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O impacto da fisioterapia no estilo de vida de pacientes com diagnóstico de esquizofrenia: alterações na postura, flexibilidade, qualidade de vida e marcadores sanguíneos

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Tese apresentada à Faculdade de Medicina da Universidade Federal do Rio Grande Do Sul como requisito parcial para obtenção do título de Doutor em Psiquiatria e Ciências do Comportamento.

Orientador: Prof. Dr. Paulo Silva Belmonte de Abreu

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“A perfeição não é alcançada quando não há mais nada a ser incluído, mas sim quando não há mais nada que se possa retirar.”

(Antonie de Saint-Exupéry)

RESUMO

A prática de uma atividade física regular traz inúmeros benefícios à saúde mental, que incluem aumento da produção de neurotransmissores, diminuição da neurotoxicidade, aumento da neuroplasticidade, aumento do suporte sanguíneo e aumento de BDNF (fator neurotrófico derivado do cérebro), além, é claro, de benefícios físicos como diminuição dos níveis de gordura, aumento da resistência vascular, aumento do trofismo e força muscular. Já um transtorno mental grave como a esquizofrenia acarreta sintomas que podem ir desde alucinações auditivas e/ou ideação delirante, retração social até perdas cognitivas importantes; os medicamentos utilizados para controle desses sintomas acabam tendo efeitos colaterais como o aumento de peso e distúrbios motores, o que leva os pacientes com esquizofrenia a terem prejuízos físicos além dos mentais. Existe uma alta incidência de doenças metabólicas, como diabetes mellitus e doenças cardiovasculares, que influencia no fato de esses indivíduos apresentarem uma sobrevida menor em até vinte anos quando comparados à população geral. Outro dado importante é o sedentarismo, que está presente na maioria dos casos, por isso a importância de estudos que avaliem e proponham a prática de atividade física orientada na esquizofrenia. Este trabalho tem como objetivo avaliar o efeito da atividade física orientada através de dois diferentes protocolos de exercício (intervenção aeróbica e intervenção funcional) com uma duração de três meses, e compará-los a controles sedentários e sem transtornos mentais, verificando assim os efeitos sobre o prejuízo físico e mental em pacientes com o diagnóstico de esquizofrenia e correlacionando a mudança com marcadores de inflamação e de lesão muscular. Foram recrutados pacientes com diagnóstico de esquizofrenia segundo o DSM-5-TR, estabilizados em acompanhamento regular em Centro de Atenção Psicossocial (CAPS) da cidade de Camaquã ou no ambulatório do Hospital de Clínicas de Porto Alegre (HCPA). O recrutamento dos controles ocorreu pelas redes sociais ou indicação dos próprios casos. Foram avaliados: postura pela fotogrametria postural (programa utilizado: SAPO), flexibilidade (banco de Wells), sedentarismo (SIMPAQ), gravidade da doença (BPRS), qualidade de vida (SF-36) e avaliação dos marcadores sanguíneos (lactato, proteína C reativa ultrassensível e creatina-quinase), antes e após a intervenção. A amostra final é composta por 38 pacientes com esquizofrenia, sendo que 24 realizaram a intervenção aeróbica e 14 a intervenção funcional (a divisão das intervenções seguiu o critério de conveniência). O grupo controle foi pareado por sexo, idade (três anos para mais ou

para menos) e nível socioeconômico (IBGE), ficando a mostra final também em 38 indivíduos (24 intervenções aeróbicas e 14 intervenções funcionais). Houve melhora significativa e positiva na maioria dos ângulos posturais, o que se repetiu na flexibilidade, no estilo de vida e na qualidade de vida. Nos marcadores sanguíneos, o lactato foi destaque, apresentando valores basais altos nos casos, que se manteve na comparação final. Houve pouca mudança na sintomatologia dos pacientes. A intervenção física funcional apresentou uma tendência significativa a ser mais benéfica tanto nos casos como nos controles em algumas variáveis posturais e no estilo de vida, e ainda esteve associada a maior capacidade de desenvolver um vínculo forte entre paciente e terapeuta. Esses achados são muito importantes, pois a literatura disponível foca em intervenções aeróbicas na população com esquizofrenia, por sua relativa praticidade na execução e benefícios sistêmicos; essa possibilidade de novas intervenções que foquem em movimentos mais amplos e complexos nos abre novos horizontes de possibilidades. A importância da atividade física orientada, seja ela qual for, e principalmente o acompanhamento em longo prazo nesta população se fazem necessários.

Palavras-chave: esquizofrenia, qualidade de vida, estilo de vida, postura, flexibilidade.

ABSTRACT

Practicing regular physical activity brings numerous benefits to mental health, which include increased production of neurotransmitters, decreased neurotoxicity, increased neuroplasticity, increased blood support and increased BDNF (brain-derived neurotrophic factor), in addition, of course, of physical benefits such as decreased fat levels, increased vascular resistance, increased trophism and muscle strength. A serious mental disorder such as schizophrenia causes symptoms that can range from auditory hallucinations and/or delusional ideation, social withdrawal to significant cognitive losses; The medications used to control these symptoms end up having side effects such as weight gain and motor disorders, which leads patients with schizophrenia to suffer physical as well as mental impairments. There is a high incidence of metabolic diseases, such as diabetes mellitus and cardiovascular problems, which influences the fact that these individuals have a shorter survival rate of up to twenty years when compared to the general population. Another important fact is a sedentary lifestyle, which is present in most cases, hence the importance of studies that evaluate and propose the practice of targeted physical activity in schizophrenia. This work aims to evaluate the effect of physical activity guided through two different exercise protocols (aerobic intervention and functional intervention) with a duration of three months, and compare them to sedentary controls without mental disorders, thus verifying the effects on physical and mental impairment in patients diagnosed with schizophrenia and correlating the change with markers of inflammation and muscle damage. Patients diagnosed with schizophrenia according to the DSM-5-TR, stabilized under regular monitoring at the Centro de Atenção Psicossocial (CAPS) in the city of Camaquã or at the outpatient clinic of the Hospital de Clínicas de Porto Alegre (HCPA) were recruited. Controls were recruited via social media or referrals from the cases themselves. The following were assessed: posture by postural photogrammetry (program used: SAPO), flexibility (Wells bank), sedentary lifestyle (SIMPAQ), disease severity (BPRS), quality of life (SF-36) and assessment of blood markers (lactate, protein ultrasensitive C reactive and creatine kinase), before and after the intervention. The final sample consists of 38 patients with schizophrenia, 24 of whom underwent the aerobic intervention and 14 the functional intervention (the division of interventions followed the convenience criterion). The control group was matched by sex, age (3 years plus or minus) and

socioeconomic level (IBGE), with the final sample also comprising 38 individuals (24 aerobic intervention and 14 functional intervention). There was a significant and positive improvement in most postural angles, which was repeated in flexibility, lifestyle and quality of life. In blood markers, lactate was highlighted, presenting high baseline values in the cases, which was maintained in the final comparison. There was little change in the patients' symptoms. Functional physical intervention showed a significant tendency to be more beneficial in both cases and controls in some postural and lifestyle variables, and was also associated with a greater ability to develop a strong bond between patient and therapist. These findings are very important, as the available literature focuses on aerobic interventions in the population with schizophrenia, due to their relative practicality in implementation and systemic benefits; The possibility of new interventions that focus on broader and more complex movements opens up new horizons of possibilities. The importance of targeted physical activity, whatever it may be, and especially long-term monitoring in this population is necessary.

Keywords: schizophrenia, quality of life, lifestyle, posture, flexibility.

LISTA DE SIGLAS

ATP – Adenosina Trifosfato

ATS – *American Thoracic Society*

AVD – Atividade de vida diária

BDNF – *Brain-derived Neurotrophic Factor*

BPRS – *Brief Psychiatric Rating Scale*

CAPES – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

CAPS – Centro de Atenção Psicossocial

CID – Classificação Internacional de Doenças

CK – Creatina-quinase

CNPq – Conselho Nacional de Desenvolvimento Científico e Tecnológico

CNS – Conselho Nacional de Saúde

CPC – Centro de Pesquisa Clínica

DCMI – Diferença de comprimento entre os membros inferiores

DSM- V – *Diagnostic and Statistical Manual of Mental Disorders – Firth Edition*

EIAS – Espinhas ilíacas ântero-superiores

FC – Frequência cardíaca

FIPE – Fundo de Incentivo à Pesquisa e Eventos

GABA – Ácido gama-amino-butírico

GAE – Grau de assimetria horizontal das escápulas em relação à T3

GAHP – Grau de alinhamento horizontal da pélvis

GAJ – Grau do ângulo do joelho

GATT – Grau de alinhamento horizontal das tuberosidades da tíbia

GAVT – Grau de alinhamento vertical do tronco

GDO – Grau de desnivelamento dos ombros

GDQ – Grau de desnivelamento do quadril com relação a horizontal

GDPAC – Grau de desalinhamento póstero-anterior da cabeça

GILA – Grau de inclinação lateral da cabeça

GILT – Grau de inclinação lateral do tronco

GVV-MID – Grau de valgismo ou varismo do membro inferior direito

GVV-MIE – Grau de valgismo ou varismo do membro inferior esquerdo

GVV-PD – Grau de valgismo ou varismo do pé direito

GVV-PE – Grau de valgismo ou varismo do pé esquerdo

HCPA – Hospital de Clínicas de Porto Alegre

IBGE – Instituto Brasileiro de Geografia e Estatística

IA – Intervenção aeróbica

IF – Intervenção funcional

IL-6 – Interleucina 6

IMC – Índice de massa corporal

MID – Membro inferior direito

MIE – Membro inferior esquerdo

MsIs – Membros inferiores

MsSs – Membros superiores

OMS – Organização Mundial da Saúde

PCR – Proteína C Reativa

PCR-us – Proteína C Reativa Ultrassensível

ReBec – Registro Brasileiro de Ensaios Clínicos

SAPO – Software de avaliação postural

SIMPAQ – *Simple Physical Activity Questionnaire*

SF-36 – *36-item Short-Form Health Survey*

SNC – Sistema Nervoso Central

SUS – Sistema Único de Saúde

SUMÁRIO

APRESENTAÇÃO

Este trabalho consiste na tese de doutorado intitulada *O impacto da fisioterapia no estilo de vida de pacientes com diagnóstico de esquizofrenia: alterações na postura, flexibilidade, qualidade de vida e marcadores sanguíneos*, apresentada em 2023 ao Programa de Pós-Graduação em Psiquiatria da Universidade Federal do Rio Grande do Sul. O material é dividido nas seguintes partes:

1. Introdução
2. Revisão da literatura
3. Justificativa
4. Objetivos
5. Materiais e métodos
6. Resultados

   Artigo 1: "Effect of assisted physical exercise over inflammatory markers and lactate in schizophrenia – a controlled trial"

   Artigo 2: "A controlled open clinical trial of positive effect of physical intervention on quality of life in schizophrenia"

   Artigo 3: "Physical therapy interventions in schizophrenia compared to normal sedentary adults: different effects of aerobic and functional programs over posture and flexibility- a controlled trial"

   Artigo 4: "Case report: the effects of photobiomodulation (modified intravascular laser irradiation) on quality life, clinical symptoms, reduction of inflammatory markers and oxidative stress in schizophrenia"
7. Considerações finais e conclusões

   Referências

   Anexos

1. INTRODUÇÃO

A esquizofrenia é classificada como um transtorno mental grave que tem como sintomas transtorno do pensamento ou ideias de cunho delirante e/ou alucinações auditivas, distúrbios emocionais, perda de interação social e agressividade, com acentuado comprometimento emocional (BATINIC, 2019; BOURQUE; MALLA, 2011; McGRATH et al., 2008). Os pacientes podem apresentar alguns desses sintomas ou todos, mas em momentos diferentes (McGRATH et al., 2008). Um dos grandes problemas pelos quais seus portadores passam é o estigma social que está associado às doenças mentais. Quadros mais graves e crônicos levam a uma dependência de terceiros que na maioria das vezes são familiares de primeiro grau, o que gera um quadro de incapacidade que é repercutido negativamente na sociedade (CHONG et al., 2016; CLOUTIER et al., 2016).

O tratamento envolve uma gama de medicamentos (antipsicóticos de primeira e/ou segunda geração) que estão associados a alguns efeitos adversos como obesidade, síndrome metabólica e sintomas extrapiramidais. E mesmo assim há uma ação limitada sobre os sintomas (ALVAREZ-HERRERA et al., 2020; BARBOSA et al., 2018). A fisiopatogenia da esquizofrenia ainda é cheia de mistérios; acredita-se tratar de uma doença pró-inflamatória (BENROS et al., 2011; FEIGENSON et al., 2014; MÜLLER, 2018) e com alterações bioenergéticas, que aumentam alguns marcadores como a proteína C-reativa (PCr) (CHUN-HUNG et al., 2019), interleucinas e lactato (ELMORSY et al., 2015; ROWLAND et al., 2016). Essa combinação de efeitos adversos, inflamação, disfunção energética e inatividade física (muito comum nesses pacientes) leva a um quadro de risco de desenvolver doenças sistêmicas como a diabetes mellitus e doenças cardiovasculares (VANCAMPFORT et al., 2011a; VANCAMPFORT et al., 2015). Por outro lado, a atividade física orientada tem desempenhado um importante papel no tratamento de transtornos mentais como a depressão, a ansiedade e até mesmo a esquizofrenia.[1] Com efeitos como o aumento da produção de fatores neurotróficos, aumento do metabolismo neuronal, diminuição da excitotoxidade neural,

[1] Abdul Rashid et al. (2019); Akbaş et al. (2021); Amiaz et al. (2016); Battaglia et al. (2013); Browne et al. (2021); Cramer et al. (2013); Dauwan et al. (2015); Dodd et al. (2011); Firth et al. (2015); Firth et al. (2016b); Girdler et al., (2018); Maurus et al. (2019); Ospina et al. (2019); Scheewe et al. (2013); Schmitt et al. (2018); Tréhout et al. (2021); Vancampfort et al. (2012b); Vancampfort et al., (2014).

estimulação da neuroplasticidade, diminuição do estresse oxidativo e neovascularização, o exercício físico orientado tem se mostrado um importante aliado no tratamento e no controle de doenças mentais como a esquizofrenia, levando a uma melhora do bem-estar geral do indivíduo (ASHDOWN-FRANKS G et al., 2018; OSPINA et al., 2019).

A maioria dos estudos sobre atividade física na esquizofrenia utilizou protocolos aeróbicos, que geraram importantes efeitos sobre a qualidade de vida (melhora da capacidade funcional, interação social e tolerância à dor), diminuição de peso e de biomarcadores (DODD et al., 2011; FIRTH et al., 2016b; FIRTH et al., 2016b; MAURUS et al., 2019; OSPINA et al., 2019; SCHMITT et al., 2018). Outras variáveis, como o estilo de vida (sedentarismo), postura e flexibilidade, bem como a comparação com outros tipos de exercícios, não foram encontradas e por isso nosso estudo se fez necessário.

2. REVISÃO DE LITERATURA

2.1 Esquizofrenia

A definição de um transtorno mental como “grave” traz consigo um enorme estigma, e o indivíduo com esquizofrenia (SCZ), além de lidar com o peso desse diagnóstico, acaba tendo consequências que geram alterações cerebrais e corporais, o que leva alguns autores a classificarem a esquizofrenia como uma doença sistêmica (BENROS et al., 2011; CHONG et al., 2016). Estima-se que cerca de 1% da população mundial apresenta essa patologia, sendo que esses pacientes têm uma sobrevida menor em até vinte anos quando comparados à população geral (BOURQUE et al., 2011; MCGRATH et al., 2008; MORENO-KÜSTNER et al., 2018). Para se ter uma ideia dessa gravidade, em um recente estudo de coorte realizado em Nova York durante a pandemia de covid-19, foi avaliado o risco de morte e sua correlação com doenças mentais; a esquizofrenia ficou atrás apenas da variável idade nesse quesito, ou seja, uma doença mental foi uma comorbidade mais grave e letal do que doenças físicas conhecidas como diabetes mellitus e/ou doenças cardiovasculares (NEMANI et al., 2021).

Para explicar melhor essas consequências físicas na esquizofrenia, temos que entender os efeitos deletérios do uso prolongado de medicamentos. Pois os mesmos tendem a levar a um ganho de peso e até a alterações metabólicas, favorecendo o surgimento de comorbidades como a diabetes mellitus e doenças cardiovasculares, que são doenças comumente encontradas nessa população (ALVAREZ-HERRERA et al., 2020; BARBOSA et al., 2018; BLANCHARD et al., 2006; BOJESEN et al., 2020).

Outro ponto importante são as alterações em diferentes marcadores inflamatórios e oxidativos (BORA, 2019) presentes na SCZ, o que sugere um padrão pró-inflamatório nesta doença e que pode estar diretamente associado ao seu curso e aos sintomas (FEIGENSON et al., 2013; MÜLLER, 2018). Vale lembrar que o processo inflamatório é algo natural e fisiológico e ocorre nos organismos para restabelecer sua função, após uma lesão ou como resposta a uma infecção. O problema é quando temos um mecanismo inflamatório crônico que leva a um estresse oxidativo alto, deixando o meio celular tóxico; esse quadro é comum em patologias crônicas como o diabetes

mellitus, aterosclerose, encefalopatias e na obesidade (VANCAMPFORT et al., 2011a; VANCAMPFORT et al., 2015; VANCAMPFORT et al., 2016a). Na SCZ muitos estudos comprovam a alteração de marcadores inflamatórios como a proteína C-reativa e interleucinas[2] confirmando a hipótese pró inflamatória.

Mesmo com uma literatura robusta sobre esse tema, a origem dessa alteração inflamatória na esquizofrenia ainda é desconhecida. Algumas possibilidades envolvem uma disfunção bioenergética de origem mitocondrial, onde haveria um prejuízo na produção de energia que desencadearia uma cascata de eventos desde o aumento dos níveis de lactato à hipóxia tecidual.[3]

2.2 Exercício físico e o cérebro

A prática de uma atividade física regular traz inúmeros benefícios à saúde mental do indivíduo, que incluem aumento da produção de neurotransmissores, diminuição da neurotoxidade, aumento da neuroplasticidade, aumento do suporte sanguíneo e aumento de BDNF (fator neurotrófico derivado do cérebro), além, é claro, de benefícios físicos como diminuição dos níveis de gordura, aumento da resistência vascular, aumento do trofismo e da força muscular.[4] Esses efeitos a curto e a longo prazo do exercício físico têm se mostrado um novo tratamento para patologias que afetam nosso sistema nervoso central (ROBERTS et al., 2021). Novos campos de pesquisas vêm buscando avaliar qual a melhor dose ou o melhor tipo de exercício para determinadas doenças, como os transtornos mentais.[5] Como exemplo, podemos citar a depressão, onde a literatura confirma os benefícios de uma atividade física regular no manejo e no controle da doença, repercutindo em uma melhora na qualidade de vida e no bem-estar geral dos indivíduos (SCHUCH et al., 2014; SCHUCH et al., 2016; VANCAMPFORT et al., 2017).

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[2] Chun-Hung et al. (2019); Sicras-Mainar et al. (2011); Monji et al. (2009); Orsolini et al. (2018); Singh et al. (2014); Szortyka et al. (2016).

[3] Dogan et al. (2018); Elmorsy et al. (2015); Morris et al. (2015); Pruett et al. (2020); Roberts (2021); Rowland et al. (2016); Silva et al. (2019).

[4] Roberts et al. (2021); Ashdown-Franks et al. (2018); Hanson et al.; 2015; Kurebayashi et al. (2018); Maurus et al. (2019); Mikkelsen et al. (2017); Scheewe et al. (2013); Schmitt et al. (2018); Sousa et al. (2021).

[5] Ashdown-Franks et al. (2018); Firth et al. (2018b); Firth et al. (2016b); Firth et al. (2018a); Garcia et al. (2018); Kaltsatou et al. (2015); Mittal et al. (2017); Ospina et al. (2019); Scheewe et al. (2013); Schmitt et al. (2018); Vancampfort et al. (2014); Vancampfort et al. (2016c).

2.3 Exercício físico e a esquizofrenia

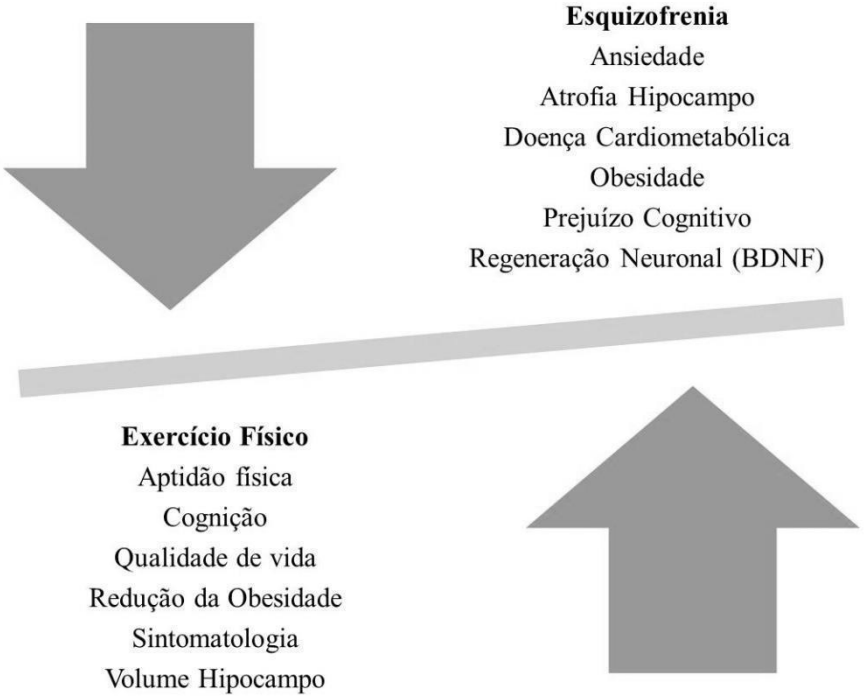
A importância da prática de uma atividade física orientada na SCZ vem sendo alvo de muitos estudos[6] que buscam os seus benefícios a curto e a longo prazo; a maioria desses estudos tem focado nas atividades aeróbicas de intensidade moderada a forte com o objetivo de estimular o processo oxidativo das células, melhorando assim o metabolismo sistêmico, aumentando a oxigenação tecidual e a resistência vascular.[7] Na figura 1 temos a representação da importância e os benefícios que o exercício traz para o paciente com SCZ representado através de uma balança. Outro fator que favorece o uso desses protocolos aeróbicos é a facilidade de replicação e a baixa complexidade de movimentos necessários, já que essa população tem alta taxa de prevalência de inatividade física (ADAMS et al., 2016).

