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Influence of a Multimodal Psychosomatic Therapy Concept with Exercise Focus on Depressive Symptoms as well as Hemodynamic Parameters and Heart Rate Variability in Depressive Patients

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Abstract

Introduction: The prevalence of depression increased over the past decades. In addition to primary symptoms, depressed patients often have an increased cardiovascular risk profile. To address these relations, the present study examined the effects of a multimodal psychosomatic therapeutic concept with a major focus of regular exercise on hemodynamics, cardiac autonomic function and self-assessment in depressed patients.

Methods: In 23 depressives in a psychosomatic clinic (aged 47.9 ± 12.3 years) peripheral and central blood pressure (BP) and pulse wave velocity (PWV) were measured using Mobil-O Graph (PWA monitor, IEM Stollberg, GERMANY). Heart rate variability (HRV) was recorded with heart rate monitor (Polar RS800 CX®, Polar GmbH, GERMANY) The severity of depressive symptoms was determined with established test procedures. The patients then took part in a multimodal, non-drug therapeutic program, which focused primarily on daily structured exercise therapy.
All examinations were carried out at the beginning and after a 3-month therapy.

Results: After intervention there were reductions in peripheral systolic (127.0 ±10.0 vs. 121.3±10.2 mmHg; p<0.01) and diastolic BP (85.7±8.3 vs. 80.7±8.1 mmHg; p<0.01), central systolic (117.6±9.8 vs. 111.7±7.6 mmHg; p<0.01) and diastolic BP (87.0 ± 8,5 vs. 81.9±8.0 mmHg: P <0.01), in the PWV (7.2±1.2 m/s vs. 7.0±1.2 m/s; p<0.01) and improvements in the HRV-parameters. All depressive scores showed highly significant improvements.

Conclusion: With a multimodal psychosomatic therapeutic concept, focused mainly on physical activity, both the psychological components and the cardiovascular risk profile in depressed patients can be favorably influenced.

Keywords: Exercise and depression, Multimodal Concept in Depression, Depression and Sports, Depression and Cardiovascular Risk, Depression and Blood Pressure

Introduction

Mental disorders are associated with reduced quality of life but also with reduced life expectancy [1]. As the Federal Statistical Office's cost of living bill shows, mental illnesses in Germany now cost almost as much as cardiovascular diseases, which continue to come first. Depression is one of the most common mental disorders with a broad clinical spectrum. Its prevalence increased rapidly in recent decades, especially in the western industrialized nations. According to WHO, around 350 million people worldwide are now suffering from depression. In addition to a genetic disposition a disbalance of neurotransmitters plays a role in its formation and expression.

Treatment strategy relies heavily on pharmacotherapy, which is often associated with significant side effects Regular physical activity (PA) has positive effects on mental health with enhancement in self-esteem and can prevent or alleviate depressive symptoms [2,3]. Compared with non-depressed persons, subjects with depression spent an average less time in overall PA and had higher volumes of sedentary behavior [4].

The "Trondheim Study" showed that children who move a lot are less likely to develop depression in later years.5 Some 200.000 participants in the Wasa-Run (an ultra-long-distance ski race) were followed up over more than 20 years for the development of depression and compared with inactive normal people. The fitter the runners were during the Run, the less often they suffered from depression in the following two decades [6].

In almost 300,000 people without previously known mental illnesses, it was shown for all age groups that regular PA significantly reduced the risk of developing depression [7]. An analysis on more than 25.000 adults reported a reduced prevalence of depressive symptoms due to regular muscle-strengthening exercise and a study of almost 1.5 million adults has shown that all PA activity routines were associated with lower depression prevalence [8]. In the S3 Guideline/National Care Guideline Unipolar Depression it is recommended to do regular PA as

an important integral part of a multimodal depression therapy [9]. However, depressives are usually physically inactive, and it is unclear whether a lack of activity precedes depression or, conversely, depression depresses physical activity.

In addition, depression is a risk factor for cardiovascular diseases as well, which significantly increases mortality in patients with coronary heart disease [10]. Meng reported that depression increased the risk of hypertension incidence [11]. Due to Bhat et al. systolic BP is associated with depression and anxiety scores, which his independent of lifestyle confounders [12]. According to a German group, the risk of cardiovascular disease as a result of depression is the same as in overweight or lipid metabolism disorders [13].

