharmacological Sciences..

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