Apesar de estarem em menor número, existem alguns estudos com exercícios mais funcionais, inclusive um trabalho recente (AKBAŞ et al., 2021) propôs um protocolo de seis semanas baseado no método Pilates. Mesmo com um curto período, esse tipo de exercício já foi capaz de produzir um efeito moderado na capacidade funcional e em sintomas clínicos, mesmo com um tamanho amostral pequeno, trazendo assim novas perspectivas na escolha de outros tipos de atividades físicas para essa população.

[6] Abdul Rashid et al. (2019); Amiaz et al. (2016); Battaglia et al. (2013); Cramer et al. (2013); Dauwan et al. (2015); Dodd et al. (2011); Firth et al. (2015); Firth et al. (2016a); Firth et al. (2016b); Firth et al. (2018b); Girdler et al. (2019); Kaltsatou et al. (2015); Maurus et al. (2019); Ospina et al. (2019); Scheewe et al. (2013); Schmitt et al. (2018); Tréhout et al. (2021); Van der Stouwe et al. (2018); Vancampfort et al. (2012a); Vancampfort et al. (2012b); Vancampfort et al. (2014); Vakhrusheva et al. (2016 a,b).

[7] Amiaz et al. (2016); Ashdown-Franks et al. (2018); Dodd et al. (2011); Firth et al. (2016a); Firth et al. (2016b); Maurus et al. (2019); Ospina et al. (2019); Schmitt et al. (2018); Vakhrusheva et al. (2016a, 2016b)

Figura 1 – Evidências do prejuízo da esquizofrenia para a saúde *versus* adaptações fisiológicas e benefícios que o exercício físico gera na população com diagnóstico de esquizofrenia



Fonte: Carvalho et al. (2021).

2.4 Postura e flexibilidade

A postura e a flexibilidade estão intimamente ligadas e são fortemente afetadas pela inatividade física. Definir o que seria uma postura "correta" é um erro que não devemos reproduzir, pois cada indivíduo tem a "sua postura" definida por suas vivências diárias e por seus hábitos (CARINI et al., 2017). Estudos prévios já demonstraram uma postura comum compartilhada em indivíduos com depressão, ansiedade e esquizofrenia (CRISTIANO et al., 2016; CANALES et al., 2010; CANALES et al., 2017; FELDMAN et al., 2020), sendo algo já muito discutido e vivenciado no dia a dia clínico de quem acompanha pacientes com essas patologias (CRISTIANO et al., 2016). A postura nada mais é do que como o indivíduo se posiciona no ambiente; ela pode transmitir ponderação ou tristeza (figura 2), por

exemplo, e essa leitura corporal pode ser mais um aliado na condução de gravidade nos transtornos mentais, onde uma postura mais introspectiva como a postura hipercifótica possa representar pacientes com maior grau de distanciamento social. Já a flexibilidade interage e sofre com posturas mantidas por muito tempo e por isso acaba influenciando nas posturas adotadas, é importante ressaltar que nossos estudos são pioneiros na avaliação da flexibilidade de pacientes com esquizofrenia (CRISTIANO et al., 2016). Outro ponto de muita relevância para ser discutido é que alguns medicamentos antipsicóticos geram uma rigidez na musculatura e aumento de peso (ALVAREZ-HERRERA et al., 2020; BARBOSA et al., 2018; BLANCHARD et al., 2006; BOJESEN et al., 2020) o que acaba interferindo na flexibilidade e consequentemente na postura.

Figura 2 – Analogia da postura de hipercifose torácica, protrusão de ombros e flexão de cabeça como uma postura "deprimida", evidenciando assim como nossas emoções e estados mentais podem estar associados à nossa postura mantida no dia a dia

Fonte: Schulz (1960).

3. JUSTIFICATIVA

A esquizofrenia é uma doença mental grave e complexa que afeta milhões de pessoas em todo o mundo. Ela é caracterizada por sintomas como alucinações, delírios, pensamento desorganizado, dificuldade de concentração, isolamento social e prejuízo nas atividades diárias. Além disso, a esquizofrenia está associada a diversas comorbidades físicas, incluindo a síndrome metabólica, obesidade, diabetes tipo 2 e doenças cardiovasculares, que levam a uma redução significativa na qualidade de vida e aumento da mortalidade prematura.

A abordagem terapêutica tradicional para a esquizofrenia consiste no uso de medicações antipsicóticas, que são fundamentais para o tratamento dos sintomas psicóticos. No entanto, os medicamentos não abordam completamente os efeitos físicos adversos da doença, e a adoção de estilos de vida sedentários frequentemente associados ao diagnóstico contribui para um quadro de saúde geralmente comprometido. Nesse contexto, a importância de intervenções não farmacológicas, como o exercício físico, torna-se evidente.

Embora haja uma crescente evidência dos benefícios do exercício físico para a saúde mental em geral, existem lacunas no conhecimento quanto à eficácia de programas de exercícios específicos para pacientes com esquizofrenia. É fundamental investigar se determinadas modalidades de exercícios podem oferecer melhorias nos sintomas psiquiátricos, bem como no perfil metabólico e cardiovascular desses indivíduos, a fim de desenvolver abordagens terapêuticas mais abrangentes e efetivas.

Ao conduzir essa pesquisa, espera-se que os resultados forneçam evidências científicas robustas para embasar a prescrição de exercícios físicos como uma abordagem complementar ao tratamento farmacológico para pacientes com esquizofrenia. Além disso, a tese contribuirá para o campo da saúde mental, fornecendo informações valiosas para profissionais de saúde, médicos e terapeutas, e destacando a importância de programas personalizados de exercícios para melhorar a qualidade de vida e bem-estar geral desses indivíduos.

4. OBJETIVOS

4.1 Objetivo primário

Avaliar os efeitos de dois programas de exercícios físicos diferentes em pacientes com esquizofrenia.

4.2 Objetivos secundários

Comparar a eficácia e os impactos dessas duas intervenções, incluindo um programa de exercícios aeróbicos de intensidade moderada e outro de treinamento de funcional, em termos de:

Sintomas psiquiátricos: analisar a redução de sintomas psicóticos, depressivos e ansiosos, bem como melhorias no funcionamento cognitivo e social.

Perfil metabólico: investigar as mudanças nos níveis de lactato no sangue, creatinoquinase e marcadores inflamatórios (proteína C reativa).

Aptidão física: avaliar a postura e a flexibilidade dos pacientes após a participação nos programas de exercícios.

Adesão, qualidade de vida e motivação: avaliar a qualidade de vida e níveis de sedentarismo para compreender os fatores que influenciam a adesão dos pacientes aos programas de exercícios e identificar estratégias para aumentar a motivação e engajamento.

5. MATERIAIS E MÉTODOS

5.1 Delineamento

Ensaio clínico controlado pareado.

5.2 Local do estudo

Avaliação diagnóstica, seleção e coleta de dados clínicos e demográficos: CAPS Camaquã e ambulatório de esquizofrenia do Hospital de Clínicas de Porto Alegre (HCPA).

Avaliações e medidas laboratoriais: Serviço de patologia clínica e Centro de Pesquisas Clínicas (CPC) do HCPA.

Protocolo de exercício aeróbico: a intervenção física foi realizada por meio do convênio com a Clínica de Fisioterapia Fisioclínica de Camaquã (RS).

Protocolo de exercício funcional: a intervenção física foi realizada no Centro de Pesquisas Clínicas (CPC) do HCPA.

5.3 Critérios de inclusão para pacientes

- Diagnóstico de esquizofrenia segundo DSM-5 e CID10.
- Idade entre 18 e 65 anos.
- Estar em tratamento medicamentoso regular.
- Não estar envolvido em outro programa de atividade física.

5.4 Critérios de exclusão para pacientes

- Usar álcool ou drogas no último mês.
- Doença sistêmica ou neurológica.
- Deficiência motora.
- Presença de risco de suicídio no momento da intervenção.
- Se em idade reprodutiva, estar grávida ou não utilizar método de contracepção.

- Não aceitar participar do estudo.

5.5 Controles

Recrutamento de 38 controles pareados, por meio de anúncio em redes sociais (Facebook) ou de sugestão dos próprios casos e/ou seus responsáveis.

5.6 Critérios de inclusão para controles

- Mesmo sexo do caso.
- Idade, 3 anos para mais ou para menos do caso.
- Mesma classe social do caso (segundo a classificação do IBGE).
- Não apresentar uma doença mental grave (demência, depressão, mania, transtorno de ansiedade generalizada ou transtorno obsessivo-compulsivo).

5.7 Critérios de exclusão para controles

- Seguiram os mesmos critérios dos casos.

5.8 Coleta de sangue

O Serviço de Patologia Clínica do HCPA foi o responsável pela coleta e análise das amostras de sangue. A proteína C reativa de alta sensibilidade (hs-CRP) foi testada por imunoensaio turbidimétrico (faixa de referência: $\leq$ 3,0 mg/L = risco baixo/moderado; $\geq$ 3,0 mg/L = alto risco), lactato por enzima colorimétrica (faixa de referência: 0,5 - 2,2 mmol/L) e creatina-quinase (CK) por UV enzyme (faixa de referência: 0 – 170 U/L).

5.9 BPRS

Para a avaliação dos sintomas clínicos da esquizofrenia foi utilizado a Escala Breve de Avaliação Psiquiátrica (*Brief Psychiatric Rating Scale*, BPRS), versão

ancorada e traduzida para o português. Ela é composta por 18 domínios de sintomas: preocupação somática, ansiedade, retração emocional, desorganização conceitual, sentimentos de culpa, tensão, maneirismos e postura, grandiosidade, humor depressivo, hostilidade, desconfiança, comportamento alucinatório, retardo motor, falta de cooperação, conteúdo de pensamento incomum, embotado afeto, excitação e desorientação. Sua aplicação leva aproximadamente de 5 a 10 minutos, em que, após uma entrevista com o paciente, o avaliador devidamente treinado classifica cada item de 0 (não presente) a 6 (extremamente grave) por meio de observação e questionamento (CRIPPA et. al, 2002; WÓJCIAK; RYBAKOWSKI, 2018).

5.10 Fotogrametria postural

Existem muitas formas de avaliar a postura estática. A maioria se utiliza de fotos e programas de computação especiais que irão transformar alterações posturais em números. A essa forma de avaliar denominamos “fotogrametria postural”. O protocolo utilizado nesta pesquisa foi descrito em 2017 (CRISTIANO et al., 2016) e foi baseado em referências na área (SANTOS , 2001; LUNES; MONTE-RASO; SANTOS et al., 2008; FERREIRA et al., 2010). Essa forma de avaliação postural apresenta vantagens como o baixo custo no sistema de imagem e fotointerpretação, boa precisão e reprodutibilidade dos resultados, bem como o pouco contato físico com o paciente (FERREIRA et al., 2010).

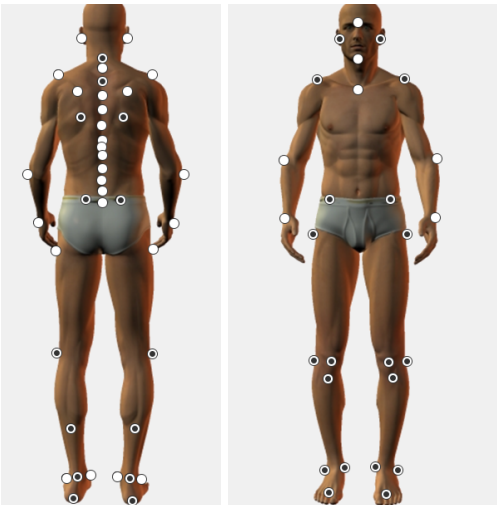
O software escolhido para a interpretação das imagens e geração das angulações posturais foi o SAPO (Software para Avaliação Postural). Ele é um programa gratuito e de fácil utilização; foi desenvolvido pela FAPESP e está disponível na internet (http://puig.pro.br/sapo/). Apesar de ter sido validado, poucos estudos o vêm utilizando, o que é uma pena, pois é uma ferramenta muito útil, que possibilita a avaliação de inúmeros ângulos, distâncias corporais e o centro de gravidade, além de possuir um banco de dados e uma anamnese própria dentro do programa (FERREIRA et al., 2010; SOUZA et al., 2011).

No presente estudo, o valor de referência utilizado foi ZERO, seguindo o protocolo de Cristiano (2016). Os ângulos foram alocados conforme a alteração que avaliavam e por graduação de gravidade, em normal (0 a 5 % acima do valor de

referência), alteração leve (> 5% a 10% acima do valor de referência), moderada (> 10% a 15% acima do valor de referência) e grave (acima de 15% do valor de referência), para fins de visualização de prevalência.

Resumidamente, dois fios de prumo eram pendurados a uma altura de 2 m e 62 cm de distância. Cada participante ficou dentro do espaço delimitado pelas duas linhas. Os pontos anatômicos foram demarcados com bolas de espuma de poliestireno expandido (3 cm de diâmetro) fixadas na pele com fita dupla face. Os pontos anatômicos utilizados para análise foram tragus, acrômio, espinha ilíaca ântero-superior, trocânter maior do fêmur, linha articular do joelho, face medial da patela, tubérculo tibial, maléolo lateral, maléolo medial, ponto médio entre as cabeças do segundo e terceiro metatarsos, processo espinhoso de C7, processo espinhoso de T3, ângulo inferior da escápula, espinhas ilíacas póstero-superiores, linha média da panturrilha, tendão do calcâneo na altura média dos maléolos e do calcâneo. Todos os pontos de referência foram bilaterais. Esses marcadores foram sempre colocados pelo mesmo investigador.

Figura 4 – Pontos anatômicos marcados no programa SAPO durante a fotogrametria postural



Fonte: Ferreira et al. (2010).

Em seguida, as fotografias foram tiradas em três planos – sujeito de frente para a parede, de frente para a câmera e em perfil direito – com uma câmera digital

point-and-shoot (Sony Cyber-shot) colocada em um tripé a uma altura de 1,25 m e 2,5 m de distância do objeto. Em seguida, as imagens capturadas foram enviadas para um computador e analisadas no SAPO.

Ao todo, 14 ângulos posturais foram medidos:

- Vista anterior: GILA = desalinhamento da cabeça (valores positivos (+): inclinação à direita; valores negativos (-): inclinação à esquerda); GDO = desnivelamento dos ombros (valores positivos (+): ombro esquerdo mais elevado; valores negativos (-): ombro direito mais elevado); GDQ = desnivelamento do quadril com relação a horizontal (valores positivos (+): EIAS esquerda mais elevada do que a direita; valores negativos (-): EIAS direita mais elevada do que a esquerda); GILT = inclinação lateral do tronco (valores positivos (+): inclinação lateral do tronco à direita; valores negativos (-): inclinação lateral do tronco à esquerda); GVV-MID = ângulo frontal do MID (valores positivos (+): joelhos varos; valores negativos (-): joelhos valgos); GVV- MIE = ângulo frontal do MIE (valores positivos (+): joelhos varos; valores negativos (-): joelhos valgos); DCMI = diferença de comprimento entre os MsIs (valores positivos (+): MID maior que o MIE; valores negativos (-): MIE maior que o MID); GATT = alinhamento horizontal das tuberosidades da tíbia (valores positivos (+): tíbia esquerda mais elevada; valores negativos (-): tíbia direita mais elevada).
- Vista posterior: GAE = assimetria horizontal da escápula em relação à T3 (valores positivos (+): significa que o ângulo inferior da escápula direita está mais afastado lateralmente da coluna do que o ângulo inferior da escápula esquerda; valores negativos (-): significa que o ângulo inferior da escápula esquerda está mais afastado lateralmente da coluna do que o ângulo inferior da escápula direita); GVV-PD = ângulo perna-retropé direito (valores positivos (+): pé em valgo; valores negativos (-): pé em varo); GVV-PE = ângulo perna-retropé esquerdo (valores positivos (+): pé em valgo; valores negativos (-): pé em varo).
- Vista lateral (direita): GDPAC = desalinhamento da cabeça com o acrômio (valores positivos (+): anteriorização da cabeça; valores negativos (-): posteriorização da cabeça); GAVT = alinhamento vertical do tronco (valores

positivos (+): aumento da cifose torácica; valores negativos (-): diminuição ou retificação da cifose torácica); GAHP = alinhamento horizontal da pélvis (valores positivos (+): diminuição ou retificação da lordose lombar – retroversão pélvica; valores negativos (-): hiperlordose lombar – anteversão pélvica); GAJ = ângulo do joelho (valores positivos (+): flexo; valores negativos (-): recurvado).

Figura 5 – Fotos utilizadas na fotogrametria postural nas três vistas: posterior, anterior e lateral direita

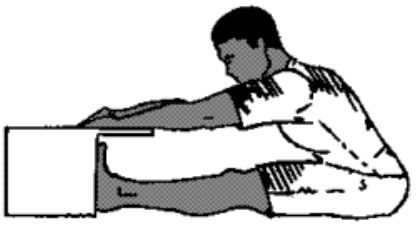
Fonte: banco de imagens da pesquisa

5.11 Flexibilidade: banco de Wells

O teste de flexibilidade de sentar e alcançar, com o banco de Wells, foi usado para medir a flexibilidade da cadeia posterior, que compreende os músculos tríceps sural, isquiotibiais, glúteos, paravertebrais e a mobilidade da articulação do quadril (coxofemoral). Para a correta execução do teste o participante senta-se no chão ou no colchonete com as pernas totalmente estendidas e as solas dos pés contra o banco; lentamente se inclina, projetando seu tronco para frente o máximo possível, com os dedos deslizando ao longo de uma escala. O total da distância alcançada após três tentativas fornece uma média, e assim uma pontuação final em centímetros. Em

seguida, esse valor final é categorizado segundo o sexo e a idade, fornecendo, assim, uma classificação em ruim, regular, normal, bom e ótimo.

Figura 6 – Execução do teste de sentar e alcançar com o banco de Wells



5.12 Atividade física: SIMPAQ

Para a avaliação do nível de atividade física dos casos e controles foi utilizado o Questionário de Atividade Física Simples – SIMPAQ (*Simple Physical Activity Questionnaire*). Ele avalia de forma abrangente a atividade nos últimos sete dias, ao longo das 24 horas. Possui cinco domínios: tempo gasto na cama; tempo sedentário; tempo caminhando; tipo e tempo gasto com exercício; tempo gasto em outras atividades. O SIMPAQ foi escolhido por ser validado para avaliar a atividade física em pessoas com doença mental e por ser de fácil aplicação, não necessitando de treinamento detalhado (ROSENBAUM et al., 2020).

5.13 Qualidade de vida: SF-36

A qualidade de vida foi avaliada utilizando a escala de qualidade de vida 36-*item Short-Form Health Survey* (SF-36) ela é uma ferramenta muito útil, usada por vários pesquisadores para diferentes condições de saúde, sendo validada no Brasil há mais de vinte anos (CICONELLI et al., 1999). Pode ser autoaplicada , possui 36 questões que são divididas em oito domínios: capacidade funcional; limitação por aspectos físicos; dor; estado geral de saúde; vitalidade; aspectos sociais; limitação por aspectos emocionais; saúde mental. Cada domínio apresenta um escore final de zero a 100, onde

zero corresponde a uma pior qualidade de vida e 100 a uma melhor qualidade de vida (LEESE et al., 2008; MARTÍN-SIERRA et al., 2011).

5.14 Intervenção física

1. Recrutamento dos pacientes com esquizofrenia no Centro de Atenção Psicossocial de Camaquã (CAPS) e no ambulatório de esquizofrenia do HCPA.
2. Avaliação inicial no CPC do HCPA: leitura para o paciente e para os responsáveis legais do termo de consentimento livre e esclarecido descrevendo as fases da pesquisa: fase 1, de avaliação física e mental; e em caso de aceitação, fase 2, de intervenção de exercício físico aeróbico (pacientes do CAPS) ou exercício físico funcional (pacientes do ambulatório do HCPA) com reavaliação no final de todos os parâmetros iniciais.

Fase 1: (a) leitura e assinatura do termo de consentimento; (b) coleta de sangue (creatina-quinase, lactato e proteína C reativa ultrassensível); (c) medição (gravidade da doença (BPRS), qualidade de vida (SF-36), fotogrametria postural (SAPO), flexibilidade (WELLS) e nível de atividade física do paciente (SIMPAQ)).

Fase 2: programa de intervenção física aeróbica ou funcional por 12 semanas em casos e controles saudáveis. Final: reavaliação.

Protocolo aeróbico: 24 pacientes com diagnóstico de esquizofrenia submetidos ao protocolo por 12 semanas com sessões de 1 hora de duração com uma frequência de duas vezes por semana. As sessões eram realizadas individualmente ou no máximo em dupla, sendo os participantes monitorizados com frequencímetro POLAR FT1® com resultados ajustados para idade, sexo, peso e altura. As medidas variaram de 70% a 80% da frequência cardíaca máxima calculada pela fórmula de Karvonen.