Apart from peripheral BP, central BP has a higher predictive value regarding future cardiovascular morbidity and mortality [14]. Pulse wave velocity (PWV), a measure of aortic stiffness, antedates and contributes to the development of arterial hypertension and cardiovascular risk and is a solid index of arterial hypertension related organ damage [15]. Measurement of PWV has been included in international guidelines for hypertension management [16]. Regular aerobic exercise attenuates age-related reductions in central arterial compliance and is effective in reducing arterial stiffness in normotensive subjects [17].

Heart rate variability (HRV) provides a sensitive non-invasive measurement of cardiac autonomic control [18]. Analysis of HRV is finding increasing use in the quantification of cardiac autonomic regulation and allows the identification of patients at increased risk for cardiac events [19]. Impaired cardiovascular autonomic function is manifested in reduced vagal and increased sympathetic activity. HRV defined by a range of time and frequency domains is an established measure of cardiac autonomic dysfunction. PA has been associated positively with cardiac vagal activity, as measured by HRV [20]. Recent studies confirm a reduced HRV in psychosomatic diseases, e.g., depression, fatigue syndrome and anxiety disorders.

To address these relations, the present prospective interventional study examined the effects of a multimodal psychosomatic therapeutic concept with a major focus on regular exercise on hemodynamic parameters, cardiac autonomic function, and self-assessment in depressed patients.

Methods

Ethical approval

All procedures performed in the present involving human participants were in accordance with the ethical standards of the institutional research committee (Medical Center Berlin (MCB), Berlin, GERMANY, Berlin, EA20170208-4, Schröter) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Study population

In a psychosomatic day clinic, 30 patients with depressive symptoms (aged 48.2 ± 11.0 years, BMI 25.0 ± 3.4 kg / m², 60% women) were examined both before and after a 3-month outpatient therapy stay. All data were collected on the same weekday morning before and after the intervention. All patients have given their informed consent for participation in the research study and have completed a health history screening.
Prior to the testing, patients were asked to refrain from caffeine and alcohol consumption for at least 12 hours and from PA for 24 hours. Five subjects were on BP-medication since more than three months. All others denied taking regular medication. All patients completed.

Hemodynamic measurements

To determine the hemodynamic status, peripheral and central BP and the PWV were measured non-invasively using Mobil-O-Graph® (PWA-Monitor, IEM, Stollberg GERMANY) as a clinically validated device for hemodynamic measurements with a novel transfer function-like algorithm, which uses waveform recordings based on brachial cuffs. To ensure standardized conditions, the recommendations of the Clinical Applications of Arterial Stiffness, Task Force III were followed [21]. The subjects rested for 10 minutes in a separate conditioned room (23 ± 1 ° C) before performing two resting measurements on each person on the right upper arm using tailored arm cuffs. The arm was placed on a custom armrest so that the heart and pressure cuff were at the same level. The same examiner performed all hemodynamic measurements with the same device before and after the observation. The average of two measurements was used for analysis. The measurement times were registered, and the repeat measurements were made at the same time of day after the observation period.

Cardiac autonomic function

The HRV was recorded by means of a heart rate (HR) monitor (Polar RS800 CX®, Polar Elektro GmbH) in a supine and standing position (5 min.), as well as during a 3-minute pulse breathing in a supine position (6 breaths per minute).

For the digital evaluation, the software "Kubios HRV" was used, which calculates all common time and frequency domain parameters. Focus was on HR, mean RR intervals, and RMSSD (square root of the mean squared difference of successive RR intervals). The Mean RR intervals are primarily of importance for descriptive purposes, since they are dependent on the HR (low mean RR means high HR, high mean RR means low HR) [22]. RMSSD was used as a reliable parameter for determining parasympathetic activity. Since the HRV was consistently measured for 15 minutes, the sections were cut out using the Kubios HRV software to make them comparable. These consisted of five minutes supine, five minutes standing, two minutes explaining and settling in and three minutes breathing.

