Uniwersytet Medyczny w Białymstoku

DZIEDZINA **NAUKI MEDYCZNE I NAUKI O ZDROWIU**

DYSCYPLINA **NAUKI MEDYCZNE**

ROZPRAWA DOKTORSKA

Wpływ przebytego zakażenia SARS-CoV-2 na skuteczność leczenia przeciwdepresyjnego z oceną funkcji neuropoznawczych oraz analizą wybranych parametrów zapalnych u osób z depresją

Autor: lek. Eliza Samaryn

Promotor: dr hab. n. med. Beata Galińska-Skok

Klinika Psychiatrii

Kierownik jednostki: prof. dr hab. Napoleon Waszkiewicz

Rozprawa doktorska została zrealizowana w ramach kształcenia w Szkole Doktorskiej Uniwersytetu Medycznego w Białymstoku

Białystok 2024

Medical University of Bialystok

FIELD OF SCIENCE **MEDICAL AND HEALTH SCIENCES**

SCIENTIFIC DISCIPLINE **MEDICAL SCIENCES**

DOCTORAL THESIS

Impact of previous SARS-CoV-2 infection on effectiveness of antidepressant treatment with assessment of neurocognitive functions and analysis of selected inflammatory parameters in people with depression

Author: lek. Eliza Samaryn

First supervisor: dr hab. n. med. Beata Galińska-Skok

Department of Psychiatry

Head of department: prof. dr hab. Napoleon Waszkiewicz

The doctoral thesis was carried out as a part of education at the Doctoral School of Medical University of Bialystok

Bialystok 2024

Składam serdeczne podziękowania promotorowi mojej pracy
Pani dr hab. n. med. Beacie Galińskiej-Skok
za inspirację, poświęcony czas, okazaną życzliwość i zaangażowanie w powstawaniu pracy.

Dziękuję ***prof. dr hab. n. med. Napoleonowi Waszkiewiczowi***
za cenne wskazówki, naukowe wsparcie i umożliwienie mi odbywania specjalizacji w Klinice Psychiatrii UMB.

Dziękuję mojemu mężowi- ***Rafałowi*** *oraz dzieciom-* ***Zofii i Dawidowi****, za miłość, cierpliwość, wsparcie oraz umożliwienie samorealizacji naukowej.*

Dziękuję moim rodzicom – ***Iwonie*** *i* ***Dariuszowi****, za okazane wsparcie oraz towarzyszenie mi od początków mojej ścieżki naukowej.*

Spis treści

1. Wykaz skrótów

4-HNE	*4-hydroxy-2-nonenal*	4-hydroksy-2-nonenal
Aβ	*β-amyloid peptide*	peptyd β-amyloidu
ALT	*alanine aminotransferase*	aminotransferaza alaninowa
AST	*aspartate aminotransferase*	aminotransferaza asparaginianowa
BDI	*Beck depression inventory*	skala depresji Becka
BMI	*body mass index*	wskaźnik masy ciała
CAT	*catalase*	katalaza
COVID-19	*coronavirus disease 2019*	choroba koronawirusowa 2019
CRP	*C-reactive protein*	białko C-reaktywne
CVLT	*California Verbal Learning Test*	Kalifornijski Test Uczenia się Językowego
DST	*Digit Span Test*	Test powtarzania cyfr
DT	*dityrosine*	dityrozyna
GPx	*glutathione peroxidase*	peroksydaza glutationowa
GSH	*reduced glutathione*	zredukowany glutation
HAM-A	*Hamilton anxiety rating scale*	skala oceny lęku Hamiltona
HAM-D	*Hamilton depression rating scale*	skala oceny depresji Hamiltona
HDL	*high-density lipoprotein*	lipoproteina o wysokiej gęstości
HPA	*hypothalamus–pituitary–adrenal*	podwzgórze-przysadka-nadnercza
ICD	*International Classification of Diseases*	Międzynarodowa Klasyfikacja Chorób
IES-R	*Impact of Event Scale—Revised*	Zrewidowana Skala Wpływu Zdarzeń
IgG	*immunoglobulin G*	immunoglobulina G
KYN	*kynurenine*	kinurenina
LDH	*lactate dehydrogenase*	dehydrogenaza mleczanowa
LDL	*low density lipoprotein*	lipoproteina o małej gęstości
M.I.N.I.	*Mini International Neuropsychiatric Interview*	Krótki Międzynarodowy Kwestionariusz Neuropsychiatryczny
NFK	*N-formylkynurenine*	N-formylokinurenina
NO	*nitric oxide*	tlenek azotu
O&NS	*oxidative and nitrosative stress*	stres oksydacyjny i nitrozowy
RBD	*receptor-binding domain*	domena wiążąca receptor

ROS	*reactive oxygen species*	reaktywne formy tlenu
RNS	*reactive nitrogen species*	reaktywne formy azotu
SCWT	*Stroop Color Word Test*	test Stroopa
SOD	*superoxide dismutase*	dysmutaza ponadtlenkowa
SSRI	*selective serotonin reuptake inhibitor*	selektywny inhibitor wychwytu zwrotnego serotoniny
TMT	*Trail Making Test*	Test Łączenia Punktów
TNF-α	*tumour necrosis factor α*	czynnik martwicy nowotworu α
TRY	*tryptophan*	tryptofan
TSH	*thyroid-stimulating hormone*	hormon stymulujący tarczycę
WAIS-R	*Wechsler Adult Intelligence Scale-Revised*	Zrewidowana skala inteligencji Wechslera dla dorosłych
WHO	*World Health Organization*	Światowa Organizacja Zdrowia
VFT	*verbal fluency test*	test fluencji słownej

2. Wykaz publikacji stanowiących rozprawę doktorską

Praca przeglądowa:

1. **Eliza Dąbrowska**, Beata Galińska-Skok, Napoleon Waszkiewicz: *Depressive and Neurocognitive Disorders in the Context of the Inflammatory Background of COVID-19.* Life 2021, 11, 1056. Doi: 10.3390/ life11101056

IF = 3,251 , MNiSW = 70

Praca oryginalna:

1. **Eliza Samaryn,** Beata Galińska-Skok, Aleksander Nobis, Daniel Zalewski, Mateusz Maciejczyk, Monika Gudowska-Sawczuk, Barbara Mroczko, Anna Zalewska, Napoleon Waszkiewicz: The Effect of Antidepressant Treatment on Neurocognitive Functions, Redox and Inflammatory Parameters in the Context of COVID-19. *Journal of Clinical Medicine* 2023. *12*(22), 7049. Doi: 10.3390/jcm12227049

IF = 3,0 , MNiSW = 140

3. Zestawienie publikacji doktoranta

Rodzaj publikacji	Liczba	Impact Factor	Punktacja MNiSW/MEiN
Prace włączone do rozprawy doktorskiej	2	6,251	210
Prace, które nie zostały włączone do rozprawy doktorskiej	2	3	147
Streszczenia zjazdowe	10	-	-
Razem	**4**	**9,251**	**357**

4. Wstęp

Pandemia COVID-19, której zakończenie ogłoszono w maju 2023 roku, wywarła ogromny wpływ na zdrowie psychiczne ludzkości [1,2]. Stresogenne czynniki związane z pandemią przyczyniły się do znacznego wzrostu częstości występowania zaburzeń psychicznych, w tym zaburzeń depresyjno-lękowych [3,4]. Według raportu opublikowanego przez Światową Organizację Zdrowia (WHO) w marcu 2022 roku, w pierwszym roku pandemii COVID-19 globalna częstość występowania lęku i depresji wzrosła o 25% [5]. Dodatkowo, coraz więcej badań wskazuje na wpływ przebytego zakażenia SARS-CoV-2 na ujawnianie się lub nasilenie objawów zaburzeń psychicznych, w tym depresyjnych [6,7].

