Effects of Exercise on Physical and Mental Health, and Cognitive and Brain Functions in Schizophrenia: Clinical and Experimental Evidence

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Abstract: Exercise promotes several health benefits, such as cardiovascular, musculoskeletal and cardiorespiratory improvements. It is believed that the practice of exercise in individuals with psychiatric disorders, e.g. schizophrenia, can cause significant changes. Schizophrenic patients have problematic lifestyle habits compared with general population; this may cause a high mortality rate, mainly caused by cardiovascular and metabolic diseases. Thus, the aim of this study is to investigate changes in physical and mental health, cognitive and brain functioning due to the practice of exercise in patients with schizophrenia. Although still little is known about the benefits of exercise on mental health, cognitive and brain functioning of schizophrenic patients, exercise training has been shown to be a beneficial intervention in the control and reduction of disease severity. Type of training, form of execution, duration and intensity need to be better studied as the effects on physical and mental health, cognition and brain activity depend exclusively of interconnected factors, such as the combination of exercise and medication. However, one should understand that exercise is not only an effective nondrug alternative, but also acts as a supporting linking up interventions to promote improvements in process performance optimization. In general, the positive effects on mental health, cognition and brain activity as a result of an exercise program are quite evident. Few studies have been published correlating effects of exercise in patients with schizophrenia, but there is increasing evidence that positive and negative symptoms can be improved. Therefore, it is important that further studies be undertaken to expand the knowledge of physical exercise on mental health in people with schizophrenia, as well as its dose-response and the most effective type of exercise.

Keywords: Brain activity, cognitive function, exercise, mental health, schizophrenia.

INTRODUCTION

There has been a growing interest in investigating the relationship between physical activity and mental health [1-4]. These studies supported the importance of doseresponse on the relationship between exercise and mental health [5, 6]. In general, the effects and improvement of cognitive performance and psychological well-being as a result of a physical exercise program has been observed in several studies [4, 7-10]. Few studies have been published correlating effects of physical exercise in schizophrenia, but there is increasing evidence that suggests that exercise can improve negative symptoms in these patients [11-14]. Schizophrenia patients tend to be more sedentary compared to general population [15-17], but increase the level of physical activity of these patients seem essential, and also an easy method for preventing, minimizing the many health problems associated with sedentary lifestyle and reduced mortality [18]. Research has showed that more physically active people tend to be less affected by mental disorders than sedentary people [19-26]. These authors also claim that physical exercise

promotes numerous benefits in mental health. These benefits are caused by biological factors that connect changes that occur during and after completing an exercise [27]. Therefore, there seems to be an eminent relationship between the amount of exercise performed and the prevalence of severe mental disorders such as schizophrenia [28-30]. There are several types of training that can be used for promoting mental health, but the prescription forms and its effects in psychiatric patients, more specifically in schizophrenia, needs to be further studied [31]. For example, in Acyl et al. [32] study the effectiveness of exercise was demonstrated, indicating that it may be a very efficient method of improving positive and negative symptoms in schizophrenia. Some studies show that effects on symptoms, cognition and brain activity as a result of exercise practice, depending exclusively on its duration, intensity, and how to conduct the exercise individually [33]. It seems that there is a discreet decrease in the severity of the disorder and improvement in cognition of schizophrenia patients who perform physical exercise [4]. These studies show a decrease in the severity of symptoms and a significant improvement in cognition in schizophrenic patients who perform aerobic exercise [4, 34]. In the study conducted by Pajonk et al. [34], it was observed that aerobic exercise promoted benefits like increasing hippocampus volume, and therefore improving memory in schizophrenia patients. Viola et al. [4] also observed higher processing speed, working memory and motor gesture. Cotman et al. [13] reported the same improvement observed in Viola et al. [4] and claim that these findings result from cortical modifications. Pereira et al. [35] also reported that regular aerobic exercise increased blood flow in hippocampus. Whiteman et al. [36] observed that genes related to neurotrophin are directly connected to hippocampus and its benefits are involved in synaptic activity and plasticity. Another study from Tomporowski et al. [37] shows that exercises performed with controlled intensities between 40 and 80% of VO2 max and estimated time of approximately 90 minutes, significantly changes mood and welfare social feeling.

Thus, this review paper aims to provide information on the current research and main findings related to the potential therapeutic effects of exercise on mental and physical health, and cognitive and brain functions of schizophrenic patients, i.e., the experimental advances of exercise that can become viable as clinical applications in the coming years.

MATERIALS AND METHODS

Eligibility Criteria

The structure of the methods in this study will follow the proposals of PRISMA (Preferred Reporting Items is Systematic reviews and Meta-Analyses) [38]. Thus, we will adopt the PICOS (population, intervention, compared to control group, results and research design) recommendation to determine the eligibility [38].

a) Population – subjects diagnosed with schizophrenia, from both gender, physically active or not, aged between 18 and 59 years;

b) Intervention - patients should undergo exercise protocols, involving aerobic, strength, flexibility or type of exercise;

c) Comparators - a control group of schizophrenia patients or healthy subjects performing psychotherapy, occupational therapy, recreational activities, cognitive rehabilitation, relaxation, nutritional education, waiting list;

d) Outcomes - for symptomatology and cognitive function variables, subjective scales/inventories for positive and negative symptoms and neuropsychological tests will be used; for brain activity neuroimaging data will be used; for physical variables physiological tests will be used;

e) Study design - randomized controlled trials and nonrandomized control trials that have evaluated acute and chronic effects of exercise protocols on mental and physical health in schizophrenia patients.