Evaluating the sensation of depression

The subjectively perceived severity of depression was determined by the BDI-II (Beck Depression Inventory II) in the first and last week of the therapy. The BDI II consists of 21 questions and contains four possible answers in ascending severity of the symptoms (0 = not available, 1 = slight severity, 2 = moderate severity, 3 = severe severity). The questions related to the condition of the last two weeks. The 21 groups of statements consist of the symptoms: "dysphoria, pessimism, failure, loss of pleasure, feelings of guilt, punishment, self-denial, self-criticism, suicidal thoughts, crying restlessness, loss of interest, determination, worthlessness, energy loss, sleep disorders, irritability, loss of appetite, difficulty concentrating, fatigue and loss of libido".23 The processing time was five to ten minutes. The evaluation was carried out by adding all answered symptom groups. The total value is between 0 and 63 points. A value greater than 18 can be considered clinically significant.

Another questionnaire (Symptom Checklist 90 R (SCL-90-R)) was used to determine the average psychological stress (Global Severity Index (GSI)), the number of symptoms with a stress (Positive Symptom Total (PST)) and the severity of impairment with a burden (Positive Symptom Distress Index (PSDI)). All assessments were taken at baseline (pre) and after 12 weeks (post) for all outcomes.

Statistics

Statistically analyses were performed using SPSS version 24 (IBM, Chicago, IL). The normal distribution of the data was checked using a histogram and the Kolmogorov-Smirnoff test. In order to determine the pre-post course with regard to the variables collected (biometric data, hemodynamic parameters, heart rate variability, BDI), the t-test was used for dependent samples. The level of statistical significance was set at $p<0.05$. All variables are reported as mean ± one standard deviation.

Multimodal psychosomatic therapeutic concept

The multimodal therapeutic concept included a variety of therapy offerings such as individual and group psychotherapy, dance, art and music therapy, yoga, Qi Gong, acupuncture, respiratory therapy, nutritional counseling, imagination training, stress regulation training, mediation and autogenic training. Exercise and body therapy were carried out daily.

The physical intervention consisted of a varied exercise program with strengthening exercises, circuit training and strength exercises with own body weight and light weights. In addition, endurance exercises were carried out, such as Nordic walking, running and ball games. Another focus was coordination training with different exercise series to strengthen the body feeling. The repertoire also included movement programs for sensory perception and exercises that strengthen trust, self-confidence and self-awareness. The range of exercise was not performance-oriented, but joyful, health-promoting and age-appropriate. Since the level of performance of the patients was very heterogeneous, the respective intervention was individually adapted to guarantee a high level of active movement time.

The daily movement intervention included ninety minutes each. It began with a playful general and specific warming-up followed by aerobic and/or strength training exercises. This was followed by exercises to promote physical body feeling as well as new forms of movement to experience group-dynamic processes. After the extensive activities, the cooling took place with relaxation and cool down exercises.

Data availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

Hemodynamics before and after intervention

After intervention, there were significant reductions in peripheral systolic (126.0±11.4 vs. 120.9±11.9 mmHg, $p<0.01$) and diastolic BP (85.8±11.2 vs 81.0±11.1 mmHg, $p<0.01$). Central BP also showed systolic (116.5±11.0 vs. 111.0±9.3 mmHg, $p<0.01$) and diastolic (87.2±11.4 vs. 82.2±11.2 mmHg, $p<0.01$) reductions. HR decreased from 77.3±10.8 to 71.1±10.8 min-1, $p<0.01$) In addition, there was a significant reduction in PWV) (Figure 1)

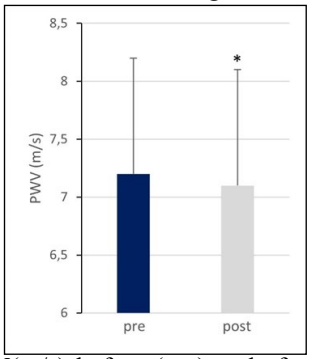

Figure 1: PWV(m/s) before (pre) and after post) intervention Values are means ± SD; *=$p<0.5$

Cardiac autonomic function before and after intervention

The HRV registration showed a significant increase in mean RR intervals in supine position (876.1 ± 121.1 vs. 930.8 ± 120.2ms, $p<0.01$), standing (725.9 ± 116.2 vs. 760.6 ± 113.0ms, $p<0.05$), and during clock breathing (901.7 ± 125.8 vs. 995.2 ± 178.7ms, $p<0.01$). HR was reduced (70.0 ± 9.5 vs. 65.9 ± 8.3 min-1, $p<0.01$) and so it was during breath (68.6 ± 9.6 vs. 62.4 ± 9.5min-1, $p<0.01$). At the same time, a significant increase in RMSSD could be shown during supine position (Figure 2).