Zaburzenie depresyjne jest bardzo powszechnym, potencjalnie zagrażającym życiu, zaburzeniem psychicznym oraz wiodącą przyczyną niepełnosprawności na świecie[8]. Statystyki wskazują, że około 3,8% światowej populacji cierpi na depresję, w tym 5% dorosłych, przy czym liczba kobiet jest dwukrotnie większa niż mężczyzn[9]. Etiologia depresji jest wieloczynnikowa, obejmująca czynniki biologiczne, genetyczne, psychologiczne i środowiskowe, które według teorii neurorozwojowej wzajemnie się uzupełniają. Obecnie oprócz głównych koncepcji neurobiologicznych depresji, takich jak teoria monoaminergiczna, dysregulacja osi podwzgórze–przysadka–nadnercza (HPA) oraz zmiany strukturalne i zaburzenia plastyczności mózgu, coraz bardziej podkreśla się rolę zapalenia u podłoża zaburzeń depresyjnych [10,11]. Teorię zapalną depresji potwierdzają liczne badania, które wskazują na towarzyszący przewlekły stan zapalny organizmu z nasilonym stresem oksydacyjnym i nitrozacyjnym (O&NS), również w ośrodkowym układzie nerwowym [12–15]. U pacjentów z depresją odnotowywano podwyższone poziomy parametrów zapalnych, w tym CRP i interleukiny prozapalne, które mogą przenikać barierę krew-mózg, a następnie przez nadmierną aktywację mikrogleju prowadzić do neurodegeneracji i w konsekwencji zaburzeń funkcji neuropoznawczych [16,17].

Zakażenie wirusem SARS-CoV-2, o właściwościach neuroinwazyjnych i neurotroficznych, może wpływać na nasilenie lub ujawnianie objawów zaburzeń depresyjnych [7]. Ma to ścisły związek z patofizjologią infekcji SARS-CoV-2, która może prowadzić do ogólnoustrojowej "burzy cytokin" z niekontrolowanym, nadmiernym uwalnianiem cytokin i chemokin powodujących stan zapalny, a następnie uszkodzenia bariery krew-mózg, aktywacji mikrogleju i neurozapalenia. Liczne badania wskazują na

przenikanie do mózgu czynników zapalnych, takich jak interleukiny i TNF-α, obecność mikrouszkodzeń i neurodegeneracji w korze przedczołowej, hipokampie i ciele migdałowatym [18]. Dodatkowo może dochodzić do zwiększonej aktywacji szlaku kynureninowego z uwalnianiem neurotoksycznych metabolitów oraz produkcji reaktywnych form tlenu (ROS) i azotu (RNS), prowadzących do oksydacyjnych uszkodzeń w mózgu [19]. Co więcej u pacjentów z COVID-19 obserwowano dysfunkcje wykonawcze, problemy z uwagą i orientacją, a w badaniach obrazowych mózgu obszary hipoperfuzji [20]. Istnieją dowody na to, że hipoperfuzja mózgu może przyspieszać akumulację amyloidu-β (Aβ), patologię białek tau i TDP-43 biorących udział w rozwoju demencji [21]. Dodatkowo stres psychologiczny związany z pandemią, poprzez nadaktywność osi podwzgórze-przysadka-nadnercza, może nasilać procesy zapalne w organizmie prowadzące do intensyfikacji procesów neurodegeneracyjnych i zaburzeń depresyjnych [22].

Infekcja COVID-19 może charakteryzować się nadmierną, niekontrolowaną odpowiedzią zapalną organizmu prowadząc do dysfunkcji układu odpornościowego i przedłużającego się stanu zapalnego. Badania potwierdzają, że osoby, które przeżyły COVID-19, mogą wykazywać podwyższone markery zapalne nawet kilka miesięcy po infekcji[23]. Niektóre badania wskazują na korelację ciężkości przebiegu infekcji SARS-CoV-2 z nasileniem i czasem utrzymywania się powikłań zespołu post-COVID-19, w tym zaburzeń neuropsychiatrycznych [24]. Zespół post-COVID charakteryzuje się zespołem objawów z zakresu różnych układów organizmu, które utrzymują się lub pojawiają się po ustąpieniu ostrej fazy infekcji wirusem SARS-CoV-2. Objawy te mogą trwać tygodnie, miesiące, a nawet dłużej [25]. Metaanaliza przeprowadzona przez Davisa i wsp. wykazała, że około jedna trzecia osób po przechorowaniu COVID-19 doświadczała utrzymującego się zmęczenia, a ponad jedna piąta cierpiała na zaburzenia poznawcze przez 12 lub więcej tygodni po diagnozie[23]. Badania wykazały, że od 30% do 40% pacjentów z zespołem post-COVID-19 doświadcza objawów depresyjnych, co jest znacznie wyższym odsetkiem w porównaniu do populacji ogólnej [26].

Farmakoterapia zaburzeń depresyjnych to przede wszystkim zastosowanie leków przeciwdepresyjnych[27]. Wykazują one szereg korzystnych efektów, takich jak łagodzenie nasilenia objawów depresji, poprawa funkcji poznawczych oraz redukcja stanu zapalnego ze zmniejszeniem poziomu prozapalnych cytokin i stresu oksydacyjnego [28,29]. Istnieje coraz więcej dowodów na antyoksydacyjne działanie leków przeciwdepresyjnych, choć mechanizmy te nie są jeszcze w pełni poznane. Badania na modelach zwierzęcych

wskazują, że leki przeciwdepresyjne mogą redukować poziom markerów stresu oksydacyjnego w mózgu, wątrobie i tkankach obwodowych oraz modulować aktywność bariery antyoksydacyjnej, w tym SOD, CAT i GSH [30]. Zaobserwowano, że leki przeciwdepresyjne, w tym selektywne inhibitory wychwytu zwrotnego serotoniny (SSRI), mogą łagodzić burzę cytokinową u pacjentów z COVID-19 stanowiąc obiecujące leczenie wspomagające w leczeniu zakażenia COVID-19 oraz zmniejszać ryzyko hospitalizacji i zgonu [31]. Przegląd literatury wskazuje, że fluwoksamina jako lek przeciwdepresyjny, należący do grupy SSRI, skutecznie łagodzi objawy depresyjne u pacjentów z COVID-19 i wykazuje dodatkowe działanie przeciwwirusowe [32]. Ponadto leki przeciwdepresyjne stosowane u osób, które przeżyły COVID-19, mogą pozytywnie wpływać na ich nastrój i poprawiać funkcje poznawcze [33]. W badaniu przeprowadzonym przez Kwan i wsp. oceniono skuteczność wortioksetyny w łagodzeniu objawów depresyjnych u pacjentów z zespołem post-COVID-19, wykazując, że leczenie to znacząco poprawiło objawy depresyjne w porównaniu do placebo, szczególnie u pacjentów ze zwiększonymi wyjściowymi markerami stanu zapalnego, zaburzeniami metabolicznymi i podwyższonym wskaźnikiem masy ciała (BMI) [34]. Niemniej jednak, przegląd literatury wskazuje, że nasilenie stanu zapalnego koreluje z słabszą odpowiedzią kliniczną na konwencjonalne terapie przeciwdepresyjne, a współwystępujące podłoże immunologiczne chorób zapalnych jest nie tylko czynnikiem ryzyka epizodu depresyjnego, ale jest również uważane za czynnik powodujący lekooporność i nawrót depresji [35].

W kontekście zespołu post-COVID-19 leczenie zaburzeń psychicznych, w tym depresyjnych, stało się nowym, złożonym wyzwaniem współczesnej medycyny. Wymaga ono interdyscyplinarnego podejścia terapeutycznego z uwzględnieniem wpływu przewlekłego stanu zapalnego na skuteczność leczenia przeciwdepresyjnego. Wobec rosnącej częstości zaburzeń depresyjnych i specyfiki ich leczenia w okresie postpandemicznym COVID-19 konieczne są dalsze badania naukowe w tej dziedzinie.