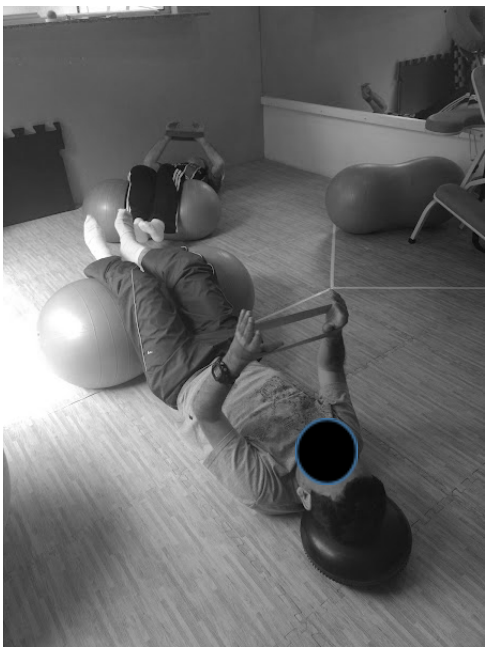
Descrição da sessão aeróbica padrão: início com aquecimento de cinco minutos de intensidade confortável e seguido com exercício aeróbico de intensidade crescente com uma de três modalidades: (a) uma bicicleta ergométrica (Embreex 367C, Brasil); (b) esteira (Embreex 566BX, Brasil); (c) treinador elíptico (Embreex 219, Brasil). Essa

estratégia foi consistente com as recomendações de saúde pública, que sugerem uma adaptação do programa às preferências individuais, e demonstrou ser factível em pacientes com diagnóstico de esquizofrenia. Um profissional treinado coordenou as sessões de intervenção com orientação, ajustes de equipamento e incentivo ao desempenho dos exercícios do participante da melhor forma possível para cada paciente. Depois de completar o exercício aeróbico, os participantes realizaram alongamento global de grandes grupos musculares. Os monitores cardíacos registraram a frequência cardíaca inicial, a frequência cardíaca máxima e as calorias gastas durante uma sessão.

Protocolo funcional: os pacientes continuaram com tratamento clínico regular, além da atividade padronizada. O programa teve duração de 12 semanas e incluiu sessões de 1 hora de duração com a frequência de duas vezes na semana. Os participantes receberam intervenção em trios ou quartetos.

Descrição da sessão funcional padrão: aquecimento de 5 minutos com caminhada estacionária, seguido de 15 minutos de exercícios de mobilidade muscular e articular. Em seguida, 25 minutos de exercícios de resistência muscular global (paravertebrais, abdominais, extensores, flexores, adutores, abdutores de quadril, flexores e extensores de ombros, joelhos e cotovelos), finalizando com 15 minutos de trabalho de consciência corporal respiratória. Os exercícios (uso de acessórios como bolas, faixas elásticas, halteres etc.) seguiram a preferência individual. Um profissional devidamente treinado realizou as consultas, demonstração de exercícios e correção.

Figura 7 – Pacientes executando exercícios do protocolo funcional



Fonte: banco de imagens da pesquisa

5.15 Análise estatística

A normalidade da distribuição dos dados foi avaliada pelo teste de Kolmogorov-Smirnov. As variáveis quantitativas com distribuição normal foram apresentadas como médias e desvios-padrão, enquanto as variáveis com distribuição assimétrica foram apresentadas como medianas e intervalos interquartis. O teste t pareado de Student/teste t independente ou o teste de Wilcoxon/teste de Mann-Whitney foram usados para comparação de variáveis normais e assimétricas, respectivamente. As comparações entre três ou mais grupos foram realizadas pelo teste ANOVA seguido de Bonferroni. As relações entre duas variáveis foram avaliadas por meio dos coeficientes de correlação de Spearman. As variáveis categóricas foram apresentadas como frequências e analisadas pelo teste qui-quadrado de Pearson ou teste exato de Fisher. A principal medida de desfecho foi avaliada por meio da análise do modelo linear generalizado (GLM) (distribuição gama) e os fatores de confusão foram determinados com base em critérios estatísticos (associação com qualquer fator do estudo e o desfecho com nível de significância $p \leq 0,2$). O nível de significância foi $p \leq 0,05$. A

análise do tamanho do efeito foi utilizada para avaliar a magnitude da diferença derivada do GLM. SPSS Statistics 22.0 processou e analisou os dados.

5.16 Aspectos éticos

O estudo seguiu as condições estabelecidas na Resolução 466/12 do Conselho Nacional de Saúde (CNS) e foi previamente aprovado pela Comissão de Ética em Pesquisa do HCPA, abrangendo os princípios bioéticos de autonomia, beneficência, não maleficência, veracidade e confidencialidade. Esse estudo envolveu risco de punção venosa para coleta de sangue, além de possível desconforto pessoal ao responder os questionários. O grupo de pesquisa garantiu a confidencialidade das informações. Todos os participantes assinaram o Termo de Consentimento Livre e Esclarecido. Os instrumentos preenchidos serão arquivados, confidencialmente, pelo período de 5 (cinco) anos. O estudo foi aprovado pelo Comitê de Ética em Pesquisa do HCPA sob número 15-0066, com registro na Plataforma Brasil sob o número 43408615.7.0000.5327 e registro no ReBec (RBR-2h2hjy).

6. RESULTADOS

6.1 Artigo 1 (submetido na revista *Psychiatry International,* em agosto de 2023)

Effect of Assisted Physical Exercise on Inflammatory Markers and Lactate in Schizophrenia—A Controlled Trial

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Abstract

Background: Schizophrenia is a mental disorder associated with inflammatory and oxidative stress markers such as lactate; in addition, the rate of physical inactivity in this population is very high, which leads to physical and metabolic alterations. Aims: This study measured the effect of assisted physical exercise on lactate levels in schizophrenia. Methods: The study involved a non-randomized clinical trial with stable outpatients with schizophrenia recruited in the Hospital de Clínicas de Porto Alegre [HCPA] and Psychosocial Attention Center [CAPS] Camaquã. It included a control group with healthy individuals recruited through social media. Both groups received two different physical exercise programs (aerobic and functional). Results: The patients presented statistical differences in lactate compared to the control group with healthy individuals before and after the intervention. They also presented a higher lactate increase rate after the activity. Creatine kinase (CK) showed differences between aerobic and functional treatments only in the beginning of the trial (in both groups). C-reactive protein (CRP) also presented differences between aerobic and functional treatments in the beginning of the study but it remained only in the functional exercise (in both groups). The finding of increased lactate in schizophrenia detected before and after physical exercise deserve further attention in studies about biomarkers and the development of physical rehabilitation in schizophrenia, suggesting different profiles of oxidative metabolism after physical exercise. Basal increased lactate may reflect mitochondrial dysfunction or metabolic dysregulation, and the higher rate of increase may reflect a different metabolic and oxidative process. Conclusion: The findings are in line with recent studies as surrogate of mitochondrial dysfunction in schizophrenia and points to the need of additional studies on mitochondrial activity in schizophrenia. It also demonstrates the need for additional care in the design of physical interventions in schizophrenia.

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Keywords: Schizophrenia. Lactate. Physical exercise. Creatine Kinase (CK). C-Reactive Protein (CRP).

Introduction

Schizophrenia (SCZ) is a severe mental disorder characterized by positive and negative symptoms, which generate many impairments in individuals' lifestyles. Comorbidities such as metabolic syndrome, heart diseases, obesity, and diabetes mellitus are common in these patients. Associated with a sedentary lifestyle, these conditions reduce patients' survival rate by up to 20%. Moreover, recent studies about schizophrenia show that there is an increase in inflammatory activity and mitochondrial-related dysfunction, which leads to an increase in the levels of C-reactive protein (CRP), in the leukocytes proportion (neutrophil/lymphocyte and monocyte/lymphocyte ratios) and lactate [1-2]. Subsequent effects of these inflammatory markers are reduced cerebral perfusion, reduction in ATPase and mitochondrial activity, and increased cognitive and behavioral deficits. .

The evidence for brain bioenergetic dysfunction has additional support from post-mortem studies with animals, which revealed increased levels of lactate in the dorsolateral prefrontal cortex, regardless of drug use or mitochondrial mutation [3]. On the other hand, regular physical exercise, besides weight loss, contributes to increases in metabolism, cellular mitosis, mitochondrial activity, neurotrophic factors production, neuroplasticity, and life quality, as well as a reduction in oxidative stress [4]. Such a sequence of events may benefit schizophrenia patients as they present lower functional capacity and higher levels of sedentary lifestyle, obesity, and heart and metabolic diseases [5], as already mentioned. It is extremely important to evaluate the response of blood lactate after exercise in this population. Some important and open questions are if it will increase as in the general population or will have a different response, and if the type of physical exercise might interfere in this response. Moreover, physical exercise has the potential of reversing metabolic deregulation and inducing better results in schizophrenia. Therefore, it is a good option for further studies. In this sense, this study aims to measure the effect of two different physical interventions (aerobic physical

intervention [AI] and functional physical intervention [FI}), regarding the blood markers of inflammation (C-reactive protein) and metabolic markers (creatine kinase and lactate) in schizophrenia patients. We aim to compare it to a control group of healthy individuals that received the same interventions.

Materials and methods

2.1. Participants and Study Design

Clinical trials of two physical interventions (aerobic physical intervention [AI] and functional physical intervention [FI]) were assigned to two groups: one of stable outpatients with diagnosis of schizophrenia and another of healthy controls. Patients were under regular care in Public Facilities (AI group at the Psychosocial Attention Center [CAPS] of Camaquã, RS, and FI at Hospital de Clínicas de Porto Alegre). The controls were paired by sex, age, social class (following the classification of IBGE – Brazilian Institute of Geography and Statistics). Such a division scheme for the intervention groups was chosen by convenience due to patients' origins and logistics regarding protocol application and evaluation. The control group followed the same division scheme according to city of origin and pairing.

2.1.1 Patients Inclusion Criteria

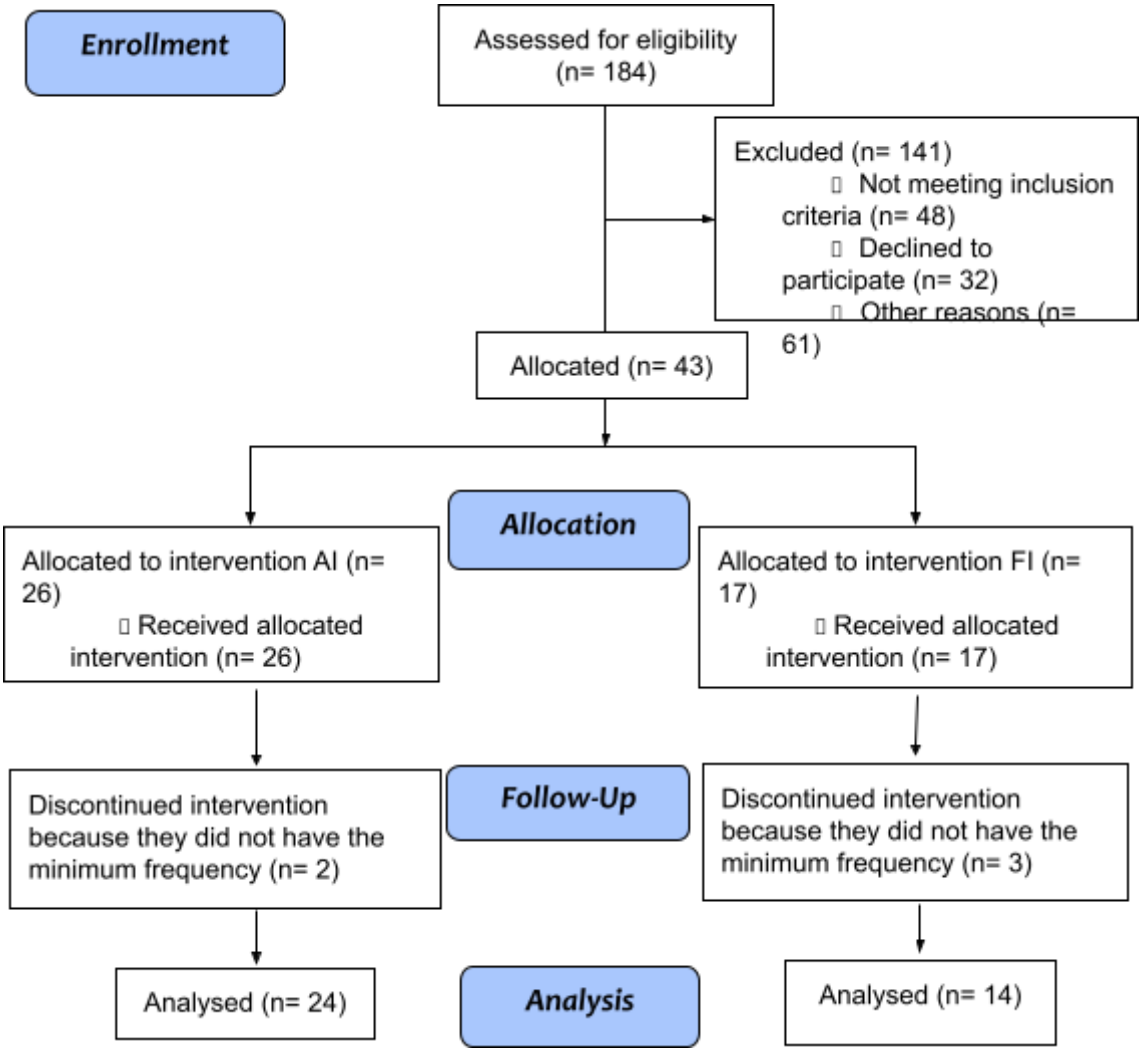
Patients should be stable for at least three months and under regular treatment. Psychiatric diagnosis was established after a three-step procedure consisting of: (1) clinical observation in at least three different evaluations; (2) a family interview; and (3) review of their medical records. A registered Psychiatrist performed all assessments. Patients should also meet the following inclusion criteria: (a) Diagnosis of Schizophrenia by the Diagnostic and Statistical Manual of Mental Disorders [6] of schizophrenia; (b) age between 18 and 65 years; (c) being clinically stable and under drug treatment for at least 3 months; and (d) not being involved in other physical activity programs during the intervention.

2.1.2 Patients Exclusion Criteria

Exclusion criteria were defined by the presence of any of the 3 following items:

a. Suicide risk confirmed by personal interaction with the patient and family; b. pregnancy or being a woman of reproductive age not using a contraceptive method; and c. not agreeing to the study after the full explanation (fig1).

Figure 1 - Study flowchart: patient selection and allocation in intervention subgroups



2.1.3 Inclusion and exclusion criteria controls

Controls were recruited through specific social networks, and paired by sex, age (3 years older or younger), and social class. Absence of any major mental illness was defined by direct interview questioning lifetime experiences of memory loss, psychosis - delusions and or hallucinations, depression, mania, generalized anxiety disorder and obsessive–compulsive symptoms. Exclusion criteria were the same as those applied for patients with SCZ.

2.2. Ethics

The study received the Brazilian Research Registry nº 43408615.7.0000.5327,

registered in the Brazilian Registry of Clinical Trials (ReBEC), under nº RBR-2h2hjy, and approved (#150066) by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre (HCPA). Patients and their legal guardians signed a written informed consent after reading and understanding the intervention program and their rights.

2.3. Clinical Assessment

After recruiting patients and controls, individuals were clinically and physically evaluated by trained physical therapists and psychologists before and after the three-month intervention period. The evaluation included the application of clinical profile questionnaires, measurements of weight and height, and blood collection. The physical intervention for both the clinical cases and the controls followed the initial evaluation that occurred after reading and signing the consent form.

2.4. Blood collection and reference values

HCPA Clinical Pathology Service collected blood samples following the routine laboratory practice before starting the intervention protool and right after its conclusion. High sensitivity C-reactive protein (hs-CRP) was assayed by turbidimetric immunoassay (reference range: < 3.0 mg/L = low/moderate risk; ≥ 3.0 mg/L = high risk), Lactate by colorimetric enzyme (reference range: 0,5-2,2 mmol/L), and Creatine Kinase (CK) by UV Enzyme (reference range: 0-170 U/L).

2.5. Physical Intervention

The physical intervention programme (aerobic or functional) lasted 12 weeks with a frequency of 2 sessions per week of 60 minutes for both clinical cases and healthy controls. Patients continued with their regular clinical treatment in addition to the standard activity. After concluding the intervention programme, they underwent a reevaluation with all the aforementioned tests and questionnaires.

The aerobic protocol was adapted from previous studies in schizophrenia [4]. It consisted of a 5-minute warm-up at a comfortable intensity, followed by 45 minutes of aerobic exercise with increasing intensity. Participants could choose from one of the three following modalities: stationary bicycle (Embreex 367C, Brasil), treadmill (Embreex 566BX, Brasil), or elliptical trainer (Embreex 219, Brasil). The session ended with a 10-minute cool down with global stretching of major muscle groups. On the other hand, the functional protocol was adjusted to the specific physical profile of each patient or group [7]. It followed this sequence: 5-minute warm-up of stationary walking;

15-minute of muscular and joint mobility exercises; 25 minutes of global muscle resistance exercises (paravertebral muscles, abdominals, extensors, flexors, hip adductors, hip abductors, shoulders, knees and elbows, flexors and extensors); and 15 minutes of body awareness work. Both groups (patients and controls) performed similar exercises with the same weekly frequency and duration of time.

2.6. Statistical Analyses

Kolmogorov-Smirnov test assessed normality of data distribution. Quantitative variables with a normal distribution were presented as means and standard deviations, while variables with an asymmetric distribution were presented as medians and interquartile ranges. Student's paired t-test/independent t-test or the Wilcoxon test/Mann-Whitney test were used for comparison of normal and asymmetric variables, respectively. Comparisons between three or more groups were performed by the ANOVA test followed by Bonferroni. Categorical variables were presented as frequencies and analyzed using the Pearson chi-square test or the Fisher exact test. The main outcome measure was assessed using the generalized linear model (GLM) analysis (gamma distribution), and confounding factors were determined based on statistical criteria (association with either study factor and the outcome with p significance level $\leq$ 0.2). Significance level was $p \leq 0.05$. The analysis of effect/size was used to evaluate the magnitude of the difference derived from GLM. The data were processed and analyzed in SPSS Statistics 22.0.

3. Results

Five of 43 individuals with SCZ who started the exercise protocol were excluded for not meeting the minimum required frequency (80%; up to 5 absences over 24 appointments were allowed). In the control group, 49 individuals started the protocol, but 11 were excluded for the same reason. Thus, the final sample size in both groups was 38 individuals, of which 24 from each group performed the aerobic intervention, and 14 from each group performed the functional intervention. The sociodemographic and clinical data of the samples are shown in Table 1, where we can observe that the groups were homogeneous for sex, weight, and BMI, showing statistical differences in

age and height.

Table 1 – Baseline sample characteristics

Variables/Group	Cases	Controls	p-value
Gender n (%)			-
Male	32 (84.2)	32 (84.2)	-
Female	6 (15.8)	6 (15.8)	
Schooling n (%)			-
Basic education	38 (100)	27 (71.1)	-
Higher education	-	11 (28.9)	-
Marital status n (%)			-
Single	37 (97.4)	11 (28.9)	-
Married	1 (2.6)	27 (71.1)	
Smoking n (%)			-
Yes	14 (36.8)	-	-
No	24 (63.2)	38 (100)	-
Years of illness n (%)			-
< 7 years	4 (10.5)	-	-
> 7 years	34 (89.5)	-	-
Antipsychotic medication n (%)			
Typical antipsychotic	13 (34.2)	-	-
Atypical antipsychotic	17 (44.7)	-	-
Combination of typical and atypical	8 (21.1)	-	-

Age (years, mean±SD)	40.95±11.37	41.68±11.22	0.039*
Weight (Kg, mean±SD)	83.77±23.56	88.66±18.51	0.274
Height (m, mean±SD)	1.69±0.080	1.73±0.070	0.011*
BMI (mean±SD)	29.23±7.96	29.55±5.88	0.829
Psychiatric hospitalizations median (p25-p75)	2.00 (0.75-4.00)	-	-

SD = standard deviation; BMI = Body Mass Index; *p ≤ 0.05

Table 2 shows the results of the biomarkers for both groups (cases and controls), compared in two moments (before and after interventions), taking into account the type of physical exercise performed (aerobic or functional).

3.1. Lactate

The serum lactate levels of the clinical cases at the outset of the study were higher than the controls. Such differences were significant ($p > 0.05$) and remained also in the comparison after the intervention ($p > 0.05$), where the clinical group again presented higher lactate levels.

The interventions similarly induced changes in lactate levels as expected, increasing the post-intervention levels. Such differences were significant ($p > 0.05$), except for the clinical group that underwent the functional intervention. Figure 2 displays Percent (%) variation of lactate from baseline. There was a trend ($p > 0.05$) of higher lactate increase in controls.