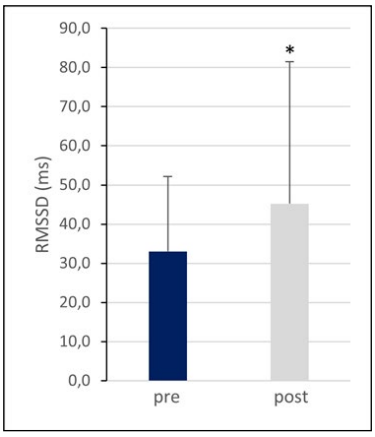

Figure 2: RMSSD (ms) before (pre) and after post) intervention,Values are means ± SD; *=$p<0.5$

Sensation of depression before and after intervention

The BDI-II score decreased significantly (Figure 3, 4). Significant improvements were also seen in the SCL-90-R, where GSI (1.4±0.8 vs. 0.5±0.4), PST (57.7±27.1 vs. 34.8±33.2) and PSDI (2.1±0.7 vs. 1.2±0.3) decreased significantly (Table I).

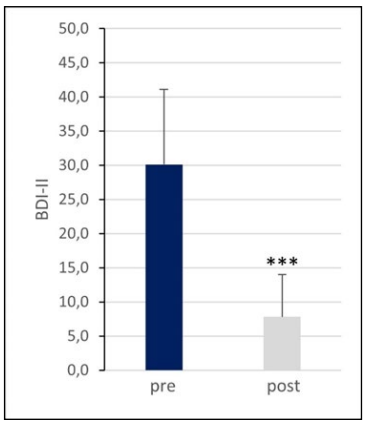

Figure 3: BDI-II before (pre) and after post) intervention, Values are means ± SD; ***= $p<0.001$

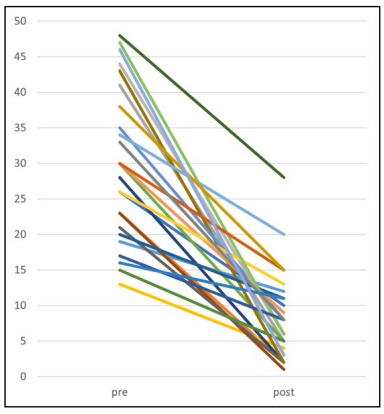

Figure 4: BDI-II in all patients before (pre) and after post) intervention

Table I: Sensation of depression before (pre) and after (post) intervention

Test	pre	post	P value
GSI	1.4 ± 0.8	0.5 ± 0.4	< 0.01
PST	57.7 ± 27.1	34.8 ± 33.2	< 0.01
PSDI	2.1 ± 0.7	1.2 ± 0.3	< 0.01

Values are means ± SD

Anthropometric data

There were no significant changes in body weight (p=0.210) and waist circumference over the experimental period (p=0.271). Thus, there were no changes in BMI (p=0.129) and WtHR (p= 0.305).

Discussion

To the best of our knowledge, this is the first clinical trial studying the effects of a multimodal psychosomatic therapeutic concept including exercise training on cardiovascular parameters and depressive symptoms in physically inactive adults with diagnosed depression. These findings suggest that multimodal intervention focusing mainly on PA induces potent stimuli leading to improvements in cardiovascular parameters. The present data show that regular Pa brings benefits to the physical but to mental health as well. The strengths of this study include the use of state-of-the-art measures of cardiovascular functions with supervised exercise training by qualified exercise instructors.