5. Cele pracy

Cel główny

Celem pracy doktorskiej była ocena wpływu przebytego zakażenia SARS-CoV-2 na skuteczność leczenia przeciwdepresyjnego z oceną funkcji neuropoznawczych oraz analizą wybranych parametrów zapalnych u osób z depresją.

Cele szczegółowe

1. Przegląd piśmiennictwa obejmujący wpływ pandemii COVID-19 na zdrowie psychiczne, ze szczególnym uwzględnieniem wpływu zakażenia SARS-CoV-2 na rozwój zaburzeń depresyjnych i neurokognitywnych.

2. Ocena nasilenia depresji i lęku oraz stresu związanego z pandemią COVID-19 u osób z depresją oraz w zależności od przebycia COVID-19

3. Porównanie parametrów stresu oksydacyjnego i nitrozacyjnego, szlaku kynureninowego, CRP i D-dimerów u osób z depresją i bez depresji oraz w zależności od przechorowania COVID-19

4. Ocena wpływu leczenia przeciwdepresyjnego na:
   - parametry stresu oksydacyjnego i nitrozacyjnego, szlaku kynureninowego, CRP i D-dimery
   - kliniczne objawy lęku i depresji oraz funkcje poznawcze

5. Określenie związku pomiędzy parametrami stresu oksydacyjnego i nitrozacyjnego, szlaku kynureninowego, poziomu CRP i D-dimerów, a zmiennymi klinicznymi

6. Określenie związku pomiędzy przeciwciałami SARS-CoV-2, a zmiennymi klinicznymi

6. Omówienie prac składających się na pracę doktorską

6.1 Praca przeglądowa pt. „ Depressive and Neurocognitive Disorders in the Context of the Inflammatory Background of COVID-19”

Celem pracy był przegląd literatury dostępnej w okresie grudzień 2020 – sierpień 2021 r., dotyczącej wpływu pandemii COVID-19 na zdrowie psychiczne, ze szczególnym uwzględnieniem wpływu zakażenia SARS-CoV-2 na rozwój zaburzeń depresyjnych i neurokognitywnych. W pracy przedstawiono ogólną problematykę zaburzeń depresyjnych, teorię zapalną depresji, patofizjologię infekcji SARS-CoV-2 i charakterystyczną dla niej specyfikę odpowiedzi zapalnej organizmu. Poruszono aspekt psychologiczny pandemii COVID-19 jako silnego stresora wpływającego na ujawnianie się lub nasilenie istniejących już zaburzeń psychicznych. Dodatkowo omówiono powikłania krótkoterminowe i długoterminowe COVID-19, w tym zespół post-COVID-19. Przedstawiono także rolę leczenia przeciwdepresyjnego oraz możliwe wyzwania terapeutyczne w leczeniu depresji w kontekście pandemii COVID-19. Na podstawie dostępnych badań stwierdzono, że przebycie infekcji SARS-CoV-2 oraz narażenia na czynniki stresowe związane z pandemią COVID-19 mogą predysponować do rozwoju zaburzeń psychicznych, w tym zaburzeń depresyjnych i neuropoznawczych. Zakażenie SARS-CoV-2 może wywołać przedłużający się stan zapalny organizmu, z podwyższonymi interleukinami, CRP i D-dimerami, nawet kilka miesięcy od zakażenia. Dodatkowo, może prowadzić do długotrwałych zaburzeń funkcji poznawczych, utrzymujących się nawet przez kilka miesięcy po wyzdrowieniu, oraz przyczyniać się do rozwoju demencji. Wykazano, że leczenie przeciwdepresyjne wykazuje właściwości przeciwutleniające i przeciwzapalne, a w przypadku leczenia COVID-19 również przeciwwirusowe. Jednoznaczny wpływ leczenia przeciwdepresyjnego na poprawę funkcji poznawczych pozostaje niejasny. U osób z depresją z przebytym COVID-19 wyjściowy poziom stanu zapalnego może być wyższy, a odpowiedź na leczenie przeciwdepresyjne mniej efektywna. Pandemia ujawniła potrzebę dalszych badań nad długoterminowymi skutkami COVID-19 celem wyodrębnienia pacjentów z grupy ryzyka i opracowania skuteczniejszych metod leczenia zaburzeń depresyjnych i neuropoznawczych.

6.2 Praca oryginalna pt. „ The Effect of Antidepressant Treatment on Neurocognitive Functions, Redox and Inflammatory Parameters in the Context of COVID-19”

6.2.1 Cel pracy

Celem badania była ocena wpływu leczenia przeciwdepresyjnego na poprawę w zakresie objawów klinicznych depresji, funkcji neuropoznawczych oraz parametrów biochemicznych stanu zapalnego, w tym parametrów stresu oksydacyjnego i nitrozacyjnego, szlaku kynureninowego, CRP i D-dimerów, u pacjentów z depresją, w kontekście przebytej infekcji COVID-19.

6.2.2 Materiał i metody

6.2.2.1 Grupa badana i kontrolna

Badanie zostało przeprowadzone w Klinice Psychiatrii Uniwersytetu Medycznego w Białymstoku w okresie od grudnia 2021 roku do lutego 2023 roku. Uczestnicy zostali zrekrutowani spośród pacjentów hospitalizowanych z powodu pogorszenia stanu psychicznego, z rozpoznaniem zaburzeń depresyjnych, na Oddziałach Ogólnopsychiatrycznych Samodzielnego Publicznego Psychiatrycznego Zakładu Opieki Zdrowotnej w Choroszczy oraz Kliniki Psychiatrii Uniwersytetu Medycznego w Białymstoku. Każdy uczestnik badania był dorosłym obywatelem Polski rasy kaukaskiej i wyraził świadomą zgodę na udział w badaniu. Badanie uzyskało zgodę Komisji Bioetycznej Uniwersytetu Medycznego w Białymstoku (nr APK.002.281.2021) i było prowadzone zgodnie z Deklaracją Helsińską oraz wytycznymi Dobrej Praktyki Klinicznej.

Łącznie zbadano 63 osoby, w tym 33 pacjentów z rozpoznaniem zaburzeń depresyjnych i 30 osób zdrowych, bez zaburzeń psychicznych. W grupie badanej, po weryfikacji przeciwciał IgG przeciwko białku N i domenie S-RBD wirusa SARS-CoV-2, kontakt z wirusem potwierdzono u 21 osób, natomiast w grupie kontrolnej u 23 uczestników badania. Grupy były porównywalne pod względem wieku (18-65 r.ż.) płci, statusu związku i BMI z wykluczeniem osób w ciąży, karmiących piersią, z otyłością (BMI > 30

kg/m2,) w trakcie sterydoterapii, uzależnieniem od substancji psychoaktywnych, z wywiadem poważnego urazu głowy, zaburzeń neurokognitywnych oraz z aktywną współchorobowością somatyczną o udowodnionym podłożu zapalnym.