Sources

The studies were retrieved from a MEDLINE/PubMed, ISI Web of Knowledge and SciELO. Experts on the subject of the present study were also contacted to send articles. To find additional articles, all tables were examined for evidence of previous systematic reviews and found references to randomized controlled trials and controlled as necessary. In addition, we analyzed the references of all selected articles. Searches were closed on the March 10th 2015.

Search

Search was conducted in all databases using the following terms: aerobic exercise OR VO_2max OR strength exercise AND schizophrenia with cognitive functions OR neuroimaging OR symptoms.

Selection of Studies

The selection of studies was performed by two independent researchers that in case of disagreement sought a consensus on the selection. The evaluation consisted of a selection of studies by analysis of the title, followed by analysis of the summary and then the analysis of the full text. With the disagreement between the two researchers, a third one was requested to finish the process. Relevant articles were obtained and assessed for inclusion and exclusion criteria described below.

Data Collection

The following data were extracted from the articles: sample size, participant characteristics, exercise type, setting exercises (intensity, exercise duration and total duration), scales/inventories used, and main significant results. In addition, other information about the methods and outcomes were collected. These procedures were performed by two independent investigators, who reached a consensus in case of disagreement.

Exclusion Criteria

We excluded articles that had no effective intervention of aerobic, strength, flexibility or other type of physical exercise, articles using other type of intervention associated with physical exercise that could create a risk of bias in the study, samples composed of elderly, children, and

adolescents, individuals with mental illness or neurological disorders, studies that have not detailed statistical procedure applied, or not presented the results of specific cognitive and physiological measures and symptoms.

Risk of Bias in Studies

For assessing the risk of bias of each article included were analyzed the following factors: the presence of eligibility criteria for participants in the sample, the results of all moments from the analysis of more than 85% of the sample, presence of the control group, presentation of results and intergroup variability of results.

RESULTS

Based on the defined criteria, a total of 1011 articles were found in the search conducted in the literature. After duplicates removal (n=41), 970 articles remained to be analyzed by title and abstracts. After the screening, 955 articles were excluded, which were not related to the proposed theme. Therefore, 15 articles were analyzed by eligibility criteria, according to "PRISMA", and by exclusion criteria (Fig. 1), and all of them were selected which were properly met the criteria for this review (see Table 1).

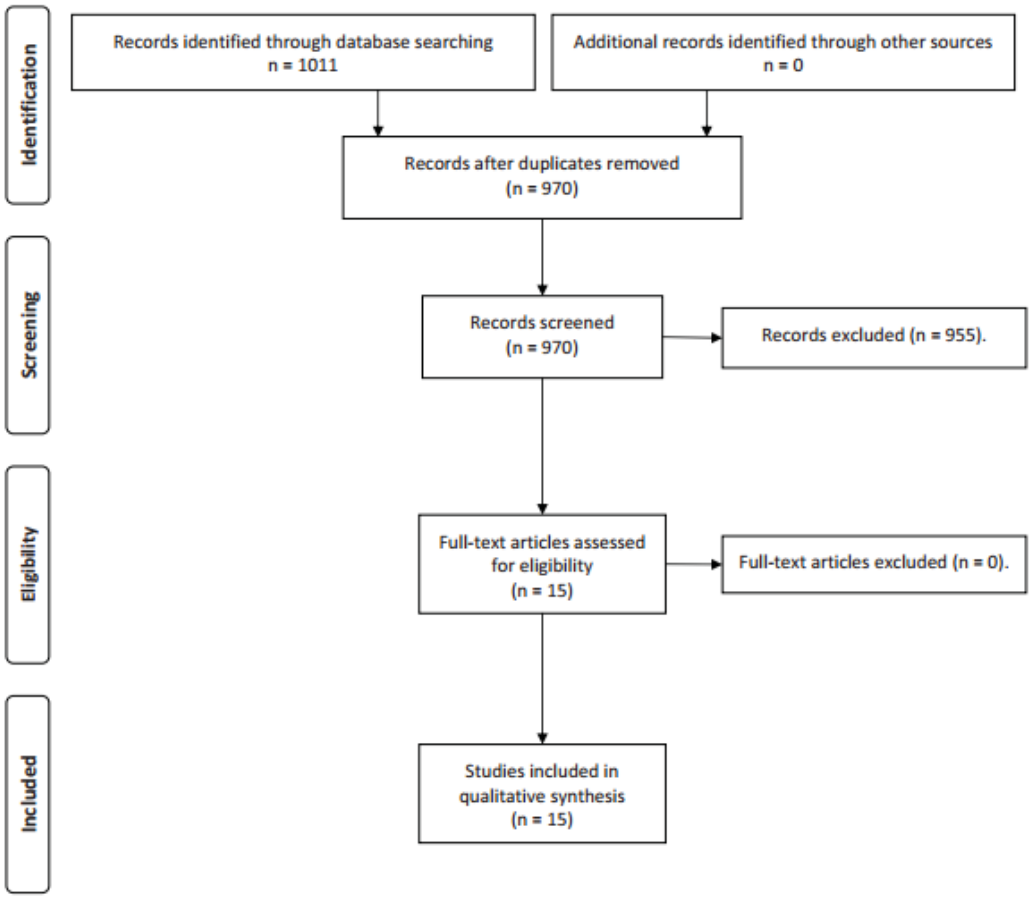

Fig. (1). Flow chart for the articles included in the systematic review.