Hemodynamics

All hemodynamic parameters were favorably influenced by the intervention. In addition to the reduction of peripheral and central BP, the PWV was significantly lowered as well. The reduction in PWV of 0.1m/sec translates to a reduction in "aortic age" of about one year [24]. In contrast, in another study in healthy subjects, no reduction in PWV was found after 12 weeks of training (3 times a week), which might be due to a lower weekly training load [25].

PWV is not a surrogate parameter but widely recognized as an independent biomarker of vascular function and a direct marker of arterial stiffness. PWV is more important for future cardiovascular risk than peripheral BP, and is, as demonstrated by younger volunteers, already increased, if ever an elevated peripheral BP is registered [26]. Large population-based studies on the relationship between depressive symptoms and depression and PWV, the gold standard measurement of large artery stiffness, are controversial. Peng found a slight increase in PWV across elevated degrees of depressive symptoms [27]. The Rotterdam Study reported both depressive symptoms and major depression to be associated with aortic stiffness in contrast to the Health, Aging, and Body Composition Study, which failed to establish a link between depressive symptoms and PWV [28,29].

Cardiac autonomic function

The reduction in HR and associated mean RR-Intervals as well as the RMSSD as parasympathetic marker demonstrate a post-intervention improved HRV and thus also in the economics of cardiac function.

HRV measures the beat-to-beat fluctuation in HR over time and reflects sinoatrial responsiveness to fluctuations in parasympathetic input. SDNN reflects total variability, whereas RMSSD estimates high-frequency variations in HR and primarily reflects parasympathetic activity. One can argue that HRV analyses from short-term recordings as performed in the present study are less reproducible compared with long-term ambulatory recordings [30]. However, all patients showed the same positive development with regard to all HRV parameters.

Literature suggests that modifiable factors such as regular PA are associated with beneficial autonomic and morpho-functional cardiovascular adjustments [31]. But studies showing a relationship between PA and HRV are limited by using self-reported PA [32].

Most studies on HRV based on HRV on longer time-measurement indicators, such as 10 minutes or 24 hours. HRV data in the present study were obtained from short recordings only and may not encapsulate effects of the circadian rhythm and daily activity compared with longer or 24-hour recordings. Furthermore, due to an earlier study HRV analyses from short-term recordings are less reproducible compared with long-term ambulatory recordings [32]. In contrast, a study in elderly patients saw an association between functional declines in elderly associated with low HRV even after a 10-second ECG recording [33]. And due to newer literature however, HRV measures derived from short recordings have been found reliable and have been used in numerous analyses as they pose a significant advantage over long recordings with respect to feasibility [34].

In conclusion, the present data provide evidence that the multimodal intervention is associated with higher HRV.

Antidepressant effects

A very pronounced effect was found regarding the subjectively perceived depressive symptoms, measured by the BDI-II, which decreased significantly during the observation period. Initially, the patients showed a mean BDI according to common criteria as a major depressive symptomatology. After intervention, the BDI was lower by more than 70%, which speaks for clinically normal and minimal symptoms. This is of importance because due to a recent analysis there is still a controversial discussion as to whether a drug-based antidepressant therapy is effective at all [35].

In a recently published paper, patients with major depressive disorder improved all three categories of affective, cognitive, and somatic symptoms of depression and showed an improvement in the psychological health after one hour of aerobic exercise 3 times a week for 3 months [36]. Schuch et al. have recently conducted a comprehensive review of PA and depression [37]. There is convincing evidence that exercise should be included in a wider toolkit to help people with depression. A review of 1.487 people found that between 40 and 50% of people with depression respond to PA, which is considered small on a scale of small, medium or large. This corresponds to the talk therapy and the intake of medication. While the drop-out rate for PA of 18%, it is 19% for talk therapy and 26 to 28% for medication, it is also important to note that these treatments are not exclusive and can be used together for a greater benefit.

The preventive potential of PA to reduce future depression was determined in a 11-year study in 33.908 adults. The extent of sports and symptoms of depression and anxiety were registered [38]. Individuals claiming to be out of sport at all showed a 44% increased likelihood of developing depression in the observation period compared to those who performed 1-2 hours of PA per week.