6.2.2.2 Protokół badania

W dniu włączenia do badania wszyscy uczestnicy zostali poddani badaniu fizycznemu i psychiatrycznemu, ocenie funkcji neuropoznawczych oraz pobrano od nich materiał biologiczny do analizy (pierwszy pomiar). Rozpoznanie depresji było stawiane w oparciu o kryteria ICD i potwierdzone przez doświadczonego psychiatrę. Stosowano ustrukturyzowany kwestionariusz wywiadu (M.I.N.I.) celem wykluczenia innych potencjalnych zaburzeń psychicznych. Dane demograficzne i kliniczne zbierano przy użyciu ustrukturyzowanego kwestionariusza przygotowanego na potrzeby tego badania. Nasilenie stresu związanego z pandemią COVID-19 oceniano za pomocą polskiej wersji Skali Wpływu Zdarzeń—Revised (IES-R). Objawy depresji i lęku oceniano przy użyciu Skali Depresji Hamiltona (HAM-D), Inwentarza Depresji Becka (BDI) i Skali Lęku Hamiltona (HAM-A). Przeprowadzono również ocenę neuropsychologiczną za pomocą Testu Fluencji Słownej (VFT), Testu Powtarzania Cyfr WAIS-R (DST), Testu Łączenia Punktów (TMT) części A i B, Testu Stroopa (SCWT) oraz Kalifornijskiego Testu Uczenia się Językowego (CVLT). Uczestnicy oceniali subiektywnie ciężkość przebytego zakażenia SARS-CoV-2 w skali od 1 do 10 punktów oraz stopień upośledzenia smaku i węchu w czasie COVID-19 w trzypunktowej skali. Powtórnej procedury testowej (drugi pomiar) dokonano po 4-6 tyg od włączenia leczenia przeciwdepresyjnego u 21 osób (13 K i 8 M), w tym u 15 osób z potwierdzonym wywiadem SARS-CoV-2. Leczenie przeciwdepresyjne obejmowało leki o właściwościach modulujących głównie przekaźnictwo serotoninergiczne, a wybór leku był dokonywany przez lekarza prowadzącego na podstawie obrazu klinicznego, wcześniejszej odpowiedzi na leczenie przeciwdepresyjne oraz możliwych skutków ubocznych. Odpowiedź na lek przeciwdepresyjny mierzono jako poprawę wyników w zakresie skal HAM-D, BDI i HAM-A przed- i po- włączeniu leczenia.

6.2.2.3 Analizy biochemiczne

U wszystkich uczestników zbadano podstawowe parametry biochemiczne z krwi: morfologia, potas, sód, kreatynina, aminotransferaza alaninowa (ALT), aminotransferaza asparaginianowa (AST), hormon stymulujący tarczycę (TSH), cholesterol całkowity, lipoproteiny o niskiej gęstości (LDL), lipoproteiny o wysokiej gęstości (HDL), trójglicerydy (TGA) oraz białko C-reaktywne (CRP) i D-dimery przy użyciu wirówki MPW M-DIAGNOSTIC i analizatora Cobas Integra 400+ (Roche).

Część surowicy zamrażano w probówkach Eppendorf i przechowywano w temperaturze −80°C do dalszych badań, w tym oznaczania przeciwciał anty-SARS-CoV-2 oraz parametrów redoks. Próbki moczu pobierano ze środkowego strumienia pierwszego porannego moczu, wirowano przy 1300× g przez 10 minut w temperaturze 4°C, a następnie zbierano supernatant, zamrażano i przechowywano w probówkach Eppendorf w temperaturze −80°C do czasu analizy biochemicznej.

Zbadano przeciwciała IgG przeciwko białku nukleokapsydu (anti-N IgG) oraz domenie wiążącej receptor (RBD) podjednostki S1 białka kolca (anti-S-RBD IgG) SARS-CoV-2 za pomocą analizatora Alinity (Abbott) zgodnie z wytycznymi producenta, wykorzystując chemiluminescencyjny test immunologiczny na mikropartykułach (CMIA). Pozytywne wyniki uzyskano dla miana ≥ 1,4 dla przeciwciał anti-N IgG oraz ≥ 50 AU/mL dla przeciwciał anti-S-RBD IgG.

Zbadane parametry szlaku kynureninowego oraz stresu oksydacyjnego i nitrozacyjnego w surowicy i moczu obejmowały: kynurenina (KN), N-formylokynurenina (NFK), dityrozyna (DT), tryptofan (TRY), dysmutaza ponadtlenkowa (SOD), katalaza (CAT), peroksydaza glutationowa (GPx), zredukowany glutation (GSH), 4-hydroksynonenal (4-HNE), tlenek azotu (NO), S-nitrozotiole i nadtlenoazotyny. Wszystkie odczynniki do oznaczeń redoks zakupiono w firmie Sigma-Aldrich. Pomiarów dokonywano za pomocą czytnika mikropłytek BioTek Synergy H1 (Winooski, VT, USA). Wszystkie oznaczenia standaryzowano do 1 mg białka całkowitego.

6.2.2.4 Analiza statystyczna

Dane zaprezentowano jako liczbę przypadków z wartością procentową dla zmiennych jakościowych lub jako medianę z 1 i 3 kwartylem dla zmiennych ilościowych. Normalność danych oceniano przy pomocy testu Shapiro Wilka. Dla zmiennych o

rozkładzie normalnym do porównania między grupami zastosowano test T-studenta, dla zmiennych o rozkładzie odbiegającym od normalnego zastosowano test Manna Whitneya. Do porównania zmiennych jakościowych zastosowano test Chi2 Pearsona. Korelacje oceniono z zastosowaniem współczynnika Spearmana. Wartości $p < 0,05$ uznawano za istotne. Analizę wykonano w języku R w środowisku RStudio.

6.2.3 Wyniki

6.2.3.1 Porównanie grupy badanej i kontrolnej

6.2.3.1 .1 Parametry O&NS, szlaku kynureninowego, CRP i D-dimery

W grupie badanej przed leczeniem przeciwdepresyjnym (pierwszy pomiar) zaobserwowano istotnie wyższe stężenie surowiczego TRY w porównaniu z grupą kontrolną. Istotne różnice stwierdzono również w stężeniach surowiczych nadtlenoazotynu, TRY i DT między grupą badaną po leczeniu przeciwdepresyjnym (drugi pomiar), a grupą kontrolną: stężenie nadtlenoazotynu było niższe, a stężenia TRY i DT wyższe w grupie badanej. Nie zaobserwowano istotnych różnic między stężeniami CRP i D-dimerów przed i po leczeniu przeciwdepresyjnym w porównaniu z grupą kontrolną, jak i w kontekście przebytego COVID-19.

Natomiast, u pacjentów z depresją i przebytym COVID-19 zaobserwowano istotnie niższą aktywność GPx w surowicy oraz istotnie wyższe stężenie NO w moczu w pierwszym pomiarze, a w drugim pomiarze stwierdzono istotnie wyższe stężenia S-Nitrozotioli w surowicy. W grupie kontrolnej u osób, które przeszły COVID-19, stwierdzono istotnie wyższe stężenia NFK w moczu.

6.2.3.1.2 Skale oceniające nasilenie depresji i lęku, wyniki testów neuropsychologicznych oraz stres związany z pandemią COVID-19

W grupie badanej wyniki skal oceniających nasilenie depresji i lęku były istotnie wyższe przed i po leczeniu przeciwdepresyjnym w porównaniu z grupą kontrolną. Nie zaobserwowano istotnych różnic w wynikach IES-R między pacjentami z depresją przed leczeniem, a grupą kontrolną, a także w odniesieniu do historii COVID-19. Pacjenci z

depresją przed leczeniem uzyskali istotnie niższe wyniki w testach funkcji poznawczych (VFT, TMT części A i B, DST, SCWT i CVLT) niż grupa kontrolna. Jednak po leczeniu przeciwdepresyjnym istotnie niższe wyniki wśród pacjentów z depresją ograniczały się tylko do testu Stroop Color Word Test.

6.2.3.2 Porównanie wyników pierwszego i drugiego pomiaru (przed i po leczeniu przeciwdepresyjnym) w grupie badanej

6.2.3.2.1 Parametry O&NS, szlaku kynureninowego, CRP i D-dimery

Po leczeniu przeciwdepresyjnym zaobserwowano istotny spadek stężenia nadtlenoazotynu w surowicy oraz istotny wzrost stężenia GSH w surowicy. Nie wykryto istotnych różnic w stężeniach CRP i D-dimerów.

6.2.3.2.2 Skale oceniające nasilenie depresji i lęku oraz wyniki testów neuropsychologicznych

Po leczeniu zaobserwowano istotne zmniejszenie nasilenia depresji i lęku ocenianego za pomocą skal HAM-D, BDI i HAM-A, oraz podwyższenie wyników w poszczególnych zadaniach CVLT oceniających procesy pamięciowe (Zadanie 1, Zadanie 1–5, Lista B, Odtwarzanie swobodne po krótkim odroczeniu, Odtwarzanie z pomocą po krótkim odroczeniu, Odtwarzanie swobodne po długim odroczeniu).