Table 1. Papers that investigated the chronic effect of the exercise in patients with schizophrenia.

Author Year	Nº Patient	Mean age	Training	Medication	Nº of Weeks	Session duration or nº of exercises	Days/Weeks	Intensity controlled	Supervised	Diagnostic Criteria	Instruments	Level of disease	Randomized	Outcomes
Viola *et al.* [4]	51	39.6	Group 1: Aerobic training Group 2: mental relaxation Group 3: no activity	Yes	4 weeks	75 minutes	3 days per week	60-70% HR_{max}	Trained exercise Instructor	DSM –IV		Moderate	Yes	Improvement in processing speed, subjective quality of life and reduction of psychopathological symptoms.
Scheewe *et al.* [42]	118	29	Strength training + therapy	Yes	24 weeks	60 minutes	2 days per week	HR and VO_2	Researchers	DSM –IV		Mild to Moderate	Yes	Improvement in $VO2_{peak}$ and positive symptoms/difference in $VO2_{peak}$ between schizophrenic patients and healthy controls
Scheewe *et al.* [48]	63	30	Strength training	Yes	24 weeks	60 minutes	2 days per week	45/65/75% HR_{max}	Researchers	DSM –IV		Mild to Moderate	Yes	Reduction in negative symptoms, increase in hippocampal volume and VO_{2peak}
Falkai *et al.* [47]	8	EG (32.9) CG (37.4)	Aerobic training (cycling)+ Table football (therapy)	Yes	12 weeks	30 minutes	3 days per week	HR corresponding to 1,5-2 mmol/L of lactate	Physiologist	RAVL/ DSM -IV		Mild to Moderate	Yes	Increase in gray matter and density in the right frontal lobe and occipital cortex in healthy controls.
Poulin *et al.* [45]	120	EG (36.1) CG (35.3)	Aerobic exercise + strength exercises + flexibility and balance exercises + nutritional guidance	Yes	18 weeks	60 minutes	2 days per week	Low intensity perceived by HR	Physical Therapist	CGIS / DSM -IV		Mild to Moderate	Yes	Increase in HDL cholesterol and decreasing in LDL cholesterol, fat percentage, BMI, triglycerides and fasting glucose.
Beebe *et al.* [46]	10	52	Aerobic exercise (Walking)	Yes	16 weeks	30 minutes	3 days per week	Target HR	Researchers	DSM –IV		Mild to Moderate	Yes	Increase in flexibility and aerobic fitness, reduction in BMI and decreased symptoms
Dodd *et al.* [43]	8	45.9	Aerobic exercise (Walking)	Yes	24 weeks	30 minutes	2 days per week	HR_{max} 65/75%	Physiologist	DSM –IV		Mild to Moderate	Yes	Reduction in body weight and BMI
Lee *et al.* [44]	232	36.9	Nutritional guidance	Yes	12 weeks	60 a 90 minutes	12 days per week	Subjective scales and HR	Researchers	DSM –IV		Mild to Moderate	Yes	Reduction in body weight and BMI

Author Year	N° Patient	Mean age	Training	Medication	N° of Weeks	Session duration or n° of exercises	Days/Weeks	Intensity controlled	Supervised	Diagnostic Criteria	Instruments	Level of disease	Randomized	Outcomes
Heggelund *et al*. [41]	25	EG (30.5) CG (38.9)	High Intensity Interval Aerobic Training + Cognitive training (computerized games)	Yes	8 weeks	+- 30 minutes	3 days per week	85-95% of VO_{2peak}	Physiologist	ICD-10		Mild to Moderate	Yes	Increase in $VO2_{peak}$, and positive changes in body composition
Heggelund *et al*. [40]	16	EG (37,5) CG (38,9) .	Strength training and Cognitive training (computerized games)	Yes	8 weeks	+-30 minutes	3 days per week	70% HR_{peak}	Physiologist	ICD-10		Mild to Moderate	Yes	Increase in muscle strength in 1 RM.
Pajonk *et al*. [34]	16	EG and CG (35)	Aerobic exercise (cycling)	Yes	12 weeks	30 minutes	3 days per week	1,5 a 2 mmol/L of lactate	Researchers	ICD-10/ DSM -IV		Mild to Moderate	Yes	Increased hippocampal volume by 12%, increase in muscle power by 11% and increased VO_2max.
Vancampfort *et al*. [49]	40	EG (31.8) CG (32.74)	Group 1: aerobic exercise (cycling), Group 2: yoga, Group 3: no activity	Yes	1 session	50 minutes	1 day	Intensity according to HR	Physical Therapist	CGIS		Moderate	Yes	Increase of subjective well-being and decreased anxiety symptoms.
Acil *et al*. [32]	30	EG (32.06) CG (32.66)	Low intensity aerobic exercise	Yes	10 weeks	40 minutes	3 days per week	$HR_{max/res}$	Trained Exercise Instructor	SANS/BSI		Moderate	Yes	Decrease in positive and negative symptoms and executive functions
Beebe *et al*. [39]	22	48.1	Pedometer with no changes in ADL	Yes	1 week	24 hours	7 days per week	Distance traveled	No	DSM -IV		Mild to Moderate	Yes	Schizophrenic patients walk less than the "healthy" population
Scheewe *et al*. [50]	118	EG (29.2) CG (30.1)	Physical exercise and occupational therapy	Yes	24 weeks	60 minutes	2 days per week	HR/BP/VO_2	Researchers	DSM -IV		Mild to Moderate	Yes	Brain changes associated with improved cardiorespiratory fitness