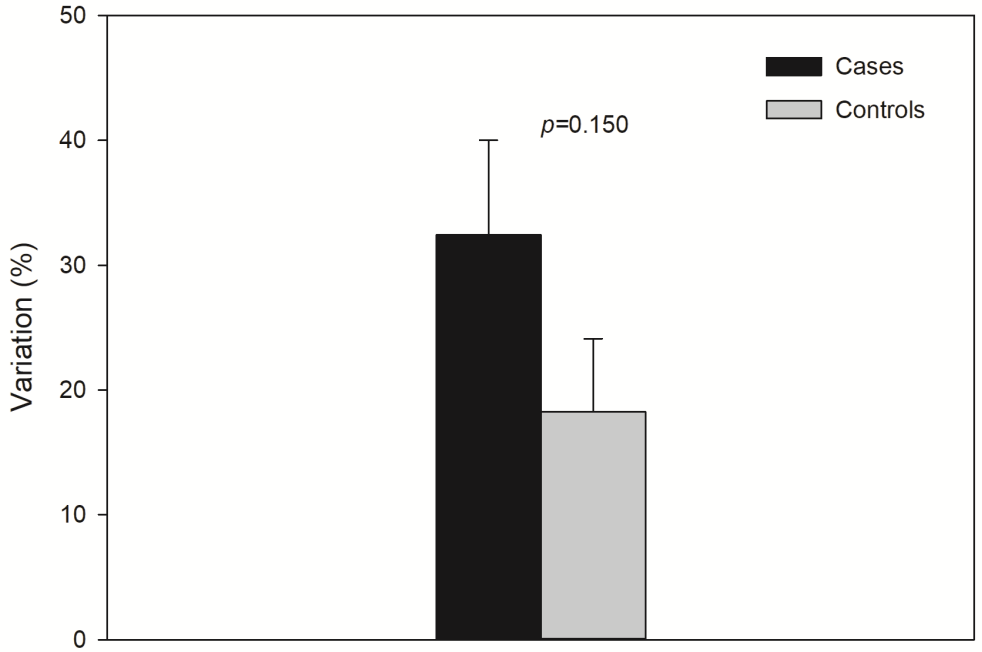
Table 2 – Assessment some biomarkers according intervention (mean and standard deviation)

	Patients (mean ± SD)				**Controls (mean ± SD)**			
Intervention	**Aerobic (n = 24)**		**Functional (n = 14)**		**Aerobic (n = 24)**		**Functional (n = 14)**	
Time	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**

Variable								
* CK	4.99±0.49	5.08±0.71	4.65±0.51	4.79±0.77	5.06±0.86	5.11±0.78	4.95±0.38	4.96±0.40
Δ ΔΔ ΔΔΔ ++ +++ Serum lactate	1.85±0.66	2.30±0.64	1.77±0.82	2.25±1.03	1.45±0.52	1.68±0.68	1.09±0.22	1.21±0.25
* ** # + usCRP	1.09±1.10	1.35±1.05	0.59±0.95	1.03±1.41	1.06±1.23	1.06±1.18	0,.70±1.12	0.50±1.19

SD = standard deviation; *difference between aerobic and functional interventions at baseline ($p< 0.05$); **difference between before and after the functional intervention ($p< 0.05$); #difference between before and after the functional intervention for the control group ($p< 0.05$); +difference between aerobic and functional interventions for the control group ($p< 0.05$); Δdifference between after and before the intervention for case and control groups ($p< 0.05$); ΔΔdifference between after and before the aerobic intervention for case and control groups ($p< 0.05$); ΔΔΔdifference between after and before the functional intervention for the case group ($p< 0.05$); ++difference between after and before the aerobic and functional interventions for the control group ($p<0.05$); +++difference between cases and controls before and after the aerobic and functional interventions ($p< 0.05$).

Figure 2. – Percent variation of lactate (mean and standard error) in patients with schizophrenia and normal controls after physical intervention ($p \leq 0.05$).



3.2. CK

There were differences in pre-intervention serum CK levels among the clinical cases. The clinical group that underwent the aerobic intervention present higher levels than the group that underwent the functional intervention ($p = 0.042$). The interventions induced a slight increase in ck levels, especially in the clinical cases; however, these changes were not statistically significant.

3.3. CRP

Serum CRP levels were similar between controls and patients that underwent the same intervention (case AI = control AI, case FI = control FI) and significantly different ($p = 0.008$) when compared with each other (case AI ≠ case FI, control AI ≠ control FI). It was expected that the interventions induced increased in CRP level after the interventions and this occurred only in the clinical cases. The controls responded

differently; those who underwent AI did not experience any changes, whereas those who underwent FI saw a decrease in levels after the intervention (p =0.016).

4. Discussion

Patients and controls exhibited different behaviors regarding blood markers. This fact suggests metabolic alterations in patients that tend to have a different response to exercise, observed in both protocols. This could be associated with a reduction in glial density and in the mitochondria of oligodendrocytes, as well as the energetic dysfunction associated with schizophrenia. The study identified an increase in patients' basal lactate, which significant increased after AI. This finding deserves special consideration, as it differs from other studies [8], which did not find differences in basal lactate levels between patients with schizophrenia and controls. However, it did observed a higher lactate increase in the group with schizophrenia during the exercise, and this increase persisted after the exercise. The finding of increased basal lactate in schizophrenia is in line with other studies with this population [9] of increased oxidative metabolism. The additional increase observed only after AI may reveal one additional step of the metabolic disturbance in schizophrenia, again in line with previous findings of decreased glutathione and lactate after exercise [10], and of mitochondrial dysfunction at rest and after AI [11].

Post-mortem studies in schizophrenia [9] also detected increased brain levels of lactate and pH in dorsolateral prefrontal cortex, frontal cortex, striatum, hippocampus, and cerebellum, whereas the Anterior limb of internal capsule (ALIC) had decreased lactate. These regional differences in brain lactate may be associated with varying mitochondrial activity based on tissue type [12], and may explain bioenergetic differences in subjects with physical and mental disorders under different physical activity. In the case of schizophrenia, this could be associated with reduced glia and oligodendrocyte mitochondria density and associated energy dysfunction. In this perspective, the observed lactate differences in schizophrenia could be a consequence of previous mitochondrial dysfunction (either inherited or acquired), generating chronic low level brain hypoxia, decreased astrocyte metabolism and downstream increased lactate levels [13]. One explanation for the observed lactate increase in AI could fit with

post-mortem evidence [14] of glial and oligodendrocyte changes and consequent reduced myelination. The energetic process associated with mitochondrial dysfunction, increased lactate, could lead to reduced synaptic plasticity, and neurotransmitter production and explain the observed cognitive deficits in schizophrenia [3]. Despite several questions about lactate still deserving better explanation in schizophrenia, increased anaerobic state, decreased tissue perfusion, adrenaline and sodium/potassium release, and pump dysfunction could also contribute to consequent lactate increase and ATPase activity. Although additional information is needed about lactate (production, utilization, and removal; particularly in the brain, where it is used for metabolic processes), altered lactate levels in schizophrenia provide evidence of energy imbalance,, and different energy and ATP production, besides being used by different organs [15]. In schizophrenia, chronic hypoxia, mitochondrial dysfunction, and increased oxidative process would contribute to positive, negative, and cognitive symptoms.

The observed bioenergetic cell changes have been previously described in other mental disorders such as depression [16] and bipolar disorder [17] where mitochondrial function and shape undergo alterations, leading to an increase in oxidative stress and inflammation, as is also described in schizophrenia.

Lactate is an important substrate for skeletal muscle contraction and, in non-pathological situations, increases during and after physical exercise and is associated with good brain functioning [18], as shown in the control group of this study. Recent animal studies detected a substance called Lac-Phe, resulting from lactate and phenylalanine induced by physical exercise [19], which has an important effect on feeding behavior. This effect raised the assumption of specific brain receptors activated by Lac-Phe, pointing to additional roles of lactate in the regulation of behavior.

The finding of different metabolic and oxidative processes in schizophrenia, allied to the limited effect of neuroleptic drugs, calls attention to different treatments with non-pharmacological strategies in schizophrenia, demonstrating an impact on mitochondrial dysfunction. This is the case of Systemic Photobiomodulation (PBM), which already demonstrated effect correcting mitochondrial dysfunction involving creatine kinase, lactate, troponin, C-reactive protein, and Cytochrome C oxidase alterations in schizophrenia [7]. Additionally, there is evidence of PBM increasing

vascular flow and neural plasticity through light absorption by ion channels, Ca2+ release, and resulting transcription factor activation, increased gene expression, increased neuronal metabolism, and increased neuronal resistance to hypoxia [20].

The results and additional evidence in patients, healthy subjects, and animal models show that PBM by laser light therapy (LLT) deserves special attention in schizophrenia due to its potential to correct basic metabolic dysfunction, in parallel to residual symptom improvement in schizophrenia. Additional PBM studies using these markers and outcome measures are essential to strengthen these initial findings regarding LLT in schizophrenia.

4.1 Limitations

The relatively small sample size in both groups, especially in the functional group, was a limitation of this study. The absence of a control group with schizophrenia not performing physical activity also contributes to uncertainty. In addition, the study collected samples in two moments, before and after intervention, not allowing the measurement of changes over time. Future studies may include more subjects with weekly analyses of expanded blood markers, with additional measurements of behavior (feeding, activity, cognition) to monitor these conditions.

4.2 Conclusions

This study is innovative in evaluating the response of blood lactate and other markers to two different physical activities in individuals with schizophrenia, comparing them to healthy individuals. Our results demonstrate the importance of an active lifestyle for this population and how it can influence their systemic metabolic responses. We hope that future studies, similar to this one, will be conducted with individuals with schizophrenia or other mental disorders in order to generate more treatment options beyond drug therapy.

Authors' contributions: "Conceptualization, Cristiano and Szortyka; Methodology, Cristiano and Szortyka; Software, Cristiano and Szortyka; Validation, Cristiano and Szortyka; Formal Analysis, Cristiano and Abreu ; Investigation, Cristiano and Szortyka; Resources, Cristiano and Szortyka; Data Curation, Cristiano, Abreu, and Szortyka;

Writing – Original Draft Preparation, Cristiano; Writing – Review & Editing, Cristiano and Abreu; Visualization, Abreu; Supervision, Abreu; Project Administration, Cristiano and Szortyka; Funding Acquisition, Cristiano, Abreu and Szortyka".

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Declaration of competing interest: The authors declare that they have no competing financial interests that could have appeared to influence the research reported in this paper.

Data availability: Data will be made available on request.

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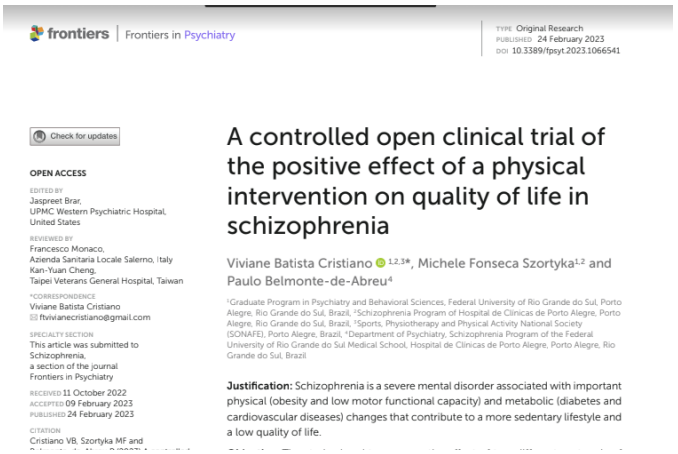

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A controlled open clinical trial of the positive effect of a physical intervention on quality of life in schizophrenia

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Justification: Schizophrenia is a severe mental disorder associated with important physical (obesity and low motor functional capacity) and metabolic (diabetes and cardiovascular diseases) changes that contribute to a more sedentary lifestyle and a low quality of life.

A controlled open clinical trial of positive effect of physical intervention on quality of life in schizophrenia

Short title: Physical intervention in schizophrenia

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ABSTRACT

Justification: Schizophrenia is a severe mental disorder associated with important physical (obesity and low motor functional capacity) and metabolic (diabetes and cardiovascular diseases) changes that contribute to a more sedentary lifestyle and a low quality of life.

Objective: The study aimed to measure the effect of two different protocols of physical exercise [aerobic intervention (AI) versus functional intervention ([FI)] on lifestyle in schizophrenia compared with healthy sedentary subjects.

Methodology: A controlled clinical trial involving patients diagnosed with schizophrenia from two different locations [Hospital de Clinicas de Porto Alegre (HCPA) and Centro de Atenção Psicosocial (CAPS) in the city of Camaquã] was carried out. The patients undertook two different exercise protocols (IA: 5-min warm-up of comfortable intensity; 45 min of aerobic exercise of increasing intensity using any of the three modalities—a stationary bicycle, a treadmill, or an elliptical trainer; and 10 min of global stretching of large muscle groups; and FI: a 5 min warm-up with a stationary walk; 15 min of muscle and joint mobility exercises; 25 min of global muscle resistance exercises; and 15 min of breathing body awareness work) twice a week for 12 weeks and were compared with physically inactive healthy controls. Clinical symptoms (BPRS), life quality (SF-36), and physical activity levels (SIMPAQ) were evaluated. The significance level was $p \leq 0.05$.

Results: The trial involved 38 individuals, of which 24 from each group performed the AI, and 14 from each group underwent the FI. This division of interventions was not randomized but was instead decided upon for convenience. The cases showed significant improvements in quality of life and lifestyle, but these differences were

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greater in the healthy controls. Both interventions were very beneficial, with the functional intervention tending to be more effective in the cases and the aerobic intervention more effective in the controls.

Conclusion: Supervised physical activity improved life quality and reduced sedentary lifestyle in adults with schizophrenia.

Keywords: Quality of life. Schizophrenia. Sedentary lifestyle. Aerobic exercise. Functional exercise.

Introduction

Severe mental disorders, such as schizophrenia, are associated with various personal impairments, including cognitive, physical, and metabolic changes (VANCAMPFORT et al., 2016; MORENO-KÜSTNER et al., 2018). These, in turn, are associated with other diseases (cardiovascular, obesity, and diabetes) (VANCAMPFORT et al., 2016; MORENO-KÜSTNER et al., 2018; NEMANI et al., 2021) that are the consequences of an unhealthy lifestyle, mental illness manifestations, and the side effects of drug treatment.

Furthermore, this population undertakes little physical activity, which contributes to these additional metabolic and cardiovascular pathologies, such as diabetes, acute myocardial infarction, and stroke (VANCAMPFORT et al., 2016; MORENO-KÜSTNER et al., 2018; NEMANI et al., 2021; SOARES et al., 2021). Additionally, the diet of these individuals is a significant factor to be considered as obesity and a sedentary lifestyle will lead to the development of metabolic and cardiovascular diseases, particularly considering that many drugs used to control the disease also contribute to weight gain (ALVAREZ-HERRERA et al., 2020).

All these scenarios of a sedentary lifestyle, obesity, and metabolic and/or cardiovascular diseases directly influence the quality of life of these individuals. Therefore, several studies have evaluated the effect of physical activity on people with

schizophrenia and demonstrated that increased physical activity may induce changes in functional capacity, social interaction, and pain tolerance, even when compared to sedentary individuals without mental disorders (VANCAMPFORT et al., 2015; CRISTIANO et al., 2016). These studies suggest that regular exercise may positively affect individuals with schizophrenia, especially those who are sedentary and overweight. This may occur because of the convergence of increased cellular mitosis, increased metabolism, increased production of endorphins and neurotrophic factors, and muscle and neuronal plasticity (VANCAMPFORT et al., 2011; FIRTH et al., 2018; ABDUL-RASHID et al., 2019; OSPINA et al., 2019; SOUSA et al., 2021). With this hypothesis in mind, many recent studies have focused on physical activity in this population. Almost all the physical activities mentioned were related to aerobic exercise because it has well known oxidative effects and results can be achieved in a relatively short period of time (on average, 8 weeks are sufficient for systemic responses (NEUFER, 1989). Another format of physical activity that can be very beneficial for this population and that has not yet been studied is functional training as it uses everyday movements, such as sitting and standing, pulling and pushing, and spinning, thus favoring and stimulating the individual's autonomy.

The main results of the studies focused on cognitive issues, functional capacity, weight, and biomarkers, revealing positive effects in this population. However, most failed to study the impact on lifestyle and compare it with other physical activities, such as anaerobic exercise. This points to the need for additional data comparing the effect of different types of physical exercise on different health outcomes. Therefore, this study aims to measure the effect of two different physical activity protocols, aerobic intervention (AI) versus functional intervention (FI), on lifestyle in individuals with schizophrenia compared with healthy sedentary individuals.

Materials and methods

Trial design

In this section, we describe the clinical trial of physical intervention [aerobic physical intervention (AI) and functional

physical intervention (FI)] in two groups of stable outpatients with a diagnosis of schizophrenia (SCZ) and one group of healthy sedentary controls. The AI group received regular care at a public health facility [Psychosocial Attention Center (CAPS)]. Patients under continued outpatient care at CAPS-Camaquã in the surrounding cities of Metropolitan Porto Alegre in southern Brazil received AI, and patients under regular care at a university-based hospital [schizophrenia outpatient clinic (Prodesq) of Hospital de Clínicas de Porto Alegre (HCPA)] received FI.

Participants

Stable outpatients under regular treatment received prior psychiatric diagnosis after a three-step procedure consisting of the following: (a) careful clinical observation with at least three evaluations; (b) a family interview; and (c) a review of their medical records performed by a trained psychiatrist. All met the following inclusion criteria: Diagnostic and Statistical Manual of Mental Disorders, DSM-5-TR; (AMERICAN PSYCHIATRIC ASSOCIATION, 2022) diagnosis of schizophrenia; aged between 18 and 65 years; under stable drug treatment adjusted to their clinical state for at least 3 months; and not involved in any other physical activity programs during the intervention. Patients were recruited from the services where they were being clinically followed (HCPA or CAPES) and were allocated to the intervention group (individuals from HCPA underwent IF, and individuals from CAPES underwent IA) (Figure 1).

The exclusion criteria were as follows: alcohol or other drug abuse in the previous month; major systemic or neurological diseases; physical disability contraindicating physical activity or any physical condition that makes physical activity

unsafe; suicide risk confirmed by direct contact with the patient and family; pregnancy or women of reproductive age that did not use a contraception method; and not agreeing to participate in the study after full explanation of the program.

Controls were recruited through specific social networks (Figure 2). Then, they were paired by sex, age (3 years older or younger), and social class [we followed the classification criteria by classes of the Brazilian Institute of Geography and Statistics (IBGE), which uses the monthly income of all the residents of the same house to list from the richest to the poorest]. Thus, they were divided into the following classes: A (monthly income above R$ 20,900), B (monthly income between R$ 10,450.01 and R$ 20,900), C (monthly income above R$ 4,180 but up to R$ 10,450), D (monthly income between R$ 2,090.01 and R$ 4,180), and E (monthly income of no more than R$ 2,090).

The absence of any major mental illness was defined by a direct interview in which questions about life experiences of memory loss, psychosis (delusions and/or hallucinations), depression, mania, generalized anxiety disorder, and obsessive-compulsive symptoms were asked. Additionally, the subjects were asked about regular physical activity as they were supposed to be sedentary. Exclusion criteria were the same as those applied to patients with SCZ.