6.2.3.3 Korelacje stresu oksydacyjnego, CRP i D-dimerów z poszczególnymi parametrami

Nie zaobserwowano istotnej korelacji w zakresie parametrów stresu oksydacyjnego z pierwszego pomiaru ze zmianami wyników skal HAM-D, HAM-A i BDI przed i po leczeniu przeciwdepresyjnym. Stwierdzono pozytywną korelację wartości CRP ze zmniejszeniem nasilenia depresji wg skali BDI po leczeniu przeciwdepresyjnym.
U pacjentów z depresją przed leczeniem zaobserwowano pozytywne korelacje wyników skali HAM-D z aktywnością CAT w surowicy i stężeniem S-nitrozotioli w moczu, a także pozytywne korelacje wyników BDI ze stężeniem GSH i aktywnością SOD w surowicy.

Dodatkowo, stwierdzono pozytywną korelację wyników IES-R ze stężeniem GSH w surowicy przed leczeniem w grupie badanej.

6.2.3.4 Korelacje przeciwciał SARS-CoV-2 z poszczególnymi parametrami

W grupie badanej przed i po leczeniu przeciwdepresyjnym nie stwierdzono istotnych korelacji między mianem przeciwciał SARS-CoV-2, a nasileniem depresji i lęku, zmianą wyników skal HAM-D, HAM-A, BDI oraz nasileniem ogólnych objawów podczas zakażenia SARS-CoV-2.

W grupie kontrolnej zaobserwowano istotną korelację między stężeniami przeciwciał anty-N IgG, a nasileniem zaburzeń smaku podczas zakażenia SARS-CoV-2. Obserwowana korelacja była dodatnia, co oznacza, że osoby z wyższymi stężeniami przeciwciał miały bardziej nasilone objawy podczas infekcji COVID-19.

6.2.4 Wnioski

1. Chociaż doniesienia z przeglądu literatury sugerują, że procesy zapalne towarzyszące zakażeniu SARS-CoV-2 mogą wpływać na skuteczność leczenia osób z depresją, niniejsze badanie nie potwierdza, że odpowiedź kliniczna na leczenie przeciwdepresyjne może być związana z przechorowaniem COVID-19 i wyjściowym stężeniem przeciwciał SARS-CoV-2.

2. Poziom odczuwanego stresu związanego z pandemią COVID-19 nie różnił się między osobami z depresją, a osobami bez depresji oraz w zależności od przechorowania COVID-19.

3. Przebycie COVID-19 wśród osób z depresją wiąże się z nasilonym stresem oksydacyjnym w porównaniu do grupy kontrolnej (niższa aktywność GPx i wyższe stężenie NO).

4. Leczenie przeciwdepresyjne wpływa na parametry stresu oksydacyjnego i nitrozacyjnego (wzrost stężenia GSH, spadek stężenia nadtlenoazotynu).

5. Leczenie przeciwdepresyjne wpływa na redukcję objawów depresji i poprawę funkcji poznawczych
   .
6. Nasilenie depresji koreluje z parametrami stresu oksydacyjnego i nitrozacyjnego (aktywnością CAT i SOD, stężeniem GSH, stężeniem S-nitrozotioli).

7. Dalsze badania są niezbędne do oceny wpływu przebycia COVID-19 na skuteczność terapii przeciwdepresyjnej. Ich wyniki mogą pogłębić wiedzę i świadomość wśród klinicystów, wspierać poszukiwanie nowych metod optymalizacji leczenia zaburzeń depresyjnych w okresie po pandemicznym oraz umożliwić lepszą identyfikację pacjentów z grup podwyższonego ryzyka, w tym z zespołem post-COVID-19.

7. Kopie publikacji wchodzących w skład rozprawy doktorskiej

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MDPI

Review

Depressive and Neurocognitive Disorders in the Context of the Inflammatory Background of COVID-19

Eliza Dąbrowska *, Beata Galińska-Skok and Napoleon Waszkiewicz

Department of Psychiatry, Medical University of Bialystok, pl. Brodowicza 1, 16-070 Choroszcz, Poland; beata.galinska@umb.edu.pl (B.G.-S.); napoleon.waszkiewicz@umb.edu.pl (N.W.)
* Correspondence: eliza.dabrowska@umb.edu.pl

Abstract: The dysfunctional effects of the coronavirus disease 2019 (COVID-19) infection on the nervous system are established. The manifestation of neuropsychiatric symptoms during and after infection is influenced by the neuroinvasive and neurotrophic properties of SARS-CoV-2 as well as strong inflammation characterised by a specific "cytokine storm". Research suggests that a strong immune response to a SARS-CoV-2 infection and psychological stressors related to the pandemic may cause chronic inflammatory processes in the body with elevated levels of inflammatory markers contributing to the intensification of neurodegenerative processes. It is suggested that neuroinflammation and associated central nervous system changes may significantly contribute to the etiopathogenesis of depressive disorders. In addition, symptoms after a COVID-19 infection may persist for up to several weeks after an acute infection as a post-COVID-19 syndrome. Moreover, previous knowledge indicates that among SSRI (selective serotonin reuptake inhibitor) group antidepressants, fluoxetine is a promising drug against COVID-19. In conclusion, further research, observation and broadening of the knowledge of the pathomechanism of a SARS-CoV-2 infection and the impact on potential complications are necessary. It is essential to continue research in order to assess the long-term neuropsychiatric effects in COVID-19 patients and to find new therapeutic strategies.

Keywords: COVID-19; SARS-CoV-2; neuroinflammation; depressive disorders; depression; neurocognitive disorders; post-covid; long-term; complications

Citation: Dąbrowska, E.; Galińska-Skok, B.; Waszkiewicz, N. Depressive and Neurocognitive Disorders in the Context of the Inflammatory Background of COVID-19. *Life* **2021**, *11*, 1056. https://doi.org/10.3390/life11101056

Academic Editors: Monika Talarowska, Dominik Strzelecki, Napoleon Waszkiewicz and Jan Chodkiewicz

Received: 3 September 2021
Accepted: 3 October 2021
Published: 8 October 2021

1. Introduction

At the time of writing this review, the entire world was struggling with the coronavirus disease 2019 (COVID-19) pandemic, which has affected nearly every aspect of society [1]. Despite the duration of the pandemic for many months, SARS-CoV-2 infection still hides many unknowns, especially regarding its long-term effects [2,3]. COVID-19 is an acute infectious respiratory disease caused by a novel virus named SARS-CoV-2. It is a single-stranded RNA virus with about 80% similarity to SARS-CoV from the coronavirus family [4]. The first cases of infection were reported at the turn of 2019/2020 in China. Rapid global transmission of the virus was observed with an increasing wave of infections and deaths. In March 2020, The World Health Organization (WHO) declared a COVID-19 pandemic [5]. As of 30 August 2021, the COVID-19 pandemic had over 216 million confirmed cases with 4.5 million deaths [6]. Along with the destabilisation of everyday life, negative psychological consequences of the pandemic and the emergence of mental disorders among societies have been observed [7–9]. In the course of a COVID-19 infection, in addition to typical respiratory symptoms, a dysfunctional effect of SARS-CoV-2 on other body systems, including the nervous system, has been noticed [10,11]. A range of COVID-19 neurological symptoms has been observed from mild symptoms such as a headache or dizziness to loss of taste, smell, meningitis and even necrotic encephalitis [12,13]. According to the latest scientific reports, the manifestation of neuropsychiatric symptoms during and after a COVID-19 infection is influenced by the neuroinvasive and neurotrophic