ADL: Activities of Daily Living; BP: Blood Pressure; RM: Repetition Maximum, RAVL: Rey Auditory Verbal Learning; CGI-S: Clinical Global Impression - Severity; DSM - IV: Diagnostic and Statistical Manual of Mental Disorders; ICD - 10: International Classification of Diseases; SANS: Scale for the Assessment of Negative Symptoms; BSI: Brief Symptoms Inventory; CG: control group; EG: Experimental Group; HDL: High-Density Lipoprotein Cholesterol; LDL: Low-Density Lipoprotein Cholesterol; BMI: Body Mass Index; HR: Heart Rate; HR_{peak}: Heart Rate Peak; HR_{res}: Heart Rate Reserve; HR_{max}: Heart Rate Maximum; VO_{2max}: Maximal Oxygen Uptake; VO_{2res}: Oxygen Uptake Reserve; VO_{2peak}: Oxygen Uptake Peak.

Assessment of risk of bias revealed that all articles selected met just one criteria. The most articles have not results from 85% of sample (Table 2). Assessment of risk of bias revealed that 8 out of 15 articles selected met just one to two criteria. Seven articles have not results for any criteria (Table 2).

Table 2. Risk of bias of the papers that investigated the chronic effect of exercise in patients with schizophrenia.

Studies	EC	CG	RD	RS	IR	RDM
Viola *et al.* [4]	Yes	Yes	Yes	Yes	Yes	Yes
Scheewe *et al.* [42]	Yes	Yes	Yes	No	Yes	Yes
Scheewe *et al.* [48]	Yes	Yes	Yes	No	No	Yes
Falkai *et al.* [47]	Yes	Yes	Yes	Yes	Yes	Yes
Poulin *et al.* [45]	Yes	Yes	Yes	Yes	Yes	Yes
Beebe *et al.* [46]	Yes	Yes	Yes	Yes	Yes	Yes
Dodd *et al.* [43]	Yes	Yes	Yes	Yes	No	Yes
Lee *et al.* [44]	Yes	Yes	Yes	Yes	No	Yes
Heggelund *et al.* [40]	Yes	Yes	Yes	No	Yes	Yes
Pajonk *et al.* [34]	Yes	Yes	Yes	No	Yes	Yes
Vancampfort *et al.* [49]	Yes	Yes	Yes	Yes	Yes	Yes
Acil *et al.* [32]	Yes	Yes	Yes	Yes	Yes	Yes
Beebe *et al.* [39]	Yes	Yes	Yes	Yes	Yes	Yes
Scheewe *et al.* [50]	Yes	Yes	Yes	No	No	Yes
Heggelund *et al.* [41]	Yes	Yes	Yes	No	Yes	Yes

EC, Eligibility Criteria; CG, Control Group; RD, Random Distribution; RS, Results from the Minimum of 85% of the Sample; IR, Intergroup Results; RDM, Result Deviation of the Measure.

DISCUSSION

For better clarity and understanding, the discussion was structured in the following subdivisions: effects of exercise on physical health and on mental health, cognitive functions and brain activity in schizophrenia and neurobiological mechanisms.

Effects of Exercise on Physical Health in Schizophrenia

Several studies have examined the physiological effects of exercise in schizophrenia. The consensus is that exercise is a very significant form of intervention for the promotion of physical health. Patients with schizophrenia tend to be less physically active than the general population. In this sense, Beebe et al. [39] conducted a pilot study on the effects of a program of 16 weeks of walking on cardiorespiratory fitness, body mass index and illness severity in patients with schizophrenia. Patients in the experimental group had a significant reduction in body fat levels compared to the control group. Furthermore, patients in the experimental group improved their cardiorespiratory fitness, body mass index and reduced some symptoms compared to control patients.