Figure 1 – Study flowchart: aerobic intervention (AI) and functional intervention (FI) in patients with schizophrenia

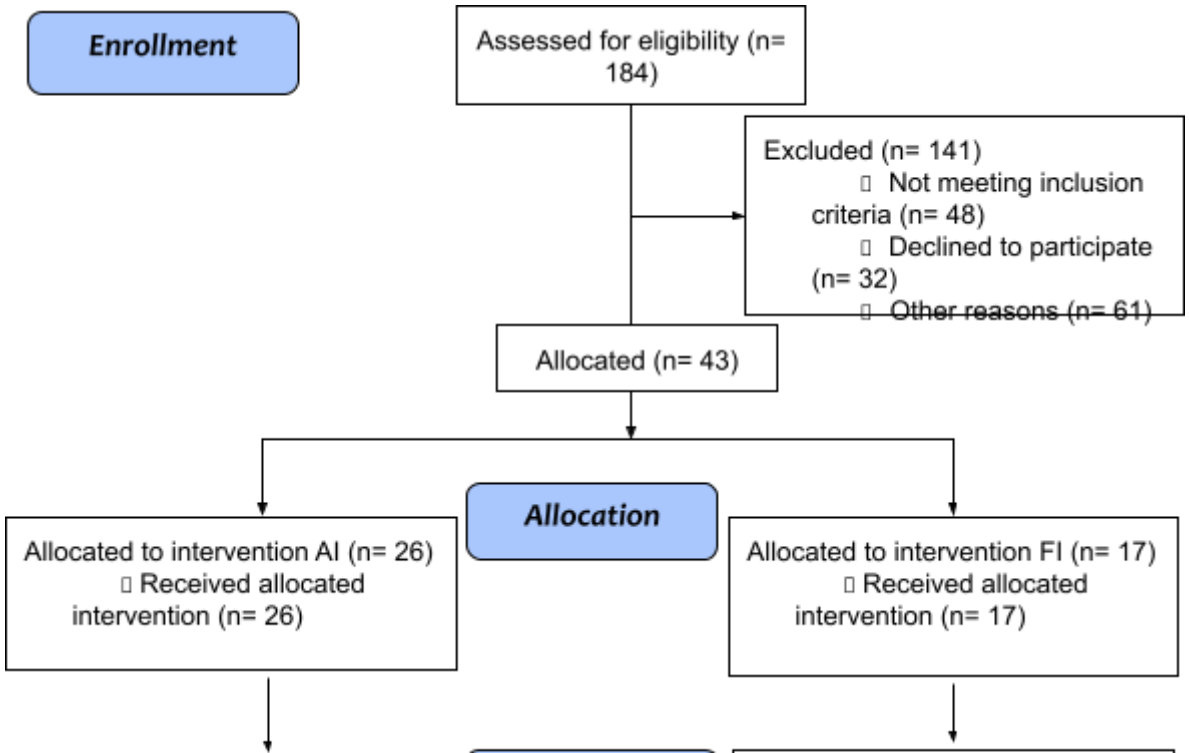
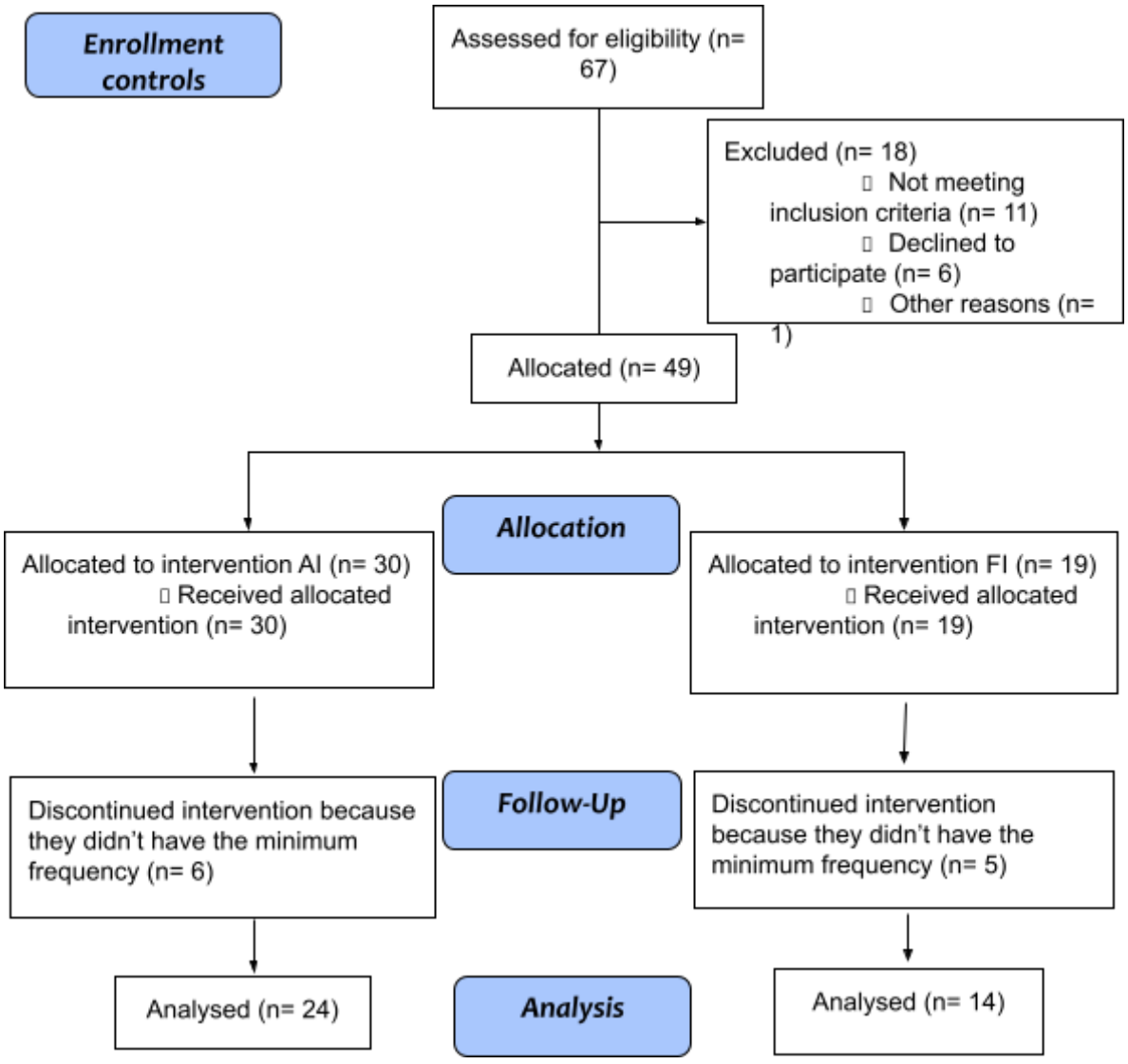


Figure 2 – Study flowchart: aerobic intervention (AI) and functional intervention (FI) in controls



Ethical standards

"The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008."

The study was registered in the Brazilian Research Registry (43408615.7.0000.5327) and the Brazilian Registry of Clinical Trials (ReBEC, 1No. RBR-2h2hjy, registration date 09/29/2020, study start date 07/22/2017) and approved (150066) by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (HCPA). Patients and their legal guardians provided written informed consent after reading and understanding the intervention program and their rights. Registration took place later because we thought it was not a randomized clinical trial, so there would be no need.

Clinical assessment

After patient recruitment, previously trained professionals performed a standardized clinical and physical assessment of the study participants before physical intervention and after 3 months of treatment.

Sedentary lifestyle

The Simple Physical Activity Questionnaire (SIMPAQ) (ROSENBAUM et al., 2020) is a 5-item clinical tool designed to assess physical activity among populations at high risk of sedentary behavior. The questionnaire evaluates the last 7 days, including time in bed, sedentary time, time spent walking, type and time spent exercising, and time spent in other activities, including leisure, domestic, work, and transportation activities. It was simultaneously developed and validated in several languages, including English, Spanish, and Portuguese. Following its validation, our group pioneered its use in clinical research.

Disease severity

The Brief Psychiatric Rating Scale (BPRS) is one of the most used instruments to assess the presence and severity of various psychiatric symptoms and has been in the public domain since 1965 (OVERALL and GORHAM, 1962). It is valid in several

languages, including Portuguese (CRIPPA et al., 2002), and in Brazil, it is used by the Brazilian Unified Health System (SUS) for monitoring patients. This tool assesses 18 symptom domains, such as somatic worry, anxiety, emotional withdrawal, conceptual disorganization, feelings of guilt, tension, mannerisms and posture, grandiosity, depressed mood, hostility, distrust, hallucinatory behavior, motor retardation, lack of cooperation, unusual thought content, blunted affect, excitement, and disorientation. The assessment takes approximately 5–10 min after an interview with the patient. The clinician then rates each item on a scale ranging from 0 (absent) to 6 (extremely severe) through observation and questioning, depending on the item assessed.

Quality of life

The Medical Outcomes Study 36-Item Short Form (SF-36) is a commonly used validated questionnaire that is provided in several languages, including Portuguese (CICONELLI et al., 1999), and has high sensitivity in detecting functional status, among other aspects of quality of life. The SF-36 questionnaire includes eight multiple-item subscales that evaluate functional capacity, physical limitation, pain, general health, vitality, social aspects, emotional limitations, and mental health. The total score on each SF-36 subscale ranges between 0 and 100; the higher the score, the better the patient is.

Physical intervention

The physical intervention for cases and controls followed an initial assessment that took place after the consent form was read and signed and measured disease severity (BPRS) (cases only), quality of life (SF-36), and physical activity level (SIMPAQ). The aerobic or functional physical intervention program lasted 12 weeks in healthy cases and controls. Patients continued with regular clinical treatment in addition to standardized activity, and after completion of the intervention program, revaluation was performed using all the tests and questionnaires mentioned above.

The aerobic protocol was as follows: 24 patients diagnosed with SCZ were paired with 24 sedentary controls without mental illness. The program lasted 12 weeks

and consisted of 1-h aerobic exercise sessions twice a week. The sessions were carried out individually or at most in pairs and monitored by a physiotherapist blinded to the evaluations. The participants were monitored using a Polar FT1R frequency meter with results adjusted for age, sex, weight, and height. Measurements ranged from 70 to 80% of the maximum heart rate calculated using Karvonen's formula.

A standard aerobic session consisted of the following: a 5-min warm-up at a comfortable intensity followed by aerobic exercise of increasing intensity with one of three modalities: (a) a bicycle ergometer (Embreex 367C, Brazil), (b) a treadmill (Embreex 566BX, Brazil), or (c) an elliptical trainer (Embreex 219, Brazil). This strategy was consistent with public health recommendations that suggest tailoring the program to individual preferences, which has been proven to be feasible in patients diagnosed with SCZ. A trained professional coordinated the intervention sessions with guidance and equipment adjustments and encouraged each participant to perform the exercises in the best way possible. After completing the aerobic exercise, participants globally stretched the major muscle groups.

The functional protocol was as follows: 14 patients diagnosed with SCZ were paired with 14 sedentary controls without mental illness. The program lasted 12 weeks and consisted of 1-h physical function training sessions twice a week. The participants carried out the program in trios or quartets and were trained by a physical therapist blinded to the evaluations. A standard session consisted of the following: a 5-min warm-up with stationary walking, followed by 15 min of muscle and joint mobility exercises. Then, 25 min of global muscle endurance exercises (paravertebrae, abdominals, extensors, flexors, adductors, hip abductors, flexors and extensors of the shoulders, knees, and elbows) based on the basic movements of functional training (sit and stand, pull and push, and rotate and advance) were performed, followed by 15 min of respiratory body awareness work. A maximum number of repetitions were performed in 30 s (only once per exercise) and accessories such as balls, elastic bands, and dumbbells were used according to the level of resistance required.

Statistical analyses

The sample size calculation for this study was performed using the WinPepi program (with the evaluation of five co-variables), using a previous study (CRISTIANO et al., 2016) as a baseline. This calculation estimated a minimum number of 30 patients in each group (group 1 patients with SCZ and group 2 controls, for 60 subjects). The normality of the data distribution was assessed using the Kolmogorov–Smirnov test. Quantitative variables with a normal distribution were presented as mean ± standard deviations, while variables with an asymmetric distribution were presented as median and interquartile ranges. Student's paired t-test/independent t-test or the Wilcoxon test/Mann–Whitney test were used to compare normal and asymmetric variables, respectively. ANOVA followed by Bonferroni correction was used for comparisons between three or more groups. Relationships between two variables were assessed through Spearman correlation coefficients. Categorical variables were presented as frequencies and analyzed using the Pearson chi-square test, Fisher exact test, or McNemar test. The main outcome measure was assessed using generalized linear model (GLM) analysis (gamma distribution), and confounding factors were determined based on statistical criteria (association with either study factor and the outcome with a $p \leq 0.2$). The significance level was $p \leq 0.05$. The analysis of effect size was used to evaluate the magnitude of the difference derived from GLM. SPSS Statistics 22.0 was used to process and analyze data.

Results

Five of 43 individuals with SCZ who started the exercise protocol were excluded for not having the minimum required frequency (80%, 5 absences over 24 appointments were allowed), whereas in the control group, 49 started, and 11 were excluded for the same reason. Thus, the final sample numbers in both groups was 38 individuals, of which 24 from each group performed the aerobic intervention, and 14 from each group performed the functional intervention. This division of interventions was not randomized but was instead decided upon for convenience. The sociodemographic and clinical data of the samples are shown in Table 1, where we can

observe that the groups were homogeneous for sex, weight, and BMI, showing statistical differences only in age and height.

Table 1 – Baseline sample characteristics

Variables/Group	**Cases**	**Controls**	**p-value**
Gender n (%)			-
Male	32 (84.2)	32 (84.2)	-
Female	6 (15.8)	6 (15.8)	
Schooling n (%)			-
Basic education (up to 12 years of schooling)	38 (100)	27 (71.1)	-
Higher education (more than 12 years of schooling)	-	11 (28.9)	-
Marital status n (%)			-
Single	37 (97.4)	11 (28.9)	-
Married	1 (2.6)	27 (71.1)	
Smoking n (%)			-
Yes	14 (36.8)	-	-
No	24 (63.2)	38 (100)	-
Years of illness n (%)			-
< 7 years	4 (10.5)	-	-
> 7 years	34 (89.5)	-	-
Antipsychotic medication n (%)			
Typical antipsychotic	13 (34.2)	-	-

Atypical antipsychotic	17 (44.7)	-	-
Combination of typical and atypical	8 (21.1)	-	-
Age (years, mean±SD)	40.95±11.37	41.68±11.22	0.039*
Weight (Kg, mean±SD)	83.77±23.56	88.66±18.51	0.274
Height (m, mean±SD)	1.69±0.080	1.73±0.070	0.011*
BMI (mean±SD)	29.23±7.96	29.55±5.88	0.829
Psychiatric hospitalizations median (p25-p75)	2.00 (0.75-4.00)	-	-

SD = standard deviation; BCI = Body Mass Index; *p< 0.05
Student's independent t-test for quantitative variables. Chi-square test for qualitative variables.

Brief Psychiatric Rating Scale

Table 2 shows the results of the BPRS clinical scale in the different protocols for both the pre- and post-moments in the case group. There was a worsening of hostility symptoms (p = 0.02) in the AI group.

Table 2 – Values of BPRS in patients according to intervention

	Total cases			
	Mean ±SD			
Intervention	**Aerobic (n = 24)**		**Postural (n = 14)**	
Time	**Before**	**After**	**Before**	**After**
Variable				
Anxiety and depression 5-2-9-1	5.71±4.83	5.75±5.11	5.29±5.34	7.36±4.88
Retardation 13-16 3-18-14-7	5.67±6.58	6.38±6.86	5.21±5.18	5.86±4.47

Thinking disorder 11-15-12-4-10-8	6.33±5.30	7.04±5.93	7.36±7.68	8.64±8.19
Activation 7-6-17-8	1.00±2.25	1.96±2.97	1.29±2.61	1.79±2.49
Hostility 10-11-14-8	2.17±2.16	3.83±4.29	2.57±3.74	3.93±4.25

SD, standard deviation; BPRS, Brief Psychiatric Rating Scale. Student's paired t-test.

36-Item short form quality of life scale

Patients with SCZ showed an increase of approximately 20% in almost all domains of the SF-36, except for the pain domain, which decreased in the AI group. Even with this clear improvement, only two domains in each intervention (AI, functional capacity, $p < 0.001$, and limitations by emotional aspects, $p = 0.014$; FI, pain, $p = 0.002$, and limitations by emotional aspects, $p = 0.039$) changed significantly (Table 3).

By contrast, the control group improved significantly in seven of the SF-36 domains in the AI (functional capacity $p < 0.001$; limitations by physical aspects, $p = 0.013$; pain, $p = 0.001$; vitality, $p = 0.002$; social aspects, $p = 0.0271$; limitations by emotional aspects, $p = 0.014$; and mental health, $p = 0.024$) and in four domains in the FI (limitations by physical aspects, $p = 0.013$; pain, $p < 0.001$; general health status, $p < 0.001$; and vitality, $p = 0.049$) (Table 3).

Table 3 - Assessment of quality of life by SF-36 before and after intervention between cases and controls according intervention (mean and standard deviation)

	Patients (mean ± SD)				**Controls (mean ± SD)**			
Intervention	**Aerobic (n = 24)**		**Functional (n = 14)**		**Aerobic (n = 24)**		**Functional (n = 14)**	
Time	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Variable								

Functional capacity	64.38 ±31.98	80.65± 20.36	69.29 ±26.23	73.21 ±22.41	75.83± 16.66	85.25 ±12.24	78.93 ±20.86	84.29 ±17.74
Physical limitations	45.83 ±45.25	57.61± 37.26	39.29 ±47.75	66.07 ±38.44	68.83± 31.82	79.79 ±27.99	61.79 ±29.52	80.36 ±24.53
Pain	68.79 ±25.99	61.65± 34.43	57.36 ±32.37	80.36 ±18.25	59.67± 27.15	74.67 ±23.87	59.57 ±11.57	80.36 ±12.48
General health	46.79 ±23.17	54.82± 23.28	55.00 ±17.72	59.29 ±21.38	53.42± 17.57	61.92 ±18.39	62.79 ±14.90	77.14 ±16.02
Vitality	56.67 ±26.89	66.14± 29.40	56.79 ±18.57	62.14 ±26.73	62.08± 18.82	71.04 ±17.51	65.36 ±15.12	74.64 ±17.27
Social aspects	56.33 ±27.00	64.22± 24.83	56.79 ±29.64	69.64 ±31.28	73.75± 28.06	83.21 ±22.12	74.11± 21.63	82.14 ±21.21
Emotional limitations	38.79 ±44.66	60.50± 44.43	38.09 ±48.67	66.66 ±43.39	70.50± 30.57	84.33 ±14.79	73.81 ±26.76	78.61 ±30.95
Mental health	64.00 ±28.48	66.00± 26.84	62.86 ±28.13	68.86 ±20.29	73.96± 20.79	81.63 ±19.50	72.00 ±11.09	78.57 ±17.37

ANOVA test followed by Bonferroni;

Simple Physical Activity Questionnaire

The AI case group showed a significant change in exercise time from 16 to 126 min per week ($p < 0.001$) but not in the other SIMPAQ items. The FI cases, on the other hand, also showed significant improvement in exercise time from 0 to 110 min per week ($p < 0.001$) and in weekly walking time (from 108 to 177 min/week; $p < 0.001$) (Table 4).

The AI control group showed significant improvement in three measures: (a) sedentary time (from 427 to 337 min/day; $p = 0.007$), (b) walking time (from 132 to 309

min/week; p = 0.004), and (c) exercise time (from 20 to 202 min/week; p < 0.001). The FI control, on the other hand, had only showed a significant improvement in exercise time (from 137 to 207 min/week; p < 0.001) (Table 4).

Table 4 - Assessment of Simple Physical Activity Questionnaire (SIMPAQ) according intervention (mean and standard deviation)

	Patients (mean ± SD)				**Controls (mean ± SD)**			
Intervention	**Aerobic (n = 24)**		**Functional (n = 14)**		**Aerobic (n = 24)**		**Functional (n = 14)**	
Time	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Variable								
Time in bed (minutes)	607.5±114.07	586.25±84.84	660.36±133.14	615.71±75.72	466.25±82.51	422.92±67.02	437.14±57.27	420.71±73.85
Sedentary time (minutes)	365.0±144.73	368.75±163.0	268.57±250.60	225.0±179.95	427.71±107.52	337.29±111.79	387.76±236.65	465.0±285.52
Time spent walking (minutes)	161.25±211.87	195.42±271.50	108.57±206.24	177.14±191.60	132.92±150.52	309.88±309.40	269.29±247.87	338.57±258.57
Type and time spent for exercises (minutes)	16.67±44.40	126.67±140.76	0	110,0±47.72	20.0±70.03	202.5±175.46	137.86±116.57	207.57±107.42
Time spent for other physical activities (minutes)	34.58±76.44	42.92±75.84	4.29±16.04	8.57±24.76	69.38±107.42	158.54±180.42	15.00±27.10	38.93±51.60

ANOVA test followed by Bonferroni;

Discussion

The results of the study on quality of life and levels of physical inactivity are promising and unprecedented, as the cases were compared with healthy controls and submitted to two different interventions. Of the eight domains of quality of life assessed by the SF-36, only two showed statistically significant differences in the AI cases (functional capacity and limitations by emotional aspects) in the comparison between before and after. Additionally, only two domains were statistically significantly different in the FI cases (pain and limitations by emotional aspects). The healthy AI controls showed significant improvement in seven domains of quality of life (pain, limitations by physical aspects, limitations by emotional aspects, general health status, social aspects, functional capacity, and vitality domain), whereas the FI controls improved in four domains in the before and after comparison (limitations by physical aspects, pain, general health status, and vitality). These results allow us to conclude that the benefits of physical activity, independent of the protocol, were superior in healthy controls, and this should be better investigated in future studies. Could the disease be responsible for this difference in response?

The sedentary lifestyle levels assessed by SIMPAQ were different from those of quality of life, with the healthy control group AI and the case group FI showing more significant results in the before and after comparison. This demonstrates that the groups respond better to a specific type of physical exercise, even though they are homogeneous and have the same previous levels of physical inactivity.

Most of the studies available in the literature with this population (SCZ) proposed an aerobic-type activity and their results, in the great majority, were positive in the symptoms of the disease, however our findings were opposite to them, highlighting the hostility variable of the BPRS, where individuals who performed aerobic exercise showed a significant worsening of symptoms (FIRTH et al., 2018; ABDUL-RASHID et al., 2019; OSPINA et al., 2019). What we can safely say is that both interventions produced positive results in cases and in controls in terms of quality of life, favoring the change in the lifestyle of these individuals, taking them out of the "comfort zone" of their sedentary lifestyle, which had made them inactive, and leading them to a more healthy life. After all, physical inactivity is responsible for numerous

pathologies, such as obesity and cardiovascular diseases, which are both very prevalent with SCZ. Data from the WHO indicate that the world population is experiencing a sedentary lifestyle; therefore, any physical activity should be encouraged and should last at least 75–150 min per week (WHO, 2022).

When we look at each variable individually, we can see that the quality of life pain domain improved scores in cases and in controls. However, although this difference occurred for both the AI and FI in the controls, it only occurred for the FI in the cases. The same occurred for the variable time spent in other activities of SIMPAQ. These two differences suggest that the functional protocol tends to produce better responses in SCZ patients. Few studies (AKBAS et al., 2021; TRÉHOUT et al., 2021) have evaluated this in terms of functional and/or postural activities in this population; therefore, it is necessary to explore new lines of research with this type of physical activity. Thus, we will feel more confident when creating protocols. Furthermore, our results emphasize the correlation between the quality of life and the physical activity levels in this population, a hypothesis that has already been discussed previously with psychoses (GOUVEIA et al., 2020). Another critical variable to be considered in studies on physical activities in this population is sleep, as recent studies have shown its correlation with sports performance, the development of chronic and inflammatory diseases (diabetes and cardiovascular diseases), and mental disorders (depression and psychoses) (ADAMS et al., 2016, WERNECK et al., 2022).

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Limitations

Our study has significant limitations, such as the small sample size. Additionally, our sample was mostly male and was already in the chronic course of the disease. Some of these factors occurred due to a selection bias, in which there was a higher male prevalence in the centers of origin (CAPES and HCPA) of individuals SCZ; to avoid interference in the results, statistical adjustments were made. Furthermore, because we depended on a specific structure and specific equipment to carry out the physical exercise protocols, we divided the groups by convenience and not by

randomization. It would have been interesting to divide the group of individuals with SCZ into sedentary and non-sedentary groups for a better comparison with healthy controls. Still, we were again restricted to the profile of the patients in the centers studied, where the majority were sedentary. We suggest further research should include a nutritional control associated with physical activity, as well as additional clinical questionnaires about the disease.