properties of SARS-CoV-2 as well as by strong inflammation in the course of the infection characterised by a specific "cytokine storm" [14–16]. Potentially life-threatening cytokine storm syndrome is characteristic of severe COVID-19 [17]. Research suggests that a strong immune response to a SARS-CoV-2 infection and psychological stressors related to the pandemic may cause chronic inflammatory processes in the body with elevated levels of inflammatory markers contributing to the intensification of neurodegenerative processes and the emergence of other psychiatric complications [18–21]. Inflammation, related changes and damages at the level of the nervous system in the course of SARS-CoV-2 have been suggested to significantly contribute to the etiopathogenesis of depressive disorders [22–24]. Furthermore, studies show that some acute viral infections can induce an abnormal immune response, affecting the manifestation of long-term neuropsychiatric consequences [25,26]. Experiences of previous viral pandemics, such as the flu of the 18th and 19th centuries, Spanish flu in the 20th century and the coronaviruses causing severe acute respiratory syndrome (SARS) in 2002 and the Middle East respiratory syndrome (MERS) in 2012, suggest a link with the manifestation of neuropsychiatric complications both during and after an acute infection [27]. Among the survivors after infection with SARS-CoV and MERS coronaviruses, there have been cases of memory, attention and concentration disturbances lasting up to 39 months after the onset of the disease [28,29]. It has been suggested that the severity of neuropsychiatric complications correlates with the severity of COVID-19. It is observed that those patients, after experiencing severe COVID-19 with respiratory symptoms, leaving intensive care units are potentially more likely to experience long-term neuropsychiatric and neurocognitive conditions such as depression, obsessive-compulsive disorder, psychosis, Parkinson's disease and Alzheimer's disease [20,30]. The consequences of SARS-CoV-2 infection on the body have a wide and serious impact and are still being investigated [31]. In this review, we focus on the problem of depressive and neurocognitive disorders in the face of COVID-19, the pathogenesis of SARS-CoV-2 infection, its long-term consequences for the body and potential therapeutic interventions, including antidepressant treatment. The studies conducted so far indicate the immunomodulatory and antiviral properties of antidepressant treatment, which may appear effective in counteracting neuropsychiatric complications after COVID-19 [32,33].

2. Materials and Methods

Articles were searched from various databases, including PubMed, Google Scholar and MEDLINE, using the following keywords: SARS-CoV-2, COVID-19, cytokine storm, inflammation, neuroinfection, neuroinflammation, depressive disorders, neurocognitive disorders, post-COVID syndrome, antidepressants. The duration for viewing potentially interesting articles was from 1 December 2020 until 18 August 2021. Selected articles concerned the issues of inflammation in the course of COVID-19 and neuropsychiatric complications after COVID-19 infection. Moreover, publications on the effect of antidepressant treatment on COVID-19 were reviewed. The conclusions were drawn up on the basis of the available literature and our own reflections.

3. Inflammatory Basis of Depression

3.1. Depression as a Global Problem

Depressive disorders are a common and serious health problem. Depression is the leading cause of disability in the world, which is a personal and socioeconomic challenge [34]. Depression affects about 5–17% of the population and is one of the most common mental disorders in the society [34]. More than 350 million people worldwide suffer from depression, and about 40–80% of them have suicidal thoughts, while 20–40% attempt suicide, of which 12–18% are successful. Each year, it is estimated that about one million people worldwide die from depression [35,36]. The prevalence of depressive disorders in the 18–29 age group is 3 times higher than that of the age of 60 and more [37]. Women suffer from depression more often than men, and incidence rates increase in women

with age. Beginning in early adolescence, the incidence rate in women is 1.5 to 3 times highthan in men [37].

3.2. *The Concept of the Inflammatory Basis of Depression*

The aetiology of depression is multifactorial, consisting of biological, genetic, psychological and environmental factors which, according to the neurodevelopmental theory, complement each other (Figure 1) [37–39]

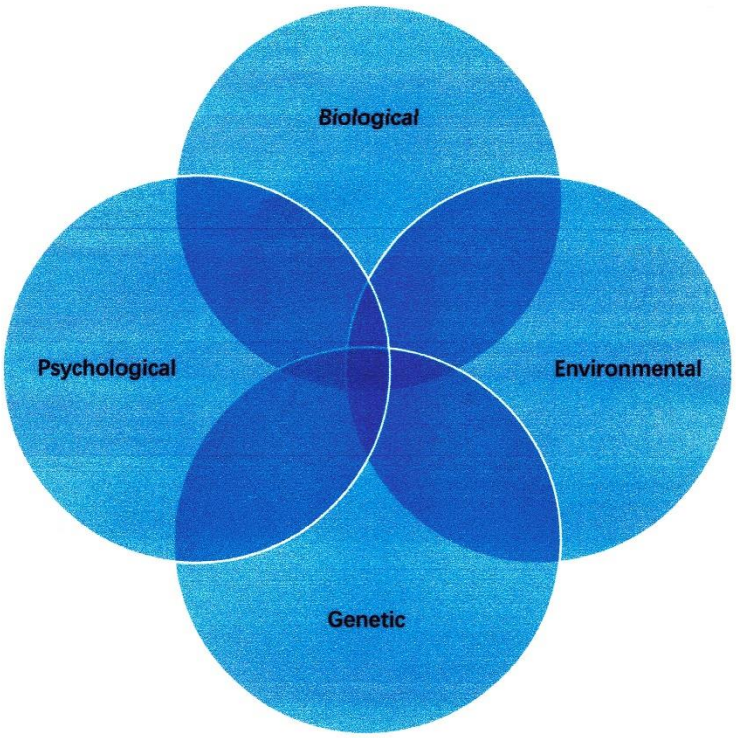

Figure 1. Multifactorial aetiology of depression.

In addition to the current main neurobiological concepts of depression—including the monoaminergic theory with brain neurotransmission dysfunction, the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis [40] and structural changes in the brain mainly in the hippocampus and frontal lobes [41,42]—the key role of inflammation in the nervous system in the development of depression is increasingly emphasised [43,44].

3.2.1. The Hypothalamic–Pituitary–Adrenal Axis (HPA) and Role of Chronic Stress

The hypothalamic–pituitary–adrenal (HPA) axis as the stress axis is adaptive in order to maintain homeostasis by the body. It plays a key role in responding to stress stimuli, both physical and mental. As a result of the activation of the HPA axis, the sympathetic nervous system is stimulated with the release of cortisol and adrenaline. In the event of a prolonged stressful situation or impaired functioning of the feedback loop, chronic stress occurs [45–47]. Chronic stress is one of the strongest inhibitors of neurogenesis, leading to a decrease in the proliferation of neuronal stem cells and the survival of new nerve cells in the dentate gyrus of the hippocampus. As a result of stress stimulation of the hypothalamic–pituitary–adrenal axis, there is an increase in the amount of glucocorticosteroids adversely affecting neurogenesis and an increase in the expression of their receptors on the hippocampus. The secretion of stress hormones is potentiated by

pro-inflammatory factors, including interleukin-1 (IL-1) [48,49]. Hypercortisolaemia with excessive autonomic activation has an adverse effect on the body, causing immunosuppression, increased blood pressure, increased cholesterol levels and the dysfunction of the production of sex hormones [45,50,51]. Moreover, the number of glucocorticosteroid receptors is lowered, and their sensitivity is reduced, which causes feedback loop disorders. In addition, the long-term activation of the HPA axis causes the influx of calcium ions to the hippocampal neurons, leading to their apoptosis. There are structural and functional changes in the hippocampus and a reduction in its volume due to the neurotoxic effect of hypercortisolaemia [45,52,53]. Recent studies show that chronic stress can lead to primary microglia activation by influencing the vessels [47,54]. As a result of chronic stress, there may also be a reduction in the level of neurotrophins and growth factors promoting neurogenesis and disturbances in the level of neurotransmitters, such as Gamma-aminobutyric acid (GABA), serotonin, glutamate, dopamine and noradrenaline, which are important in maintaining mental well-being [48]. Changes in the brain caused by a reaction to long-term or severe stress may appear with memory and learning difficulties as well as affecting the manifestation of affective disorders and depression [35,41,43]. In terms of pathophysiology, depressive disorders resemble chronic stress [55]. In the group of people with depression, an increased concentration of corticotropin releasing factor (CRF) in the cerebrospinal fluid and an increase in the secretion of the hypothalamic neurohormone arginine vasopressin (AVP) were both observed [56]. This is associated with an impaired pituitary response to stimulation by CRF as a result of receptor down-regulation for CRF of the anterior pituitary lobe. One study evaluating the pituitary response to CRF stimulation in women with/without an episode of major depression and/or with a history of sexual abuse with assessment of CRF and AVP concentrations in CSF showed nearly 60% variability in the ACTH response to CRF stimulation [56].