Another important point is that to date there is still no agreement about volume and intensity of training for people with mental disorders. Thus, Jorn Heggelund et al. [40] found that patients with schizophrenia may participate of a secure program of maximum strength training, resulting in an improvement in physical health. In this study of 16 patients, 9 were assigned to the experimental group and 7 for the control group. The control group underwent computer games. The experimental group performed 8 weeks of specific training of muscle strength. The training consisted of five minutes of warm up on a work load corresponding to 70% of peak heart rate (ie, HRpeak, the highest heart rate measured during the last minute of maximal oxygen

consumption). After that it was carried out a test of maximal strength (1RM) in the leg press. The training volume was four sets of four repetitions with a load equivalent to 85-90% of 1RM. During all sessions heart rate (HR) was checked and patients were encouraged to improve performance throughout time. The study found that training improved maximal strength performed in schizophrenic patients to the same level that was observed in other studies with patients with other disorders and healthy controls. Furthermore, it was found that differences in the level of force were significantly different between the experimental group and the control group, which in turn showed no difference in strength. In another study, Jorn Heggelund et al. [41] showed that patients with schizophrenia were able to attend to a high intensity training program and consequently improved their VO2 peak. Schizophrenic patients usually have low VO2 peak values, thus increasing mortality rates due to their body composition and other impairments associated with disease. In this study, 25 refractory patients users antipsychotics for at least 6 weeks before testing were included. Sixteen patients were allocated to the experimental group and nine to the control group. Despite the severity of the illness, patients underwent the whole program. The control group trained in a computer game for an identical period. The experimental group underwent a high intensity aerobic interval training on a treadmill in which performed four minutes of activity at 85-95% of VO2 peak monitored, scheduled with 3 minutes of active rest. Patients underwent training sessions three times a week for eight weeks. It was necessary the execution of 80% of the training during the period of 8 weeks to be included in the study analyses. The ability to improve VO2 peak is highly related to the ability to adhere physical training in daily life, which is considered a challenge for patients suffering from schizophrenia. After 8 weeks of training, no significant differences were shown in positive symptoms. However, the experimental group improved their VO2 peak by 12%, while the control group showed no differences. In addition, changes in body composition of the practitioners were observed, as well as more mechanical efficiency on gait. The improvement in VO2 peak is in line with the effects of eight weeks of training in healthy controls and in patients with cardiovascular diseases. Thus, it can be concluded that, in line with what was shown for healthy individuals, patients with schizophrenia also benefit from the same type of training. This study shows that a physical exercise program of 8 weeks can reduce the risk of cardiovascular and metabolic diseases associated with low VO2 peak.

Thomas et al. [42] analyzed the effects of physical exercise in the cardiorespiratory fitness of patients with schizophrenia. There were recruited 63 patients with schizophrenia and 55 healthy subjects. Patients with schizophrenia were on stable antipsychotic medication for at least 1 month prior to study entry. These patients were randomized to exercise (n = 31) or occupational therapy (n = 32), while the healthy control participants were recruited and randomized to exercise (n = 27) or normal life (n = 28). Thirty-nine patients (62%; Exercise, n = 20; occupational therapy, n = 19) and 53 controls (96%; Exercise, n = 26; life as usual, n = 27) met minimum requirements for compliance corresponding to 50% of the 52 sessions offered. The randomization allocation was designated for the exercise or occupational therapy in 1x1 randomly. Patients not randomized exercised occupational therapy 1 hour, twice a week for 6 months. Including creative and recreational activities. Healthy controls performed specific exercise tests on a cycle ergometer. The tests were terminated voluntarily by exhaustion. Heart rate and oxygen consumption peak were analyzed during the tests execution. The results demonstrated that schizophrenia patients had reduction in VO_2peak and peak load compared to the control group. Furthermore, comparison of individual and reference values for VO_2peak ratio shows 10% and 15% reduction in the levels of negative symptoms, particularly in male patients with schizophrenia. The difference relative to VO_2peak between practitioners and

controls (4.3 mL.kg. min) corresponds to more than 13% increased risk of mortality in patients with schizophrenia. The results show that the exercise performed once or twice a week for 6 months slightly increased the volume ratio of oxygen. In the control group, the exercise improved VO_2peak ratio by an average by 2.2 ml.kg.1.min, indicating that the intervention was effective in increasing cardiorespiratory fitness in healthy individuals. However, patients with schizophrenia have obtained significantly lower mean values than healthy controls. This may be partly due to the fact that performing high-intensity exercise is not usual for them. Knowing that there is a strong relationship between the total and peak volume of oxygen with severity of illness, exercise can be considered as an interesting method of intervention. The low levels of physical activity in people with psychiatric disorders leave them more vulnerable to disease. Body weight is directly associated with these disorders. Therefore, Dodd KJ et al. [43] conducted a study that evaluated the feasibility and effects of an exercise program for individuals with severe schizophrenia. One group was followed for 24 weeks, in small groups of aerobic exercise up to 30 minutes each session, twice a week. Compliance was assessed by attendance, and analyzing the comments of the exercises supervisor in a diary for each participant. Body weight, cardiorespiratory fitness (VO_2max), and psychiatric symptoms were measured at each time point. Eight participants (6 men, 2 women, mean age 45 years, 9 months, body mass index 27.0) participated in an average of 73% of scheduled exercise sessions, and 83% of the walking sessions without adverse effects and interruptions. All participants had positive and negative behaviors during the training sessions. There were significant reductions in weight (2.4%) and body mass index (2.2%), but no changes in other measures.