Conclusion

The results of our study are significant and unprecedented for this population. We were pioneers in comparing different physical protocols and assessing lifestyle, as well as the importance of quality of life. Our findings, although preliminary, prove the effectiveness of the practice of guided physical activity among patients with a severe mental disorder, such as SCZ, and serve to guide further studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee of Hospital de Clínicas de Porto Alegre (HCPA). The patients/participants provided their written informed consent to participate in this study.

Authors contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Physical therapy interventions in schizophrenia compared to normal sedentary adults: different effects of aerobic and functional programs over posture and flexibility- a controlled trial

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Abstract

Background: Schizophrenia has disabling effects over mental and physical integrity involving changes in posture and flexibility, which reduce mobility, autonomy, and quality of life. Physical activity has been tested with uncertain effects in schizophrenia, mostly due to trial design, methodology, comparison groups, intervention length, and attrition. Inconsistency led to poor dissemination of active interventions in this population, which may benefit these individuals' health.

Objective: To evaluate the response of two different protocols: Aerobic and Functional exercises, in two groups of sedentary adults—patients with the diagnosis of schizophrenia and healthy controls.
Methods: A clinical trial of two standardized physical interventions in adults diagnosed with schizophrenia and healthy controls. Posture was assessed by digital photogrammetry with the aid of a software and the flexibility by the Wells Fargo's Test.

Results: A total of 38 individuals completed the intervention, with 24 in Aerobic group and 14 in Functional group. The groups were homogeneous for gender, weight, and body mass index, with small differences in age and height. Posture and Flexibility changed according to group and intervention. In this study, guided physical activity improved posture and flexibility in both groups, with higher effect of the Functional protocol than the Aerobic protocol in cases and controls.

Conclusions: Despite a preliminary and relatively small sample size, the study evidences the feasibility and clinical utility of physical intervention in schizophrenia.

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Additional data about specific adaptations in schizophrenia are needed to improve outcomes, such as individualized assistance, support, instructions and intensity.

Trial registration: Clinical trial registration: Brazilian Registry of Clinical Trials (ReBEC) under No. RBR-2h2hjy; date: 09/29/2020, retrospectively registered (https://ensaiosclinicos.gov.br/rg/RBR-2h2hjy).

Keywords: Schizophrenia. Posture. Flexibility. Physical activity. Sedentary lifestyle.

Background

Schizophrenia (SZC) is classified as a serious mental disorder with disabling symptoms such as auditory hallucinations and/or delusional ideas, loss of emotional and social interaction, and aggressiveness, with accentuated cognitive and emotional impairment (MORENO-KÜSTNER et al. 2018) that bring social stigma, dependency, and incapacity (MORENO-KÜSTNER et al. 2018; SOARES et al. 2021). Usual treatment with antipsychotics is associated with adverse effects such as obesity, metabolic syndrome, and extrapyramidal symptoms, with limited potency over symptoms (ALVAREZ-HERRERA et al. 2020). The combination of adverse effects and physical inactivity progressively increases due to muscle stiffness, rigidity, and pain (CRISTIANO et al. 2017).

Posture and Flexibility are strongly affected. Posture is defined by the position of the body in the environment in which it is placed (CARINI et al. 2017) and is changed in major mental illnesses (depression, anxiety, and schizophrenia) (CRISTIANO et al. 2017; CANALES et al. 2010; CANALES et al. 2017; FELDMAN et al. 2020). Flexibility interacts with the posture and is changed by the use of antipsychotic medications that interfere with the musculature and weight (ALVAREZ-HERRERA al. 2020; CRISTIANO et al. 2017).

On the other hand, guided physical activity has been essential to treat mental disorders, such as depression, anxiety, and schizophrenia (GOUVEIA et al. 2020; BROWNE et al. 2021; VAKHRUSHEVA et al. 2016; GARCIA 2018). The preferred

protocol of physical activity works at a submaximal level, from 65% to 80% of the total capacity, to correctly stimulate the oxidative process (aerobics). On the other hand, postural exercise is based on body consciousness and motor control. One unanswered question is if flexibility and posture deficits are consequences of physical inactivity and sedentary lifestyle, part of the natural course of the disease, or consequence of medication. Additional knowledge is needed about positive effects of different types of physical activity.

Based on previous data about postural changes in schizophrenia, such as head anteriorization, scoliosis, pelvic anteversion, and flexibility deficits 4, this study assessed the effects of two physical exercise protocols over the posture and flexibility of individuals with schizophrenia compared to people without major mental illness, but with similar sedentary lifestyles.

Methods

This is a clinical trial of physical intervention (aerobic physical intervention [AI] and functional physical intervention [FI]) in two groups of stable outpatients with diagnosis of SCZ. The AI group received regular care at a public health facility (Psychosocial Attention Center [CAPS]) in a mid-sized municipality of Southern Brazil. FI group received regular care at a public health facility (Psychiatry outpatient clinic of schizophrenia and dementia [PRODESQ] in the Hospital de Clínicas de Porto Alegre [HCPA]), in the capital of the state of Rio Grande do Sul, in the Southern Brazil.

Patients were compared with a control group paired by gender, age, and social class (following classification of the Brazilian Institute of Geography and Statistics), and allocated into two different protocols (AI and FI).

Participants

Stable outpatients under regular treatment in two different health care services: AI group at the Psychosocial Clinic - CAPS, in Camaquã and FI group in Outpatient PRODESQ at the HCPA in Porto Alegre. All individuals received a psychiatric

diagnosis after a three-step procedure: (1) clinical interview and observation over at least three evaluations; (2) family interview; and (3) medical record review by a trained psychiatrist. Inclusion criteria were: a) Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) (American Psychiatric Association 2022) diagnosis of SCZ; b) individuals aged 18–65 years; c) the patients were under stable drug treatment adjusted to their clinical state for at least three months; and d) no involvement in other physical activity programs during the intervention. Exclusion criteria were: a) alcohol or other drug abuse in the last month; b) major systemic or neurological diseases; c) physical disability contraindicating physical activity; d) risk of suicide confirmed by direct contact with the patient and family; e) pregnancy or women of reproductive age not using a contraception method; and f) patients who did not agree to participate in the study after full explanation of the program.

Control group was recruited with the aid of specific social networks paired by gender, age (3 years older or younger); social class. Absence of any major mental illness was defined by enrollment interview directly questioning experiences of memory loss, psychosis (delusions and/or hallucinations), depression, mania, generalized anxiety disorder, or obsessive–compulsive disorder. Exclusion criteria were the same as those applied for patients with SCZ.

Clinical assessment

After recruiting patients and controls, the subjects were clinically and physically evaluated by a group of trained professionals. This evaluation was conducted before the intervention and three months after the treatment.

Postural analysis

The postural evaluation was performed by a postural photogrammetry and the protocol that was applied was previously described in patients with schizophrenia (CRISTIANO et al. 2017). To take the pictures in three different plans (anterior, posterior, and right side), the individuals were marked with extended polystyrene foam balls (3 cm diameter) attached to the skin with double sided tape. The anatomical points

marked were: tragus, acromion, anterior superior iliac spine, greater trochanter of the femur, joint line of the knee, medial aspect of the patella, tibial tubercle, lateral malleolus, medial malleolus, midpoint between the heads of the second and third metatarsals, spinous process of C7, spinous process of T3, interior angle of the scapula, posterior superior iliac spines, midline of calf, point over the calcaneal tendon at the mid-height level of the malleolus, and calcaneus. The same evaluator made all markings.

A postural evaluation software (SAPO 0.67) was used for the analysis and interpretation of the images (FERREIRA et al. 2010). In total, 14 postural angles were described and evaluated by it: LHT (lateral head tilt), FHT (front head tilt, lateral view), SM (shoulder misalignment), HPM (horizontal pelvic misalignment), LTT (lateral trunk tilt), SA (scapular asymmetry), VTA (vertical trunk alignment, lateral view), HPA (horizontal pelvic alignment, lateral view), VV-RLL (varus, valgus right lower limb), VV-LLL (varus, valgus left lower limb), HATT(horizontal alignment tibial tubercle), VV-RF (varus, valgus right foot), VV-LF(varus, valgus left foot), KA-LV (knee angle, lateral view). Previous protocols described in the literature were followed to interpret these angles (CRISTIANO et al. 2017, FERREIRA et al. 2010), in which the positive angles are counterclockwise, thus, showing that the left side is higher than the right side and the reference value for all angles is zero. The measures were expressed in degrees or percentages, according to what was appropriate for each variable.

Stretching: Well's Bank (WB)

Wells sit and reach tests are easy to apply and to reproduce. It evaluates the upper chain flexibility of lower limbs, which is composed by muscles (hamstring and triceps surae) and fascias, and it also receives the interference of the spine. To perform the test, the individual must sit on the floor or on a mat with the legs totally outstretched and the feet flat against the front of the test box, leaning against the bench (specially developed for this test), leaning forward, keeping knees straight, sliding the hands as far as the participant can reach. The results are recorded in cm, repeating three times (WELLS et al. 1952).

Physical interventions

The patients and controls were subjected to two types of interventions: aerobic and functional (Fig 1 and 2). Both interventions lasted one hour and happened twice a week for 12 weeks.

Figure 1 – Aerobic physical intervention

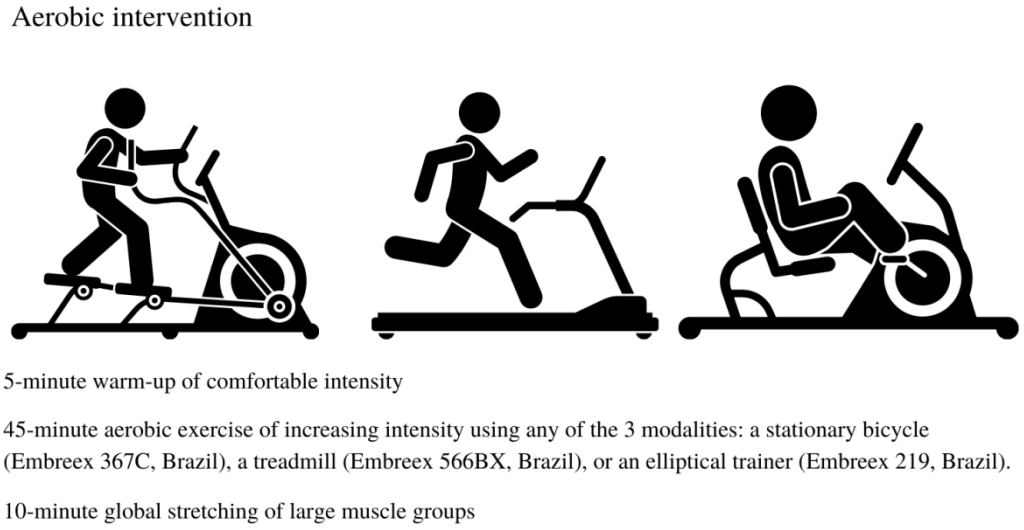
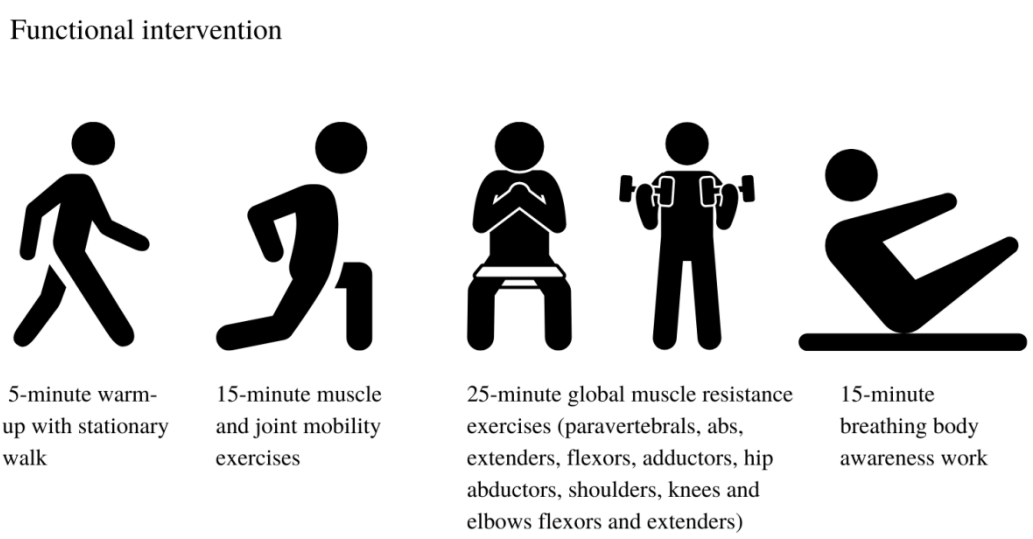


Figure 2 – Functional physical intervention



Both cases and controls needed 80% frequency to avoid exclusion from the study. The patients kept receiving regular clinical treatment besides a standardized physical intervention. Most individuals from both genders had never practiced any physical exercise. Therefore, the participants had to adapt to the first appointments. The participants who performed the aerobic intervention were monitored by a heart rate digital monitor that should go up to 70% to 80% of the maximum heart rate calculated by the Karvonem equation (TANAKA et al. 2001). These individuals were followed by a professional all the time, with guidances, adjustment of equipments and encouragement. On the other hand, the participants who performed the functional intervention were divided in trios and quartets to perform the exercises. For each exercise, three sets of 10 to 15 reps were performed, according to the individuals' endurance. Balls, dumbbells, and elastic bands were used and were evaluated by a professional, according to the individuals' progress and their preferences.

Statistical analysis

The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Quantitative variables with a normal distribution were presented as means and

standard deviations, while variables with an asymmetric distribution were presented as medians and interquartile ranges. Student's paired t-test/independent t-test or the Wilcoxon test/Mann-Whitney test were used for comparison of normal and asymmetric variables, respectively. Comparisons between three or more groups were performed by the ANOVA test followed by Bonferroni. Categorical variables were presented as frequencies and analyzed using the Pearson chi-square test or the Fisher exact test. The major outcome measure was assessed using the generalized linear model (GLM) analysis (gamma distribution) and confounding factors were determined based on statistical criteria (association with either study factor and the outcome with a p significance level ≤ 0.2). The significance level was $p \leq 0.05$. The analysis of effect size was used to evaluate the magnitude of the difference derived from GLM. The data were processed and analyzed in SPSS Statistics 22.0.

Results

Table 1 shows the sociodemographic and clinical data. Out of 43 individuals with SZC in the study, five were excluded due to insufficient frequency; out of 49 controls, 11 were excluded for the same reason. The final sample comprised 38 subjects in two groups: AI (N=24) and FI (N=14). The groups were homogeneous for gender, weight, and body mass index (BMI), with statistical difference in age and height.

Table 1 – Baseline sample characteristics

Variables/Group	Cases	Controls	p-value
Gender n (%)			-
Male	32 (84.2)	32 (84.2)	-

Female	6 (15.8)	6 (15.8)	
Schooling n (%)			-
Basic education	38 (100)	27 (71.1)	-
Higher education	-	11 (28.9)	-
Marital status n (%)			-
Single	37 (97.4)	11 (28.9)	-
Married	1 (2.6)	27 (71.1)	
Smoking n (%)			-
Yes	14 (36.8)	-	-
No	24 (63.2)	38 (100)	-
Years of illness n (%)			-
< 7 years	4 (10.5)	-	-
> 7 years	34 (89.5)	-	-
Antipsychotic medication n (%)			
Typical antipsychotic	13 (34.2)	-	-
Atypical antipsychotic	17 (44.7)	-	-
Combination of typical and atypical	8 (21.1)	-	-
Age (years, mean±SD)	40.95±11.37	41.68±11.22	0.039*

Weight (Kg, mean±SD)	83.77±23.56	88.66±18.51	0.274
Height (m, mean±SD)	1.69±0.080	1.73±0.070	0.011*
BMI (mean±SD)	29.23±7.96	29.55±5.88	0.829
Psychiatric hospitalizations median (p25-p75)	2.00 (0.75-4.00)	-	-

SD = standard deviation; BCI = Body Mass Index; *$p \leq 0.05$

Table 2 Measurements of postural angles, according to the intervention

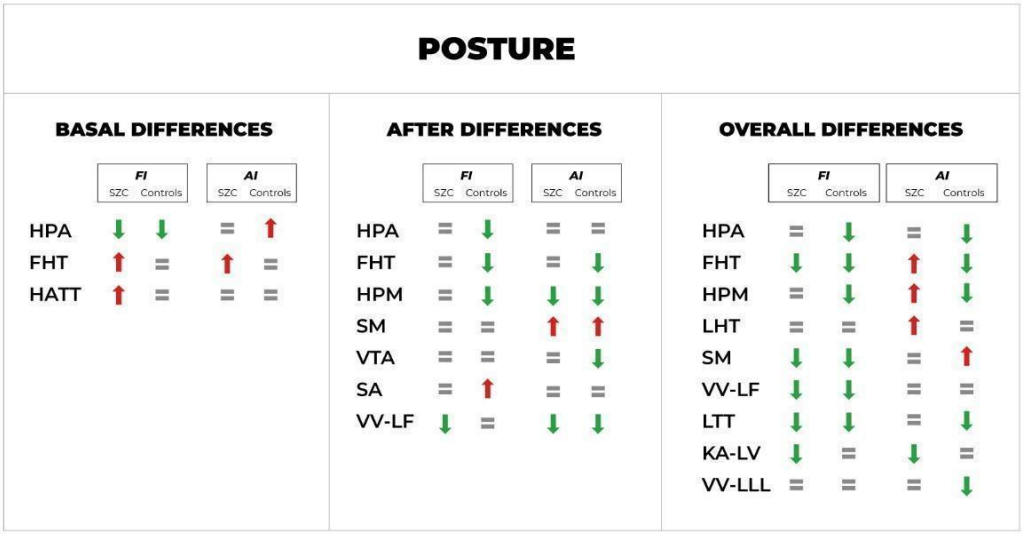
	Patients (mean ± SD)				Controls (mean ± SD)			
Intervention	**Aerobic (n = 24)**		**Functional (n = 14)**		**Aerobic (n = 24)**		**Functional (n = 14)**	
Time	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Characteristic								
SM	2.00±1.33	3.14±2.15$^{\mu}$	3.17±2.21	2.09±1.81$^{\pi}$	2.62±2.57	2.97±2.24$^{\pi\mu}$	2.19±1.51	1.72±0.93$^{\pi}$
HPM	2.33±1.75	4.15±3.52$^{\pi\mu}$	2.81±2.40	2.57±2.73$^{\mu}$	2.99±1.57	1.68±1.96$^{\Omega\pi\mu}$	1.77±1.29	1.00±0.65$^{\Omega\pi\mu}$
LTT	2.78±1.75V	3.33±2.99	4.02±2.74	2.44±2.43$^{\pi}$	3.20±2.13	2.63±2.19$^{\Omega}$	2.98±2.25	1.85±1.62$^{\Omega\pi}$
VV-LLL	3.63±2.47	4.43±2.94	3.41±2.35	2.95±2.74	4.30±3.12	4.04±2.82$^{\pi}$	3.98±3.34	3.77±3.51
LHT	2.57±1.82	4.00±3.16$^{\pi}$	4.48±4.89	3.52±3.12	3.05±2.76	2.76±3.07	3.00±1.84	4.26±4.61
HATT	3.29±3.87	3.44±3.25	4.36±3.38$^{\beta}$	3.87±3.21	2.44±2.16	2.80±2.02	2.37±1.98$^{\beta}$	1.86±2.86
SA	16.66±15.74	20.38±18.73	20.56±16.13	21.17±14.71	16.64±12.50	11.82±10.98	18.75±15.07	22.07±13.97
VV-LF	8.83±5.60	9.59±5.85$^{\mu}$	6.86±7.01	4.91±4.84$^{\pi\mu}$	6.01±4.80	8.29±5.54$^{\mu}$	9.55±6.54	7.70±6.28$^{\pi\mu}$
FHT	26.18±18.83$^{\alpha}$	27.94±17.36$^{\pi\mu}$	25.78±16.64$^{\alpha}$	23.09±17.02$^{\pi\mu}$	15.77±9.80$^{\alpha}$	12.00±8.34$^{\Omega\mu}$	14.63±7.65$^{\alpha}$	12.46±9.82$^{\Omega\pi\mu}$
VTA	3.21±4.89	5.52±4.27	5.24±3.93	4.81±4.29	4.04±2.90	3.18±2.84	4.16±2.71	3.26±2.07
HPA	14.45±9.40$^{\alpha}$	14.42±8.48	14.74±7.38$^{\alpha}$	14.66±7.75	17.73±6.36$^{\alpha}$	13.92±5.28$^{\Omega\pi\mu}$	10.62±3.55$^{\alpha}$	9.01±4.25$^{\Omega\mu}$

KA-LV	8.32±5.54	6.08±4.98$^{\Omega}$	12.75±20.96	8.81±13.77$^{\Omega}$	4.70±2.98	4.86±3.58	3.84±2.81	4.11±2.76
VV-RL	4.25±3.32	4.10±2.98	3.19±3.18	2.96±2.92	3.83±243	3.29±2.42	4.09±3.40	3.93±3.76
VV-RF	8.39±5.04	6.13±4.65	7.46±6.57	8.63±5.89	6.58±5.83	7.90±6.65	8.01±5.09	6.47±5.29

SD = standard deviation; α $p \leq 0.05$ intergroup before intervention; β $p \leq 0.05$ intragroup before intervention; π $p \leq 0.05$ intergroup before X after; Ω $p \leq 0.05$ intragroup before X after; μ $p \leq 0.05$ intergroup after; $\sum$ $p \leq 0.05$ intragroup after

Table 2 shows postural data from AI and FI from cases and controls pre and post intervention. Figure 3 shows 12 statistical differences out of the 14 angles evaluated.