3.2.2. Neuroinflammation and Brain Changes in Depression

In patients with depression, the presence of inflammation and activation of the immune system both in the periphery and in the central nervous system is found [57]. There is a diminished T-lymphocyte profiling response and over-activation of the non-specific inflammatory response and the acute-phase inflammatory response mechanisms [58]. There is an increase in oxidative stress and lipid peroxidation and a decrease in the activity of antioxidant enzymes, with an increase in the production of reactive oxygen species [59,60]. The results of the studies indicate the presence of elevated levels of acute phase proteins, including C-reactive protein (CRP), haptoglobin, α1-antitrypsin (A1AT) and Alpha-1-acid glycoprotein (AGP), in some depressed people (who do not develop the inflammatory process of a known aetiology) [61]. Studies also indicate the presence of inflammatory mediators such as prostaglandin E (PGE2), a pro-inflammatory nitric oxide-NO molecule [62–64]. In addition, prolonged and severe depressive states may be accompanied by increased plasma levels of pro-inflammatory cytokines IL-1, IL-2, a soluble IL-2 receptor (sIL-2R), tumour necrosis factor α (TNF-α), IL-8, IL-18 and interferon- γ (IFN-γ) and a decrease in acute phase protein concentrations of albumin and transferrin as well as IL-10 and IL-12 [61,65,66]. Inflammatory cytokines have the ability to penetrate the blood–brain barrier and activate microglia, which in turn increases the activity of the enzyme indoleamine-2,3-dioxygenase (IDO), which catabolises tryptophan to kynurenine (KYN) [22,67,68]. The serotonergic transmission is disturbed, and kynurenine, due to its neurotoxic properties, leads to the processes of neurodegeneration of the frontal lobes, hippocampus and amygdala [44,69,70]. The alteration of the kynurenine pathway with the dysregulation of the HPA axis leads to an increase in extracellular glutamate levels and the neurotransmission of glutamate, affecting the neurogenesis of the hippocampus [45,48,71]. It is suggested that this pathophysiological cascade is triggered or sustained and enhanced by chronic inflammation with increased levels of circulating inflammatory markers that are capable of activating microglia and exacerbating inflammation in the nervous system and in consequence leading to the possible disclosure of depressive disorders [34,45,72]. Furthermore,

there are studies indicating that the severity of neuroinflammation in the prefrontal cortex, anterior cingulate cortex and insula is associated with the severity of a depressive episode by assessing the expression of translocation protein 18 kDa (TSPO) in positron emission tomography (PET) study [73–75]. TSPO is considered a specific biomarker of brain inflammation, particularly due to its high expression in brain immune cells, including activated microglia and stimulated astrocytes, and it can be quantified in PET [73,75]. In addition, Richards et al. show a correlation of IL-5 levels in cerebrospinal fluid, with TSPO binding on PET scan in areas of the subcallosal prefrontal cortex (sgPFC) and anterior cingulate cortex, proving an inflammatory background of depression [73].

4. Inflammation in a SARS-CoV-2 Infection

4.1. The Renin–Angiotensin–Aldosterone System and the Role of ACE2

The renin–angiotensin–aldosterone system (RAS) plays an important role in the pathophysiology of a SARS-CoV-2 infection [76]. RAS is responsible for the regulation of the circulating blood volume in the body and the concentration of potassium and sodium ions in body fluids [77]. Furthermore, it is also involved in the pathogenesis of many diseases, such as hypertension, cardiac hypertrophy and fibrosis, atherosclerosis, diabetic micro- and macroangiopathy and inflamed and fibrotic kidneys, as well as in immune disorders [78,79]. The decrease in renal blood flow causes the secretion of renin, which converts angiotensinogen to angiotensin 1 (Ang1), which is then converted by angiotensin-converting enzyme (ACE) to angiotensin 2 (Ang2). The effect of an excessive amount of angiotensin 2 is an increase in vasoconstriction and vascular permeability, activation of cellular pathways and the release of proinflammatory factors including prostaglandins, vascular endothelial growth factor (VEGF), nuclear factor kappa B (NF-κB), TNF-α, interleukin-1β (IL-1β), IL-6 and IFNγ. The SARS-CoV-2 virus enters the cell by binding the S-spike virus to angiotensin-converting enzyme 2 (ACE2) as a specific receptor in the form of a transmembrane protein. ACE2 is widely expressed on the surface of many organ cells, especially in the lungs and intestine, as well as in the cardiovascular system, kidneys, adipose tissue and central nervous system. That is why we observe a range of symptoms in the course of COVID-19, from the symptoms typical of the respiratory and digestive system, to thrombotic events, kidney failure and a number of neuropsychiatric symptoms [80,81]. The appropriate level of ACE2 is necessary for the proper maintenance of homeostasis in cells. ACE2 is responsible for the conversion of angiotensin 2 to angiotensin (Ang) (1–7), which by binding to the Mas receptor (MasR) and angiotensin AT2 receptors (AT2R) produces the opposite effect to angiotensin 2. The ACE2/Ang1–7/MasR axis causes vasorelaxation and suppresses inflammation, oxidative stress, apoptosis, fibrosis and coagulation. Blocking ACE2 by SARS-CoV-2 and down-regulating ACE2 expression leads to the accumulation of angiotensin 2 in the cytoplasm of cells, with a predominance of the pressor arm of the renin–angiotensin system (RAS) [82,83].

4.2. Pathophysiology of SARS-CoV-2 Infection

SARS-CoV-2 first infects alveolar epithelial cells, replicates and then induces cell death via a pyrocytosis mechanism causing the release of damage-associated molecular structures (DAMPs) and pathogen-associated molecular patterns (PAMPs) that are recognised by receptors (Toll-like receptors-TLR-s) of neighbouring epithelial cells, endothelial cells and macrophages [84,85] (Figure 2). The activation of the innate and adaptive inflammatory response occurs with inflammatory responses (NF-κB, IL1-β, IL-18 activation) and pro-inflammatory secretion. There is a release of inflammatory cytokines and chemokines typical of T-helper-1 (Th-1), such as IL-6, IFNγ, interferon gamma-induced protein 10 (IP-10) and the chemokine ligand 2 (CCL2), which then attracts and activates monocytes, macrophages and T cells with the aggravation of inflammation at the site of infection. Furthermore, there is an overproduction of TNF-α, IL-2, IL-7, granulocyte colony-stimulating factor (G-CSF) and macrophage inflammatory protein 1α (MIP1α) [18,86,87]. Moreover, there is an increase in T-helper-2 (Th-2) cytokines, including interleukin-1 receptor an-

tagonist (IL-1RA), IL4 and IL-10, with anti-inflammatory effects [86,88–90]. IL-6 has a pleiotropic effect and is involved in immune regulation and inflammatory response by inducing various acute phase proteins, such as CRP, SAA, fibrinogen, antitrypsin, hepcidin and complement components that worsen the inflammatory reactions and activate the coagulation pathway leading to coagulation disorders [91–93]. When there is inadequate, uncontrolled over-release of cytokines (especially IL-6, IL-1β, TNF-α), a specific "cytokine storm" may occur, with the spread of systemic cytokines and chemokines causing inflammation with over the activation of neutrophils and organ damage leading to multiple organ dysfunction/failure characteristic of high mortality [84,94].