Lee SJ et al. [44] examined the effectiveness and feasibility of a program of weight control for overweight and obese patients with schizophrenia, using a large sample in various clinical contexts. Psychiatric patients using antipsychotics participated in a weight management program for 12 weeks in 33 clinical centers throughout South Korea, and the data for 232 individuals they had a body mass index (BMI) of 25 kg/m (2) or more and diagnosed with schizophrenia or schizoaffective disorder were included in the final analysis. The primary efficacy measures were changes in body weight and BMI. These patients showed significant mean reductions in BMI (0.98 +/- 1.01 kg/m (2), p<.001) and body weight (2.75kg +/- 2.64, p<.001) with moderate compliance after the 12-week intervention. Compliance with the diet was the strongest predictor of weight loss. The overall results suggest that a program of weight management can be disseminated and adopted by professionals in all settings, resulting in weight loss in the short term in schizophrenic and schizoaffective patients. Poulin et al. [45] conducted a study that consisted in the analysis of body composition and cognitive functioning in people with schizophrenia and bipolar disorder when under changes in lifestyle, including exercise and dietary reeducation. A total of 120 individuals were recruited and randomized to the experimental group (n=69) and to the control group (n=51). The average age of participants was 35 years. All had been diagnosed with schizophrenia or bipolar disorder, were sedentary or moderately active and were taking regular antipsychotics. At the beginning of the study they received flyers containing information about the importance of proper nutrition and the practice of physical activity. The program lasted 18 months. The active group participated on cardiovascular exercises on treadmills and stationary bikes sessions, in addition to performing strength, flexibility and balance training. The control group showed a significant increase in body weight (4.1%), BMI (5.5%) and fat percentage (4.2%), while the active group significantly reduced body weight (3.5%), BMI (4.4%), and body fat percentage (4.6%). The control group also had a significant increase in Low-density lipoproteins (LDL) cholesterol (14.8%) and triglyceride (12.3%), observed at the 18 month. In contrast, High-density lipoproteins (HDL) cholesterol

significantly increased (21.4%) and LDL cholesterol (13.7%), triglycerides (26,2%), total cholesterol (12.1%), and fasting glucose concentrations (12.0%) was significantly decreased compared to the active group. Physical health improved only for subjects in the active group at 18 months. In contrast, mental health showed no significant differences at the end of the tests. The present study shows that body weight and metabolic risk profile in schizophrenic patients and users of antipsychotics bipolar disorder can be managed with weight control, including physical activity. The study conducted by Lora et al. [46] has proposed an exercise program for 16 weeks. At the beginning of the study participants walked toward a target heart rate for 10 minutes, and gradually the periods were increased until reaching 30 minutes. Participants were 10 patients aged between 40 and 63 years. Most were male and 6 male participants reached the final result. All antipsychotics used, and were divided into control groups and performers. The results show that a short program of walking on a treadmill promotes statistically and clinically significant benefits for middle-aged people with schizophrenia. Participants who were in the performing group showed significant reductions in their percentages of fat (0.02%) in comparison to the other group, and in addition, we observed increased aerobic conditioning, reduction in body mass index by 0.14% and less symptoms related to psychiatric disorder. Although they look small decreases, the authors state that these are significant reductions within a short exercise program. Collaborators who helped in the preparation of the program noted increased flexibility of joints and muscles of patients. Thus it is believed that even with all the limitations and small sample of the study a physical exercise program of short duration and low intensity can be coupled in a large treatment and amelioration of symptoms and cognitive health of people with schizophrenia.

Effects of Exercise on Mental Health, Cognition and Cortical Architecture in Schizophrenia

The effects of exercise programs on physiological functions are fairly well known. Recently there has been the effort of expanding this knowledge by observing the effects of exercise on cognitive function and brain plasticity. Peter et al. [47] analyzed the effect of aerobic exercise on the cortical architecture of patients with chronic schizophrenia. A randomized controlled study was performed to determine if exercise increases the density of the gray matter of the brain and the expansion surface using magnetic resonance imaging. Male patients diagnosed with schizophrenia and regular users of antipsychotics participated in the program. They were randomized to exercise training (cycling; n=8) and to a control condition consisting table football (n=8). These were compared to a control group of healthy participants. The total program duration was 3 months. Cycling was performed at a heart rate corresponding to a blood lactate concentration of 1.5-2 mmol/L. The exercise was monitored and adjusted by measuring power (W/kg) heart rate and gas exchange (VO_2 production of carbon dioxide). The stimuli were given in a strategic manner in order to approximate the groups and their respective times and intensities. Only Healthy controls showed increased gray matter in the frontal and the right lobe and occipital cortex density. In general, aerobic exercise had no significant effect on cortical regions in patients with schizophrenia. The authors correlated the greatest effects in the healthy group due to greater stimulation received by them during their daily everyday life. However, the respective effects of exercise may be attenuated in chronic schizophrenia, which should be checked more thoroughly. Pajonk et al. [34] conducted a study aimed at analyzing the hippocampal plasticity in response to exercise. The randomization was designed by an independent statistician. Individuals with schizophrenia (mean 10 years of illness length), stable antipsychotic users and ages ranging from 20 to 51 years, were recruited and randomized in