Chekroud showed that subjects spent fewer days in poor mental health when exercising 3 to 5 training sessions/week for 45

minutes than inactive persons [39]. But more exercise was not always better. In an earlier study, it could be shown that jogging for 30 minutes a week was just as effective as an antidepressant [40]. A cross-sectional study found that replacing 30 minutes a day of sedentary behavior with light PA was negatively associated with self-rated depression [41]. PA was associated with a decrease of 3.75 depressive days (minus 34.5%), in patients with a history of depression. However, only last month's telephone interviews were retrospectively queried, so that one can assume that perhaps not all respondents could remember correctly. At the same time, it could be shown that antidepressants plus PA had a better effect than antidepressants alone.

The longer-term benefits of a regular intervention also seem to be guaranteed for depressives, as Hallgreen could show [42]. Twelve months after the end of a 3-months, 3x weekly PA program, a follow-up survey was conducted, which demonstrate that the symptoms of depression were significantly reduced and that these effects persisted for a further 9 months. Recently it has been shown in patients with coronary artery disease that a progressive aerobic interval training (AIT) significantly improved depression scores more than moderate-intensity continuous exercise (MICE) [43].

Like an Irish-Swedish group of authors have shown, regular strength training after 12 weeks, three times a week, could reduce depressive symptoms and consequently also the need for medical therapy [44]. There was an increase in well-being and mental health through everyday activities. With neuroimaging (MRT) they showed a specific association of activity with energy in two independent samples mediated by the subgenual part of the anterior cingulate cortex (sgACC), which is a key emotion regulatory site that increases resistance to mental illness.

Of course, the question arises as to the mechanism by which regular PA has an antidepressant effect. A substantial part in depressives engaging in PA may bolster self-efficacy and self-esteem which has been suggested to prevent and positively influence depression [45]. However, there are some more hypotheses. Thus, depression is associated with chronic inflammation and regular PA can favorably influence inflammatory processes. Most of depressive patients have reduced levels of phenylacetic acid resulting from the breakdown of phenylethylamine, an amphetamine-like substance. An essential antidepressant effect of sports obviously results from an increase of phenylethylamine and thus also an increase of the antidepressant phenylacetic acid levels. Already through 30 minutes of running with 70% of the max. HR reserve, the mean 24-hour value of phenylacetic acid in urine was increased by 77% [46]. Depression is also associated with lower levels of BDNF (brain-derived neurotrophic factor), which helps the brain to grow and reshape itself. Increases in BDNF, a mediator of neuroprotective and neuroplastic processes, have been shown in response to acute moderate and regular PA in mild to moderate depressed individuals [47,48]. Recent research suggests that the neuromodulatory endocannabinoid (eCB) system may play a role in pathways that translate exercise into positive mood responses [49]. For instance, individuals suffering from depression may have lower levels of endocannabinoids. Research of Crombie et al. shows that acute exercise increases endocannabinoids and improves mood in subjects with PTSD (Post-traumatic stress disorder) [50]. Influences on cortisol regulation and likely other pathways and mechanisms must be discussed but were not focused on the present study.

Study limitations

The lack of a control group, however, which was rejected for ethical reasons, limits the interpretation of the findings. Due to the multimodal character of the intervention, we are unable to determine the role of exercise alone in the interpretation of the observed improvements in cardiovascular parameters.

Conclusion

Regular PA has a positive effect on the cardiovascular system but, in particular, endurance loads are considered to be the strongest impetus for psychological processing operations up to the complete emptying of the subconscious problem memory. Even if, due to the multimodal therapeutic approach, the sole effect of PA is not clearly evident in the present study, it can be assumed that regular PA was certainly an essential enhancer of the complex effect structure of the overall therapy.

Despite some limitations but based on the evidence of beneficial effects of the present intervention study, a multimodal psychosomatic therapeutic concept with exercise as a major part can improve hemodynamic parameters, cardiac autonomic function and depressive symptoms in people with depression.

It raises the question if those effects be sustained and what is the threshold of exercise needed to deliver those benefits. It should be recommended that individualized training recommendations be formulated for patients with a known mental health risk, but especially for previously known depression, to supplement the guideline-based therapies. The findings are important and add to the body of evidence supporting beneficial effects of regular exercise on depressive symptoms and depressive disease.

Conflict of interest: The authors have no conflict of interest.

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