Figure 3 – Postural angles that showed statistical differences ($p \leq 0.05$) in cases and controls, according to the intervention



We observed that the groups were homogeneous in the first moment and showed differences in only three angles (HPA, HATT, and FHT). The results were better for the control group post intervention, which show that even people with a sedentary lifestyle evolved in contrast with the cases. On the other hand, the difference between the interventions is clear when comparing the initial moment with the ending moment, in which people who performed the functional protocol (both cases and controls) improved in a higher number of angulations. Thus, the cases who performed the aerobic protocol had worsened in the posture changes.

Figure 4 – Variation of flexibility in cases and controls, according to the intervention

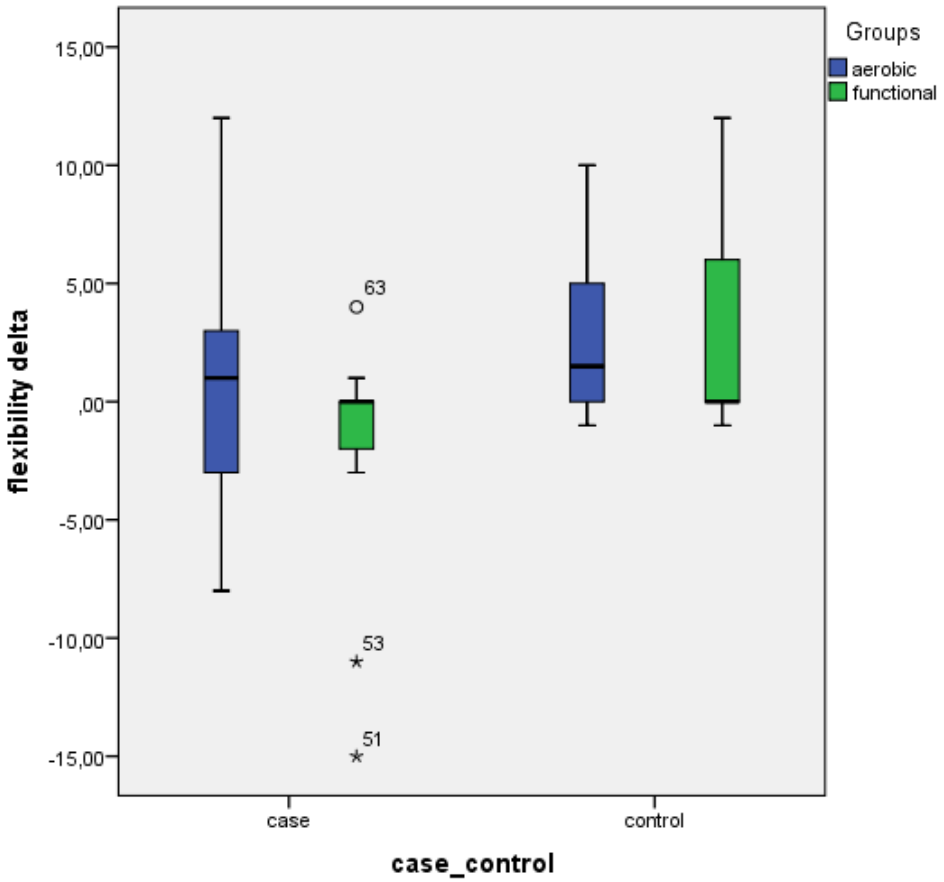


Figure 4 shows changes in flexibility, with relevant changes in those receiving FI ($p = 0.003$) and higher changes in controls (mean change of 3 points) compared to cases (mean change of 1.93 points).

Discussion

Guided physical activity induced significant changes in both groups. The type of protocol significantly affected the posture and flexibility, suggesting that FI had better results than AI. The groups were firstly homogeneous in most variables, being the group case with a major gravity in the three posture angles (HATT, HPA, and FHT) and in the flexibility. When we put these individuals under two different types of intervention, the results showed that the functional protocol was superior to the aerobics in the

improvement in many posture angles and in the flexibility, both in cases and controls. The studies that suggest the practice of physical activities for this population are mostly aerobic exercises, which makes our findings relevant, since we suggest that more complex exercises and in groups, such as functional training, might be more efficient and able to benefit more of this population. The AI worsened the posture change in the cases in some angles, which raises a major concern and doubts. What could be generating this worsening in some posture changes? Could it be the type of exercise or the way the practice is oriented? More studies are necessary to answer this question.

In the final moments, the controls presented better results regardless of the protocol, even if having a sedentary lifestyle, and the answers in their bodies were totally different from the cases. This emphasizes the deleterious physical effects of schizophrenia.

Regarding flexibility, similar to the posture angles, the group case presented a major gravity in the beginning, and those who performed the functional protocol significantly improved, regardless of the group they were in.

A better flexibility interferes in the posture angles because it allows a major extent of movement and mobility, helping in the performance of the exercises and decreasing possible restrictions, thus, creating a better posture (WELLS et al. 1952). There are no previous studies on flexibility in SZC, which makes this study more relevant.

Since posture is the position that the individual assumes in an environment and is influenced by it, the posture is, therefore, related to psychobiological mechanisms5. Although posture has been already observed in depression and SZC (CRISTIANO et al. 2017; CANALES et al. 2010; CANALES et al. 2017; FELDMAN et al. 2020), our study is the first to propose specific intervention to improve posture control.

Since chronic SZC has a high level of sedentarism and associated features (obesity, muscle atrophy, and physical shortening), we selected controls by similar levels of sedentarism to control the changes from a sedentary lifestyle.

Cases had poorer posture before participating in the program—which improved their posture—but only FI had statistically significant changes. We expected the difference among AI if these changes were not only due to a sedentary lifestyle. Subjects who received AI had to stay alone in the treadmill, stationary bike, or elliptical

with the evaluator watching them closely without interacting to avoid distractions and accidents. The individuals with FI had strong interaction, with about four subjects interacting with the tutor, who always guided them during the exercises. This difference of behavior possibly reflected in the outcomes, favoring the individuals who received FI.

This study's limitations were the lack of randomization, small sample size, and high degree of chronicity. Future studies should control nutritional status and chronic diseases in the control group.

Conclusions

The study evidenced the effectiveness of guided physical activity in patients with severe mental disorders, such as SZC, which improved posture and flexibility. Posture induced more changes than aerobic intervention. Although preliminary, the results had clinical relevance and can help additional studies.

List of abbreviations

AI – Aerobic intervention
BMI – Body Mass Index
CAPS – Psychosocial Attention Center
DSM – Diagnostic and Statistical Manual of Mental Disorders
FI – Functional intervention
FHT – Degree of forward head tilt, lateral view
GLM – Generalized linear model
HATT – Degree of horizontal alignment of the tibial tubercles
HCPA – Hospital de Clínicas de Porto Alegre
HPA – Degree of horizontal pelvic alignment, lateral view
HPM – Degree of horizontal pelvic tilt
IBGE – Brazilian Institute of Geography and Statistics
KA-LV – Knee angle, lateral view

LHT – Degree of lateral head tilt

LTT – Degree of lateral trunk tilt

PRODESQ – Psychiatry Outpatient Clinic of Schizophrenia and Dementia

ReBEC – Brazilian Registry of Clinical Trials

SA – Degree of horizontal scapular asymmetry in relation to the third thoracic vertebra

SAPO – Postural assessment software

SD – Standard deviation

SM – Degree of shoulder misalignment

SZC – Schizophrenia

VTA – Degree of vertical trunk alignment, lateral view

VV-LF – Degree of varus or valgus alignment, left foot

VV-LLL – Degree of varus or valgus alignment, left lower limb

VV-RF – Degree of varus or valgus alignment, right foot

VV-RLL – Degree of varus or valgus alignment, right lower limb

WB – Well's Bank

Declarations

Ethics approval and consent to participate

The study was registered in the Brazilian Research Registry under No. 43408615.7.0000.5327, registered in the Brazilian Registry of Clinical Trials (ReBEC) under No. RBR-2h2hjy and approved (150066) by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre (HCPA). Patients and their legal guardians provided written informed consent form after reading and understanding the intervention program and their rights.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during our study are available from the corresponding author on reasonable request.

Competing interests

The authors state that this study is part of the results from the doctorate degree dissertation of the authors VBC and MFS.

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Authors' contributions

VBC and MFS evaluated the cases and controls and supervised the application of the interventions. VBC and PBA were the main contributors in the manuscript elaboration. All authors read and approved the final manuscript.

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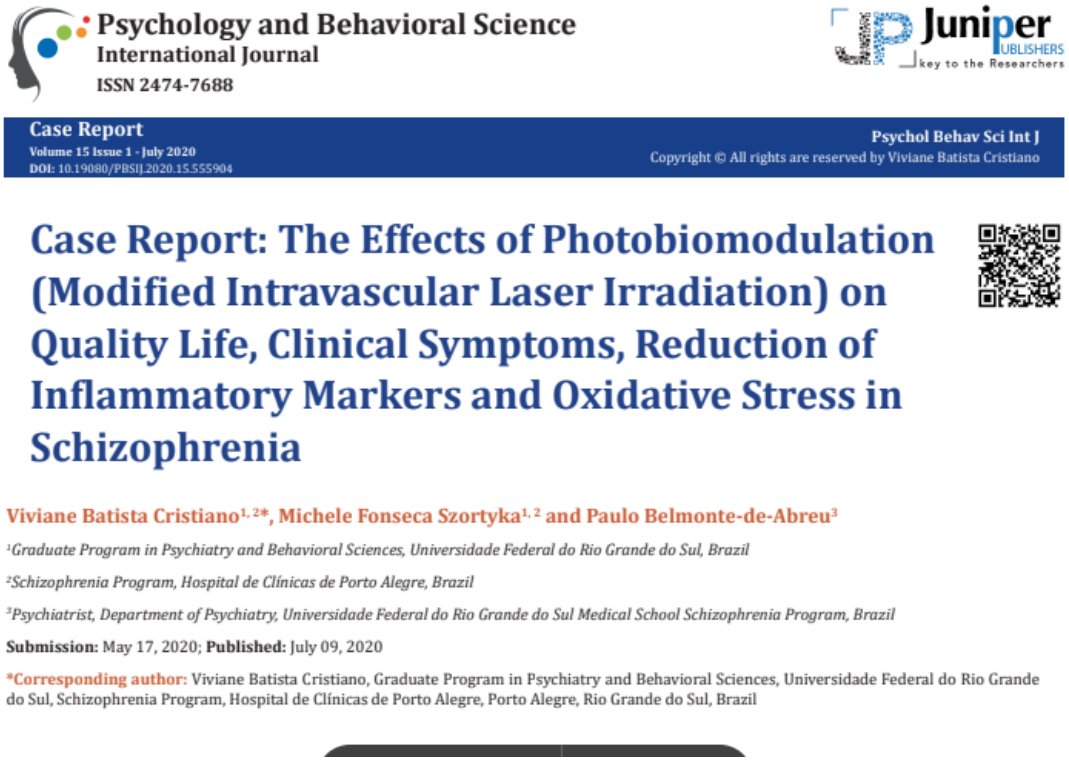

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Case Report: The Effects of Photobiomodulation (Modified Intravascular Laser Irradiation) on Quality Life, Clinical Symptoms, Reduction of Inflammatory Markers and Oxidative Stress in Schizophrenia

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Case report: The effects of photobiomodulation (modified intravascular laser irradiation) on quality life, clinical symptoms, reduction of inflammatory markers and oxidative stress in schizophrenia

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Abstract

Schizophrenia is a chronic mental disorder; these patients have life expectancy and comorbidities. They usually have different altered inflammatory and oxidative markers. Already Modified Intravascular Laser Irradiation of Blood (mILIB) is a Photobiomodulation technique with direct laser (606 nm) and continuously placed over the radial artery with a bracelet. We investigated the clinical effects of mILIB on inflammatory and oxidative markers and evaluated the therapeutic effect in patients with schizophrenia. Patient concerns: The 49-year-old male with DSM V diagnosis of Schizophrenia. He is a smoker, hypertensive and using medication (Risperidone). Intervention: Once the patient was in stable condition, 20 sessions of 30 minutes each, in the following order: 10 daily sessions of 30 minutes, followed by 20 days of interval, and 10 additional daily 30 minutes sessions. Instruments: quality of life using the SF-36 questionnaire, clinical symptoms using the BPRS questionnaire, Blood tests included high sensitivity C - reactive protein, high sensitivity troponin, lactate, and creatine kinase. After the mILIB protocol, the patient showed improvement in 6 domains in the assessment of quality of life, in the severity of the disease, the patient showed na improvement in the percentage of scale change, in addition to improvement in the inflammation marker and oxidative stress; only troponin presented the opposite result. It is an initial study from which we obtained favorable results for the patient with schizophrenia.

Keywords: Case report. Schizophrenia. Modified intravascular laser irradiation. Photobiomodulation. Inflammatory. Oxidative markers and quality of life.

Abbreviations: SCZ: schizophrenia; mILIB: modified intravascular laser irradiation of blood; LLLT: low-level laser therapy; hs-CRP: high sensitivity C-reactive protein; hs-Troponin: high sensitivity troponin; LC: lactate; CK: creatine kinase; QLSF-36: quality of life was assessed by SF-36; BPRS: Brief Psychiatric Rating Scale.

Introduction

Schizophrenia (SCZ) is a mental disorder that affects around 1% of the world population and that generates progressive brain and body changes, which leads many authors to classify it as a systemic disease (GIRDLER; CONFINO; WOESNER, 2019; MCGRATH et al., 2008). Patients with this diagnosis have short life expectancy, on average 20 years less than the general unaffected population (MCGRATH et al., 2008). A plausible explanation for this decrease in life expectancy is the deleterious effects of long-term drug treatment (including weight gain and metabolic alterations) and comorbidities such as diabetes mellitus and cardiovascular diseases that are more prevalent in this disease than in the general population (MCGRATH et al., 2008). They usually have different altered inflammatory and oxidative markers, suggesting a pro-inflammatory pattern of illness that may be directly associated both to disease onset, course and even symptoms (MÜLLER, 2018). Recently that have been several studies targeting inflammation, with drugs like minocycline, celecoxib, methotrexate, with variable results, but some with positive effects over brain atrophy and symptoms (CHAVES et al., 2015). Additional anti-inflammatory therapeutics, photobiomodulation (PBM), acts at the cellular level by stimulating cell metabolism, mainly mitochondria, cytochrome C oxidase, increasing ATP synthesis, with clear anti-inflammatory actions (SALEHPOUR et al., 2018). Although evidence in several inflammatory diseases (muscular and vascular), it was never used specifically in SCZ (SALEHPOUR et al., 2018). mILIB is a PBM technique with direct laser and continuously placed over the radial artery with a bracelet, with frequency and duration fitted according to specific pathology (15, 30 and 60 minutes). Taking into account the pro-inflammatory and oxidative condition that SCZ generates in its patients, and in contrast the beneficial effects of PBM/mILIB provides, we made an open-label study of add-on mILIB in a chronic patient with the diagnosis of schizophrenia that had indication of PBM due to its clinical and metabolic profile.

Case report

The subject was a male, 49 years old, caucasian; single, smoker, hypertensive with DSM V diagnosis of SCZ, followed at the SCZ Outpatient Clinic of a major University Hospital (Hospital de Clínicas de Porto Alegre) in Southern Brazil, under Public Health coverage. First episode was at the age of 18, after 3 years of cannabis use. The patient had 3 psychiatric hospitalizations and he was stabilized in the last 10 years. He uses medication (Risperidone). Patient and relatives signed a consent form, after receiving the explanation of the technique. mILIB consisted of 20 sessions of 30 minutes each, in the following order: 10 daily sessions of 30 minutes, followed by 20 days of interval, and 10 additional daily 30 minutes sessions. The patient received mILIB in the dorsal position, with a protective eyeglass, with light applied over the radial artery (interspersed right/left) with a bracelet fitting the equipment Recover MM Optics® (Red laser 660nm). The laser had a power of 100mW, providing 180J/session. Quality of life was assessed by SF-36 (QLSF-36), and symptoms by Brief Psychiatric Rating Scale (BPRS). QLSF-36 has 8 domains (functional capacity, vitality, pain, mental health, limitations due to physical aspects, limitations due to emotional aspects, limitations due to social aspects and general health status), with a score from 0 to 100 (where 0 is the worst quality of life and 100 the best quality of life); BPRS was composed by 18 items, based on the patient's verbal information and on the observed behavior during the interview (where 0 is the best symptom and 6 the worst symptoms) and the blood samples were collected at the HCPA Clinical Pathology Service as per routine laboratory practice; hs-CRP, hs-Troponin, Lactate and Creatine Kinase.

Results

The patient followed all the protocol, without complications. Table 1 shows the results of the mILIB protocol in relation to quality of life using the QLSF-36. Of the 8 domains, 6 improved. Highlighting the emotional limitations domain that showed 100% improvement. Table 2 shows the results of the mILIB protocol in relation to clinic symptoms using the BPRS questionnaire. We can see that we got an improvement that ranged from 70 to 100% of the symptoms.

In Figure 1 we have the results of inflammatory markers and oxidative stress. hs-CRP presented a drop of 6,53%, as well as the CK (drop of 51,20%) and the LC (drop of 63,3%). The hs-Troponin showed an increase of 14,76%.

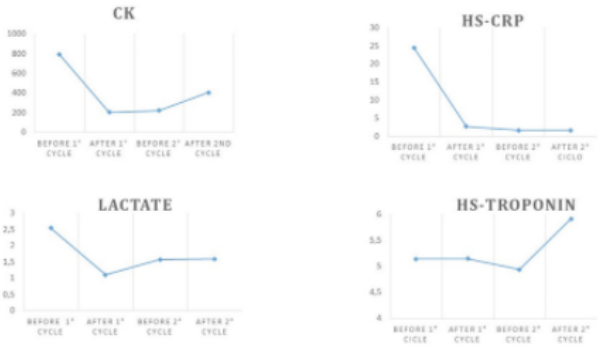

Figure 1: Display results of inflammatory and oxidative proteins in 4 moments of the patient with SCZ (day 1, before the 1st cycle, day 10, after 1st cycle, day 30, before 2nd cycle and day 40, at the end of the 2nd cycle).
CK= Creatine Kinase.
Hs-CRP= high sensitivity C-reactive protein.
Hs-Troponin= high sensitivity troponin.

Table 1: Changes over 2 cycles of PBM of a patient with SCZ.

SF36	Before	After	Difference	%Difference
Functional Capacity	85	65	-20	24
Physical Limitation	100	75	-25	48
Pain	20	74	54	27
Mental Health	64	80	16	25
General Health	52	77	25	48
Vitality	50	50	0	0
Social Life	50	100	50	50
Emotional Limitation	0	100	100	100

Table 2: BPRS over 2 cycles of PBM of a patient with schizophrenia.

BPRS Factors	BPRS Items	Before	After	Change %	Change
Anxiety/Depression	5+2+9+1	5	5	0	0.00
Withdraw/Isolation	3+13+14+16+18	6	0	-6	100.00
Thought Disorder	11+15+12+4+10	5	0	-5	100.00
Activation	7+6+17+8	5	1	-4	80.00
Total	1-18	20	6	-14	70.00

Discussion

The clinical and biochemical changes observed in this case of a man with SCZ maintained in stable medication that is in line with recent PBM studies in patients with

depression, Alzheimer and other types of dementia (SALEHPOUR et al., 2018). Two cycles of PBM evidenced significant changes not only in inflammatory markers, but also in psychotic symptoms. This observed effect if repeated in large series of patients and further in randomized controlled studies may put PBM as add-on treatment for patients with mental disorders such as SCZ early. These are promising findings, with improvement not only in metabolic parameters, but also in psychopathology and quality of life. Confirming a very broad effect of systemic PBM (mILIB). Psychopathology improvement was on three dimensions: Delay-isolation, Thought Disorder and Activation. Clinically, this would mean reduced isolation from others, more organized thinking, and increased energy. Additionally, beneficial effects in six of the eight different dimensions of quality of life, social, family and health functioning improved with PBM. Hs-CRP was the most significant metabolic change. The drop was constant in both cycles, even after being maintained in the interval period. LC, on the other hand, showed a considerable drop at the end of the first cycle, reaching a plateau of normality after the second application cycle. CK was extremely high at the beginning of the study, with exponential drop at the end of the first cycle, stability along the interval and further increase at the end of the second cycle. Since CK increases with physical activity, and the patient reported increased physical activity after the first part of treatment, this could explain the effect in CK (FERRARESI; HUANG; HAMBLIN, 2016; SCHWARTZ et al., 1988). Hs-Troponin dropped at the end of the first cycle, reached a plateau during pause and increased at the end of the second cycle probably accompanied the increase in CK, since hs-troponin is also a marker of muscle damage (SCHWARTZ et al., 1988; SHAVE et al., 2010).