blocks from 2 to 4 for a group exercise or a group without exercise. Sixteen were randomized, 10 to the exercise group and 6 to the control group. This strategy was adopted to increase motivation for joining the exercise and for intervention by participating as a small group for without exercise. The training was performed in a closed gym, 3 times per week over a 12 week period. Each session lasted 30 minutes. Patients were required to participate in at least 75% of the sessions to be computed. Heart rate was monitored throughout the training. The cycling program consisted of a pre-stipulated heart rate corresponding to a blood lactate concentration of 1.5 to 2 mmol/L (14-18 mg/dl) derived from the pre-test results. The comparison group of patients played table football for 30 minutes 3 times a week, in an environment with comparable levels of stimulation to that provided for aerobic exercise. The tests were run in a fixed time sequence and began at the same time of the day in each individual. Exercise is believed to improve over a number of factors neural plasticity. In this study it was observed that the group of individuals which combined and completed the physical training, hippocampal volume increased by 12%. The change on the cortical pattern was not statistically different. The total brain volume and total volume of gray matter did not change after exercise. The change in hippocampal volume over time in the schizophrenic group was compared between subjects who participated in aerobic exercise and those who participated in the control group. Extending the aerobic exercise group was 12% being greater than the difference observed in the non-exercise group. The increase of the muscle power was higher in aerobic exercise group by 11% compared to the non-exercise group was higher than 1%. Similar results were observed for change in VO_2max. The measures were higher in the exercise group compared with no exercise. Another significant difference was observed when comparing the two groups on memory functioning, for which the exercise group scored better than the non-exercise group. In a multicentric randomized clinical trial, Scheewe et al. [48] evaluated the improvement in physical and mental health of 63 patients with young adults (i.e., 30 years) with schizophrenia. All patients were stable antipsychotic users. Patients performed muscular strength exercises, six sessions per week of 3 sets of 10-15 repetitions for the following muscle groups: biceps, triceps, abdominal, quadriceps, pectoral and deltoid. The intervention lasted for a period of 6 months. The exercises were gradually increased (week 1-3: 45% HRres; 4-12 weeks: 65% HRres; 13-26 weeks: 75% HRres, to avoid drop outs). Patients randomized to the control group received occupational therapy for 1 hour twice a week for 6 months. Compared with exercise group, occupational therapy group provided a similar amount of structure and attention and, thus minimizing the influence of non-specific mechanisms of action. The results of the study show that exercise significantly increased VO_2peak in comparison with occupational therapy. In addition, there was a trend of reduction in fasting triglycerides over 6 months of exercise. While changes in BMI, waist circumference, blood pressure, HDL cholesterol, and fasting glucose were not significantly different between the two groups in the study, the results consistently favored the group of exercise. Possibly, the frequency, duration, and intensity of exercise sessions need to be substantially larger in the analysis of physical parameters. Even with a tendency to decrease negative symptoms and number of admissions there was no difference between exercise group versus occupational therapy group, even though cardiovascular fitness has increased during exercise compared with occupational therapy. The exercise may be beneficial in reducing core symptoms in schizophrenia and this exercise-induced brain plasticity can instigate the improvement of mental health in schizophrenia. Vancampfort et al. [49] in a pioneering study analyzed the effect on state anxiety, psychological stress and wellbeing, after one individual session of yoga and aerobic exercise in people with schizophrenia. The study included 40 volunteers in the final analysis, of which 22 males and 18 females with an average age of 31 years old, treated with antipsychotics. The active group consisted of one class session of yoga

with individual set time of 30 minutes and subsequently aerobic exercise set time of 20 minutes. In the control group the condition was reading in a quiet room for 20 minutes. Groups underwent a pilot test in which the main objective was to introduce the next session. The yoga session was based on the principles of technique which included breath awareness, relaxation, and accompanying postural techniques, strength, flexibility, coordination and balance. The session of aerobic exercise consisted of pedaling a static ergometric bicycle for 20 minutes at a high intensity heart rate. This rate was monitored throughout time and simultaneously displayed on a monitor during exercise. The study results point to the current knowledge of the yoga and acute bouts of aerobic exercise provide a transient elevation of subjective well-being and a transient reduction of stress and psychological state of anxiety in this clinical sample. Compared to the control group, anxiety level decreased after the session of yoga and aerobic exercise, but no differences between the two modalities. In both yoga and aerobic exercise were significantly lower than in the control group condition. Thomas et al. [50] conducted a study to examine the effects of exercise on global brain volume, hippocampal volume and cortical thickness in patients with schizophrenia compared to healthy controls. Aged between 18 and 48 years, 63 patients with schizophrenia and 55 healthy controls participated in this randomized controlled trial. Global brain volume, hippocampal volume, and cortical thickness were estimated from 3 Tesla MRI. Cardiorespiratory fitness was assessed with an ergometer cardiopulmonary exercise testing. The subjects were divided into groups: exercise therapy, occupational therapy and exercise (healthy controls) for six months 2 hours per week. The effects of exercise were analyzed in individuals if they completed at least 50% of sessions. A significant increase in ventricles of patients was observed in the exercise group when compared to the control group; however, there were no changes in global brain matter, hippocampal volume and cortical thickness between groups. The improvement in cardiorespiratory fitness was related to volume changes in the brain matter. One to two hours of exercise did not cause significant changes in brain volume in patients or controls. However, the improvement in cardiopulmonary fitness attenuated changes in brain volume in schizophrenia and increased thickness over large areas of the cortex in both schizophrenia patients and healthy controls. Acyl et al. [32], in a study of 30 patients with schizophrenia users of antipsychotics for an average of about 10 years, with mean age between 21-45 years, were divided into control group and experimental group, and performed a program of aerobic exercise for 10 weeks 3 days a week and 40 minutes per day. After 10 weeks of exercise of applying found a significant decrease in hallucinations and delusions of patients. There were also positive outcomes at the level of interpersonal somatization. Also, it was not detected decrease in cognitive analogy post-training period, which includes the amount of thoughts, deficiencies verbal fluency and productivity. This study shows a decrease in positive and negative symptoms and increase in quality of life in patients who participated of exercise program when compared to controls. Viola et al. [4] performed a complex study to analyze the effect of an exercise program compared to other techniques used for people with schizophrenia and depression. Fifty one patients with a mean age of 39 years (28 women and 23 men) were recruited. Participants had mental illnesses with an average of 10 years and had stable drug interventions in the preceding month testing. The patients were divided into 3 groups randomly. The first group of 16 participants received cognitive and physical training; the group 2 with 17 participants received cognitive training and relaxation; and the group 3 with 18 participants received only relaxation. The total intervention comprised three weekly sessions each lasting 75 minutes for 4 weeks, totaling 12 sessions, depending on the group, each session included 30 min of cognitive training and 45 min of exercise or physical relaxation agents. Both intervention groups receiving cognitive training had three sessions per week of cognitive training, lasting 30 min each. These sessions addressed multiple cognitive

domains, including motor skills, executive functioning, memory, concentration, attention, vigilance, learning and problem solving in various sensory systems. Each exercise session consisted of three phases, including a 10 minutes warm up, followed by a 25 minutes cardiovascular workout, finishing with a period of calm around 10 minutes, with a total duration of 45 min. Session is included as part of primary dynamic exercises including strength, coordination and aerobic. The relaxation period lasted 45 minutes. The exercises included breathing techniques, exercises for all sensory modalities, relaxation and awareness training. There were significant differences in the cognitive domain, more specifically, the processing speed and working memory in favor of group 1 compared to the other groups, which performed physical and cognitive training.

Neurobiological Mechanisms

Some studies demonstrate that schizophrenia patients have decreased brain derived neurotrophic factor (BDNF) in certain cortical areas and in hippocampus [51]. BDNF is an essential neuroprotector regardless the effects of exercise on neurogenesis and synaptogenesis [52]. In line with this, animal studies showed, for example, exercise increases BDNF (or BDNF mRNA expression) and insulin-like growth factor (IGF-1) levels in hippocampus and cerebral cortex [53, 54], while human studies also found that physical exercise is related to increased serum levels of BDNF and IGF-1 [54, 55]. For instance, a study in mice showed that elevated BDNF levels can sustain up to 3-4 weeks after a protocol of 3 weeks of aerobic exercise [56]. With respect to the investigation of the contribution of IGF-1 and BDNF to cognitive improvement after exercise, important antibodies have been use in mice to block receptors associated with IGF-1 and BDNF. This procedure when applied to IGF-I receptors could revert exercise-induced increase in BDNF level and improved recall effect in water maze task, suggesting that neuroprotective effects of IGF-I may be partly associated with the modulation of BDNF [57]. Moreover, it has been demonstrated that exercise could effectively reverse the negative effects of neurotoxin and neurodegenerative processes, including behavioural impairments and neuronal [58]. However, the subcutaneous administration of anti-IGF-1 antibody stopped this effect. Thus, this research highlights the central role of IGF-1 as a neuroprotective agent and shows that exercise probably improves cognition by controlling peripheral insulin resistance and inflammation and up-regulating IGF-1 and BDNF, which stimulates neurogenesis and synaptogenesis. Dropping peripheral insulin resistance and inflammation will enable insulin and glucose transport into the brain through the blood–brain barrier. Enhanced insulin transport could upregulate insulin-mediated glucose uptake and N-methyl-Daspartate (NMDA) receptor activity.

CONCLUSION

Individuals with schizophrenia have less active lifestyles than the general population [15, 17]. This is linked to several diseases, which reduces their life expectancy by approximately 20 years less than the general population [59- 61]. Although still little is known about the benefits of exercise on mental health, cognition and brain activity of schizophrenic patients, exercise training has been shown to be a very beneficial intervention in the control and reduction of disease severity. The type of training, their form of execution, duration and intensity need to be better studied as the effects on physical and mental health, cognition and brain activity depend exclusively of interconnected factors, such as the combination of exercise and medication.

However, one should understand that exercise is not only an effective non-drug alternative, but also acts as a supporting linking up interventions to promote improvements in process performance optimization. In general, the positive effects on mental health, cognition and brain activity as a result of an exercise program are quite evident [7-10]. Few studies have been published correlating effects of exercise in patients with schizophrenia, but there is increasing evidence that positive and negative symptoms can be improved. Therefore, it is important that further studies be undertaken to expand the knowledge of physical exercise on mental health in people with schizophrenia, as well as its dose-response and the most effective type of exercise.

LIST OF ABBREVIATIONS

BDNF = Brain Derived Neurotrophic Factor

BMI = Body Mass Index

HR = Heart Rate

IGF-1 = insulin-Like Growth Factor

RM = Repetition Maximum

VO_2max = Maximum Oxygen Uptake

VO_2peak = Oxygen Uptake Peak

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