Recent studies with ILIB used different protocols in different pathologies (WAN-HUA, Y.; SHIOU-PING, L.; SHIN-TSU, 2017; JORDÃO et al., 2019). Although the protocols vary from 10 to 30 sessions, with 30 to 60 minutes of application. The wavelength used was the same as our study (660nm), as well as the continuous mode. The results of these studies are promising because, through ILIB therapy, they were able to reduce systolic and diastolic pressure in patients with systemic arterial hypertension (JORDÃO et al., 2019), and in cerebellar injury after stroke, they managed to accelerate functional recovery (WAN-HUA et al., 2017). Associating these results with our findings, we can verify the potential of the technique in different pathologies. This is the

first case report using photobiomodulation in this pathology in which they showed an expressive and important clinical improvement for this population that has limited access to general health care and fewer opportunities for prevention and treatment that would be expected in a non-psychiatric population. But we have limitations such as being just one case, possible transition effect, and for the success of this treatment we need more studies on mILIB in SCZ and other diagnoses.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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8. CONCLUSÕES E CONSIDERAÇÕES FINAIS

Os achados de nosso estudo são de suma importância para essa população de pessoas com esquizofrenia, as quais carecem de atenção nas esferas física e social. Por meio da prática orientada de uma atividade física, pudemos proporcionar muito além de benefícios clínicos: introduzimos os participantes em uma nova rotina, com interação social fora do seu meio comum, deixando de lado o termo "doença" e buscando a qualidade de vida desses indivíduos.

Nossos resultados mostraram os benefícios de ambas as intervenções e seu potencial de mudança no estilo de vida desses pacientes. Podemos destacar os efeitos sobre os marcadores sanguíneos, em especial o lactato, que possivelmente está ligado a fisiopatologia desse transtorno e que deve ser objeto de muitos outros estudos para elucidar o mecanismo por trás dos níveis elevados presentes nesses indivíduos. Outro ponto importante são os resultados na postura e na flexibilidade. Mesmo sendo um protocolo de tempo curto (12 semanas), já foi possível observar uma melhora nessas variáveis mais complexas, que demandam várias adaptações físicas (corticais, musculares, tendíneas etc.) e que vão refletir em como o "indivíduo" se posiciona no espaço que ele ocupa.

Mesmo ambas as intervenções tendo apresentado resultados positivos, o protocolo funcional teve uma tendência à superioridade, e isso nos leva a muitas discussões. Uma vez que a maioria dos estudos de atividade física com essa população utilizou exercícios aeróbicos, os achados do estudo recomendam a inclusão de protocolos funcionais às demais formas de intervenção com atividade física. Especialmente por seu desfecho adicional de proporcionar uma maior interação entre os indivíduos envolvidos e melhor desempenho na execução de tarefas mais complexas, com consequente ganho na capacidade funcional.

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ANEXO I – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO (TCLE)

Grupo caso – FASE 1

Você está sendo convidado (a) a participar do projeto de pesquisa *Inflamação e Lesão Muscular em Esquizofrenia: através de marcadores fisiológicos e bioquímicos – FASE 1: Avaliação da postura, flexibilidade, funcionalidade, resposta inflamatória e lesão muscular*. Esta é uma pesquisa para identificar o perfil físico e postural de pacientes esquizofrênicos que fazem uso de diferentes tipos de medicamentos, realizada pelo Serviço de Psiquiatria do Hospital de Clínicas de Porto Alegre (HCPA).

O estudo tem por objetivo avaliar por meio de testes específicos a postura, a flexibilidade e a capacidade funcional motora, levando em consideração marcadores de resposta inflamatória e marcadores de lesão muscular de indivíduos com esquizofrenia e compará-los com indivíduos sem esta doença. Você está sendo convidado a participar por possuir o diagnóstico clínico de esquizofrenia.

Justifica-se sua realização pela importância de avaliar fisicamente esta população, ainda mais levando em consideração os marcadores de resposta inflamatória e de lesão muscular, pois assim poderemos adotar novos métodos de prevenção e propor novos tratamentos adequados a essa população, para assim melhorar sua capacidade motora e qualidade de vida.

Nesta pesquisa você passará por entrevistas de aproximadamente 10 minutos, em que você deverá responder questionários sobre características sociodemográficas e condições clínicas da sua doença. Não há riscos à saúde física ou mental em responder esses questionamentos. Também irá participar de um protocolo de avaliação postural por meio da marcação de alguns pontos de seu corpo com bolinhas de isopor e posterior retirada de fotos. Isso poderá gerar um desconforto mínimo e é assegurada a sua integridade física. Além disso, será avaliada a sua flexibilidade por meio de teste específico de sentar e alcançar que poderá gerar leve desconforto, sem riscos físicos. Também será avaliada sua capacidade funcional motora por meio do teste de caminhada de 6 minutos, que consiste em você caminhar o mais rápido possível durante 6 minutos em um corredor, sendo que este pode gerar desconforto e cansaço muscular mínimo. Ao

final da avaliação, será coletado sangue para posterior análise de fatores inflamatórios e de lesão muscular; essa coleta de sangue poderá causar algum desconforto no momento da picada da agulha e deixar uma mancha roxa (hematoma) que deve desaparecer em alguns dias. A coleta será realizada por profissional habilitado e o local será devidamente coberto com um curativo. Todos esses procedimentos durarão em torno de 90 minutos. Ao final desses procedimentos, você será convidado a participar da FASE 2 do projeto, que consiste na aplicação de um protocolo de tratamento fisioterapêutico focado na postura ou na capacidade motora, durante 12 semanas. Caso não concorde em participar da FASE 2, sua participação neste estudo acaba ao final da coleta de sangue.

A participação no estudo não trará benefício direto ao participante, mas o estudo poderá contribuir para o aumento do conhecimento sobre o assunto estudado e os resultados poderão auxiliar na realização de estudos futuros. Além disso, você receberá uma avaliação completa em relação ao perfil físico e postural.

Fica desde já comunicado o caráter confidencial destas informações e/ou imagens, ou seja, seu nome ou fotos não serão divulgados em momento algum. Todas as informações (questionários, testes físicos, fotos e testes de sangue) serão utilizadas apenas para este estudo.

Além disso, novas informações, obtidas durante o estudo, lhe serão fornecidas e você terá a liberdade de retirar o seu consentimento de participação a qualquer momento, sem que isso lhe traga prejuízo à continuação do seu cuidado e tratamento.

Fui informado que caso existam danos à minha pessoa ou saúde, causados diretamente pela pesquisa, terei tratamento médico adequado. Além disso, minha participação neste estudo é totalmente voluntária, ou seja, não receberei nenhum tipo de pagamento pela participação no estudo, e também não terei nenhum custo com respeito aos procedimentos envolvidos.

Todas as suas dúvidas serão respondidas com clareza e você poderá solicitar novos esclarecimentos a qualquer momento com o pesquisador responsável, Drº Paulo Belmonte de Abreu, ou com as pesquisadoras Viviane Batista Cristiano e Michele Fonseca Vieira Szortyka, no Serviço de Psiquiatria, no 4º andar do HCPA ou pelo telefone (51) 3316-5588. O Comitê de Ética em Pesquisa também poderá ser contatado para esclarecimento de dúvidas, no 2º andar do HCPA, sala 2227, ou pelo telefone (51) 3359-7640.

Você e/ou seu responsável estará assinando em duas vias; uma ficará com você e a outra com o pesquisador responsável.

Nome do participante_____ Assinatura_____
Nome do responsável_____ Assinatura_____
Nome do pesquisador_____ Assinatura_____
Local e data:_____

ANEXO II – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO (TCLE)

Grupo controle – FASE 1

Você está sendo convidado (a) a participar do projeto de pesquisa *Inflamação e Lesão Muscular em Esquizofrenia: através de marcadores fisiológicos e bioquímicos - FASE 1: Avaliação da postura, flexibilidade, funcionalidade, resposta inflamatória e lesão muscular*. Esta é uma pesquisa para identificar o perfil físico e postural de pacientes esquizofrênicos que fazem uso de diferentes tipos de medicamentos, realizada pelo Serviço de Psiquiatria do Hospital de Clínicas de Porto Alegre (HCPA).

O estudo tem por objetivo avaliar, por meio de testes específicos, a postura, a flexibilidade e a capacidade funcional motora, levando em consideração marcadores de resposta inflamatória e marcadores de lesão muscular de indivíduos com esquizofrenia e compará-los com indivíduos sem essa doença. Você está sendo convidado a participar por não possuir o diagnóstico clínico de esquizofrenia.

Justifica-se sua realização pela importância de avaliar fisicamente essa população, ainda mais levando em consideração os marcadores de resposta inflamatória e de lesão muscular, pois assim poderemos adotar novos métodos de prevenção e propor novos tratamentos adequados a essa população, para assim melhorar sua capacidade motora e qualidade de vida.

Nesta pesquisa você passará por entrevistas de aproximadamente 10 minutos, em que você deverá responder questionários sobre características sociodemográficas e condições clínicas da sua doença. Não há riscos à saúde física ou mental em responder esses questionamentos. Você também irá participar de um protocolo de avaliação postural por meio da marcação de alguns pontos de seu corpo com bolinhas de isopor e posterior retirada de fotos. Isso poderá gerar um desconforto mínimo e é assegurada a sua integridade física. Além disso, será avaliada a sua flexibilidade por meio de teste específico de sentar e alcançar, que poderá gerar leve desconforto, sem riscos físicos. Também será avaliada sua capacidade funcional motora por meio do teste de caminhada de 6 minutos, que consiste em você caminhar o mais rápido possível durante 6 minutos em um corredor, sendo que isso pode gerar desconforto e cansaço muscular mínimo. Ao

final da avaliação será coletado sangue para posterior análise de fatores inflamatórios e de lesão muscular. Essa coleta de sangue poderá causar algum desconforto no momento da picada da agulha e deixar uma mancha roxa (hematoma) que deve desaparecer em alguns dias. A coleta será realizada por profissional habilitado e o local será devidamente coberto com um curativo. Todos esses procedimentos durarão em torno de 90 minutos. Ao final desses procedimentos, você será convidado a participar da FASE 2 do projeto, que consiste na aplicação de um protocolo de tratamento fisioterapêutico focado na postura ou na capacidade motora, durante 12 semanas. Caso não concorde em participar da FASE 2, sua participação neste estudo acaba ao final da coleta de sangue.

A participação no estudo não trará benefício direto ao participante, mas o estudo poderá contribuir para o aumento do conhecimento sobre o assunto estudado e os resultados poderão auxiliar na realização de estudos futuros. Além disso, você receberá uma avaliação completa em relação ao perfil físico e postural.

Fica desde já comunicado o caráter confidencial destas informações e/ou imagens, ou seja, seu nome ou fotos não serão divulgados em momento algum. Todas as informações (questionários, testes físicos, fotos e testes de sangue) serão utilizadas apenas para este estudo.

Além disso, novas informações, obtidas durante o estudo, lhe serão fornecidas e você terá a liberdade de retirar o seu consentimento de participação a qualquer momento, sem que isso lhe traga prejuízo à continuação do seu cuidado e tratamento.

Fui informado que caso existam danos à minha pessoa ou saúde, causados diretamente pela pesquisa, terei tratamento médico adequado. Além disso, minha participação neste estudo é totalmente voluntária, ou seja, não receberei nenhum tipo de pagamento pela participação no estudo, e também não terei nenhum custo com respeito aos procedimentos envolvidos.

Todas as suas dúvidas serão respondidas com clareza e você poderá solicitar novos esclarecimentos a qualquer momento com o pesquisador responsável, Dr. Paulo Belmonte de Abreu, ou com as pesquisadoras Viviane Batista Cristiano e Michele Fonseca Vieira Szortyka, no Serviço de Psiquiatria, no 4º andar do HCPA, ou pelo telefone (51) 3316-5588. O Comitê de Ética em Pesquisa também poderá ser contatado para esclarecimento de dúvidas, no 2º andar do HCPA, sala 2227, ou pelo telefone (51) 3359-7640.

Você e/ou seu responsável estará assinando em duas vias; uma ficará com você e a outra com o pesquisador responsável.

Nome do participante_____ Assinatura_____

Nome do responsável_____ Assinatura_____

Nome do pesquisador_____ Assinatura_____

Local e data:_____

ANEXO III – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO (TCLE)

Grupo caso – FASE 2

Você está sendo convidado (a) a participar do projeto de pesquisa *Inflamação e Lesão Muscular em Esquizofrenia: através de marcadores fisiológicos e bioquímicos – FASE 2: Protocolo de tratamento fisioterapêutico com enfoque postural e capacidade funcional motora em esquizofrênicos*. Esta é uma pesquisa para identificar os resultados de um tratamento fisioterápico na postura e na capacidade funcional motora de pacientes esquizofrênicos que fazem uso de diferentes tipos de medicamentos, realizada pelo Serviço de Psiquiatria do Hospital de Clínicas de Porto Alegre (HCPA).

O estudo tem por objetivo avaliar os resultados de um tratamento fisioterápico na postura e na capacidade funcional motora de indivíduos com esquizofrenia e compará-los com indivíduos sem essa doença. Você está sendo convidado a participar por possuir o diagnóstico clínico de esquizofrenia.

Justifica-se sua realização pela importância de avaliar os resultados desse tipo de tratamento nessa população, ainda mais levando em consideração os marcadores de resposta inflamatória e de lesão muscular, pois assim poderemos quem sabe adotar esses novos métodos de tratamento na rotina ambulatorial.

Nesta pesquisa você já passou pela FASE 1, em que realizou uma avaliação minuciosa, e agora passará por um período de tratamento fisioterapêutico de 12 semanas, em que será sorteado aleatoriamente se você ficará no grupo com foco em treinamento de força e flexibilidade ou no outro grupo que será submetido a treinamento aeróbico. Ambos os grupos terão 2 encontros semanais com duração de aproximadamente 40 minutos, tendo um risco mínimo na sua participação. Nesses encontros você realizará vários exercícios e/ou atividades orientadas por uma fisioterapeuta, a qual irá estar sempre atenta às suas necessidades, podendo interromper o exercício a qualquer momento, caso ele lhe cause algum desconforto ou dor. Ao término das 12 semanas, você passará por uma avaliação, que será por meio de entrevistas que durarão aproximadamente 10 minutos, em que você deverá responder a questionários sobre características sociodemográficas e condições clínicas da sua

doença. Não há riscos à saúde física ou mental em responder esses questionamentos. Você também irá participar de um protocolo de avaliação postural por meio da marcação de alguns pontos de seu corpo com bolinhas de isopor e posterior retirada de fotos. Isso poderá gerar um desconforto mínimo e é assegurado a sua integridade física. Além disso, será avaliada a sua flexibilidade por meio de teste específico de sentar e alcançar, que poderá gerar leve desconforto, sem riscos físicos. Também será avaliada sua capacidade funcional motora por meio do teste de caminhada de 6 minutos, que consiste em você caminhar o mais rápido possível durante 6 minutos em um corredor, sendo que isso pode gerar desconforto e cansaço muscular mínimo. Ao final da avaliação, será coletado sangue para posterior análise de fatores inflamatórios e de lesão muscular. Essa coleta de sangue poderá causar algum desconforto no momento da picada da agulha e deixar uma mancha roxa (hematoma) que deve desaparecer em alguns dias. A coleta será realizada por profissional habilitado e o local será devidamente coberto com um curativo. Todos esses procedimentos durarão em torno de 90 minutos.

A participação no estudo não trará benefício direto ao participante, mas o estudo poderá contribuir para o aumento do conhecimento sobre o assunto estudado e os resultados poderão auxiliar na realização de estudos futuros. Além disso, você receberá uma avaliação completa em relação ao perfil físico e postural.

Fica desde já comunicado o caráter confidencial destas informações e/ou imagens, ou seja, seu nome ou fotos não serão divulgados em momento algum. Todas as informações (questionários, testes físicos, fotos e testes de sangue) serão utilizadas apenas para este estudo.

Além disso, novas informações, obtidas durante o estudo, lhe serão fornecidas e você terá a liberdade de retirar o seu consentimento de participação a qualquer momento, sem que isso lhe traga prejuízo à continuação do seu cuidado e tratamento.

Fui informado que caso existam danos à minha pessoa ou saúde, causados diretamente pela pesquisa, terei tratamento médico adequado. Além disso, minha participação neste estudo é totalmente voluntária, ou seja, não receberei nenhum tipo de pagamento pela participação no estudo e também não terei nenhum custo com respeito aos procedimentos envolvidos.

Todas as suas dúvidas serão respondidas com clareza e você poderá solicitar

novos esclarecimentos a qualquer momento com o pesquisador responsável, Dr. Paulo Belmonte de Abreu, ou com as pesquisadoras Viviane Batista Cristiano e Michele Fonseca Vieira Szortyka, no Serviço de Psiquiatria, no 4º andar do HCPA, ou pelo telefone (51) 3316-5588. O Comitê de Ética em Pesquisa também poderá ser contatado para esclarecimento de dúvidas, no 2º andar do HCPA, sala 2227, ou pelo telefone (51) 3359-7640.

Você e/ou seu responsável estará assinando em duas vias; uma ficará com você e a outra com o pesquisador responsável.

Nome do participante_____ Assinatura_____

Nome do responsável_____ Assinatura_____

Nome do pesquisador_____ Assinatura_____

Local e data:_____

ANEXO IV – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO (TCLE)

Grupo controle – FASE 2

Você está sendo convidado (a) a participar do projeto de pesquisa *Inflamação e Lesão Muscular em Esquizofrenia: através de marcadores fisiológicos e bioquímicos – FASE 2: Protocolo de Tratamento fisioterapêutico com enfoque postural e capacidade funcional motora em esquizofrênicos*. Esta é uma pesquisa para identificar os resultados de um tratamento fisioterápico na postura e na capacidade funcional motora de pacientes esquizofrênicos que fazem uso de diferentes tipos de medicamentos, realizada pelo Serviço de Psiquiatria do Hospital de Clínicas de Porto Alegre (HCPA).

O estudo tem por objetivo avaliar os resultados de um tratamento fisioterápico na postura e na capacidade funcional motora de indivíduos com esquizofrenia e compará-los com indivíduos sem esta doença. Você está sendo convidado a participar por não possuir o diagnóstico clínico de esquizofrenia.

Justifica-se sua realização pela importância de avaliar os resultados desse tipo de tratamento nessa população, ainda mais levando em consideração os marcadores de resposta inflamatória e de lesão muscular, pois assim poderemos quem sabe adotar esses novos métodos de tratamento na rotina ambulatorial.

Nesta pesquisa você já passou pela FASE 1, em que realizou uma avaliação minuciosa e agora passará por um período de tratamento fisioterapêutico de 12 semanas, em que será sorteado aleatoriamente se você ficará no grupo com foco em treinamento de força e flexibilidade ou no outro grupo que será submetido a treinamento aeróbico. Ambos os grupos terão 2 encontros semanais com duração de aproximadamente 40 minutos, tendo um risco mínimo na sua participação. Nesses encontros você realizará vários exercícios e/ou atividades orientadas por uma fisioterapeuta, a qual irá estar sempre atenta às suas necessidades, podendo interromper o exercício a qualquer momento, caso ele lhe cause algum desconforto ou dor. Ao término das 12 semanas, você passará por uma avaliação, que será por meio de entrevistas que durarão aproximadamente 10 minutos, em que você deverá responder questionários sobre

características sociodemográficas e condições clínicas da sua doença. Não há riscos à saúde física ou mental em responder esses questionamentos. Você também irá participar de um protocolo de avaliação postural por meio da marcação de alguns pontos de seu corpo com bolinhas de isopor e posterior retirada de fotos. Isso poderá gerar um desconforto mínimo e é assegurada a sua integridade física. Além disso, será avaliada a sua flexibilidade por meio de teste específico de sentar e alcançar, que poderá gerar leve desconforto, sem riscos físicos. Também será avaliada sua capacidade funcional motora por meio do teste de caminhada de 6 minutos, que consiste em você caminhar o mais rápido possível durante 6 minutos em um corredor, sendo que isso pode gerar desconforto e cansaço muscular mínimo. Ao final da avaliação, será coletado sangue para posterior análise de fatores inflamatórios e de lesão muscular. Essa coleta de sangue poderá causar algum desconforto no momento da picada da agulha e deixar uma mancha roxa (hematoma) que deve desaparecer em alguns dias. A coleta será realizada por profissional habilitado e o local será devidamente coberto com um curativo. Todos esses procedimentos durarão em torno de 90 minutos.

A participação no estudo não trará benefício direto ao participante, mas o estudo poderá contribuir para o aumento do conhecimento sobre o assunto estudado e os resultados poderão auxiliar na realização de estudos futuros. Além disso, você receberá uma avaliação completa em relação ao perfil físico e postural.

Fica desde já comunicado o caráter confidencial destas informações e/ou imagens, ou seja, seu nome ou fotos não serão divulgados em momento algum. Todas as informações (questionários, testes físicos, fotos e testes de sangue) serão utilizadas apenas para este estudo.

Além disto, novas informações, obtidas durante o estudo, lhe serão fornecidas e você terá a liberdade de retirar o seu consentimento de participação a qualquer momento, sem que isso lhe traga prejuízo à continuação do seu cuidado e tratamento.

Fui informado que caso existam danos à minha pessoa ou saúde, causados diretamente pela pesquisa, terei tratamento médico adequado. Além disso, minha participação neste estudo é totalmente voluntária, ou seja, não receberei nenhum tipo de pagamento pela participação no estudo e também não terei nenhum custo com respeito aos procedimentos envolvidos.

Todas as suas dúvidas serão respondidas com clareza e você poderá solicitar

novos esclarecimentos a qualquer momento com o pesquisador responsável, Dr. Paulo Belmonte de Abreu, ou com as pesquisadoras Viviane Batista Cristiano e Michele Fonseca Vieira Szortyka, no Serviço de Psiquiatria, no 4º andar do HCPA, ou pelo telefone (51) 3316-5588. O Comitê de Ética em Pesquisa também poderá ser contatado para esclarecimento de dúvidas, no 2º andar do HCPA, sala 2227, ou pelo telefone (51) 3359-7640.

Você e/ou seu responsável estará assinando em duas vias; uma ficará com você e a outra com o pesquisador responsável.

Nome do participante_____ Assinatura_____

Nome do responsável_____ Assinatura_____

Nome do pesquisador_____ Assinatura_____

Local e data:_____