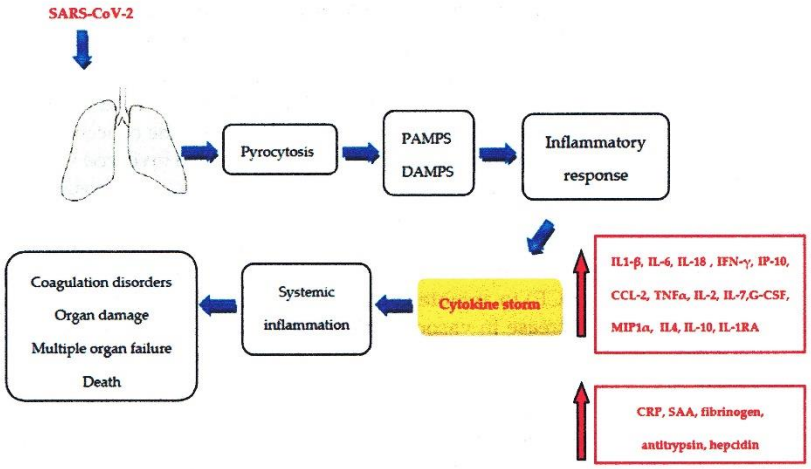

Figure 2. Pathophysiology of SARS-CoV-2 infection. SARS-CoV-2 first infects alveolar epithelial cells, replicates and then induces cell death via a pyrocytosis mechanism causing the release of damage-associated molecular structures (DAMPs) and pathogen-associated molecular patterns (PAMPs) that are recognised by receptors (Toll-like receptors-TLR-s) of neighbouring epithelial cells, endothelial cells and macrophages. The activation of the innate and adaptive inflammatory response results in the release of inflammatory cytokines and chemokines, including IL1-β, IL-6, IL-18, IFN-γ, IP-10, CCL-2, TNF-α, IL -2, IL-7, G-CSF and MIP1α, in addition to IL4, IL-10 and IL-1RA with anti-inflammatory properties. In addition, the level of CRP, SAA, fibrinogen, antitrypsin, hepcidin and complement components that worsen inflammatory reactions and activate the coagulation pathway leading to coagulation disorders increases. As a result of a cytokine storm, systemic inflammation occurs and, as a consequence, organ damage and failure can lead to death. Abbreviations: IL1-β, interleukin 1 beta; IL-6, interleukin 6; IL-18, interleukin 18; IFN-γ, interferon gamma; IP-10, interferon gamma-induced protein 10; CCL-2, the chemokine ligand 2; TNF-α, tumour necrosis factor alpha; IL-2, interleukin 2; IL-7, interleukin 7; G-CSF, granulocyte colony-stimulating factor; MIP1α, macrophage inflammatory protein 1α; IL4, interleukin 4; IL-10, interleukin 10; IL-1RA, interleukin-1 receptor antagonist; CRP, C-reactive protein; SAA, serum amyloid A.

4.3. Laboratory Findings

The severity of COVID-19 is correlated with a high level of interleukins IL-6 and IL-1 and with CRP, D-dimers, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), lactate dehydrogenase (LDH), creatinine, low albumin, high erythrocyte sedimentation rate (ESR), low eosinophils, thrombocytopenia and lymphopenia [95,96]. Elevated LDH levels are associated with cell damage. In approximately 80% of patients, lymphopenia and an increased ratio of neutrophils to lymphocytes are observed [16,18,97,98]. Mahat et al. in their review and meta-analysis concluded that in patients with severe COVID-19, serum levels of CRP, ESR, PCT (procalcitonin), IL-6, IL-10, IL-2R, ferritin, SAA (serum amyloid A) and NLR (neutrophil-to-lymphocyte ratio) are

significantly increased compared with people with a mild COVID-19. Moreover, they showed increased levels of CRP, PCT, IL-6, ferritin and NLR in non-survivors compared with survivors [99]. Elevated levels of interleukin 6 are characteristic of COVID-19 patients with poor outcomes and are one of the best laboratory indicators of respiratory failure and death. [100,101] IL-6 is considered to be the most significant cytokine in COVID-19, and its increased concentration was also detected in the course of SARS and MERS [102,103]. Elevated serum amyloid A (SAA) levels and disturbances in other biochemical parameters relevant to the development of Alzheimer's disease have been reported among SARS-CoV-2-positive individuals [99,104,105] (Figure 3). Moreover, the presence of antiphospholipid autoantibodies, which contribute to coagulopathy and ischemic changes in the brain, was observed among COVID-19 patients [24,84,106,107].

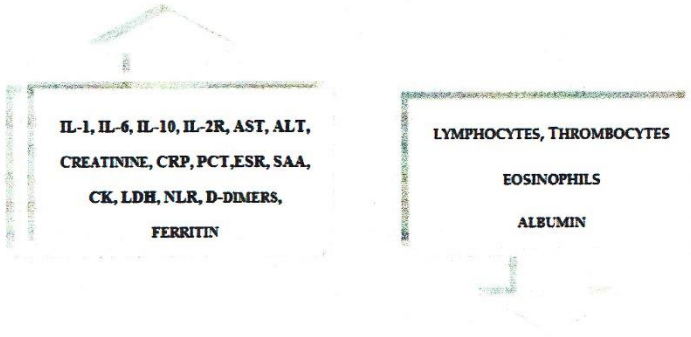

Figure 3. Changes in laboratory parameters in a SARS-CoV-2 infection. COVID-19 infection may be manifested by elevated levels of interleukins (IL-1, IL-6, IL10, IL-2R) and other inflammatory markers (CRP, PCT, ESR, ferritin, SAA) and by liver (AST, ALT) and kidney (creatinine) parameters, as well as by CK, LDH, NLR, D-dimers, correlating with inflammation and decreased levels of lymphocytes, thrombocytes, eosinophils and albumin, depending on the course of infection. Abbreviations: IL-1, interleukin-1; IL-6, interleukin-6; IL-10, interleukin-10; IL-2R, the interleukin-2 receptor; CRP, C-reactive protein; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; SAA, serum amyloid A; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio.

4.4. The Specificity of Inflammation in COVID-19

SARS-CoV-2 virus induces heterogeneous immune responses [108]. Some have a lack of or mild immune system response, others develop a strong immune response with a cytokine storm and multi-organ damage, including damage to the brain [86,96,109]. The autoimmune response can be induced by a "molecular mimicry" mechanism, whereby autoimmune cells cross-react with autoantigens [15,110,111]. Research suggests that acute SARS-CoV-2 infection causes a subclinical damage accumulation that predisposes to chronic pro-inflammatory disease and may impair the ability to take full advantage of a strong immune system response to infection or trauma. Infected cells persist for up to 6 weeks from the onset of symptoms, and inflammation may persist for weeks after infection has stopped, suggesting an inadequate, excessive inflammatory response from COVID-19, contributing to multiple organ failure [112]. In response to many stressors, such as oxidative stress, metabolic derangement, altered proteostasis, genome instability, macromolecular damage and many others, cell senescence accumulates, which is involved in the pathogenesis of sustained inflammation of the organism [18]. There is a hypothesis that SARS-CoV-2 may influence cellular ageing by causing excessive oxidative stress, DNA damage and metabolic derangement, as well as resulting in a direct effect of viral infection on tissue damage with activation of inflammation [18]. Additionally, overlapping bacterial infections can exhaust the immune response, with physiological dysregulation contributing to immunoageing [18]. As a result of SARS-CoV-2 infection, innate and adap-

tive immunity may be exhausted. A hallmark of cellular ageing is the release into the blood of senescence-associated secretory phenotype (SASP) factors, such as cytokines and chemokines, which sustain inflammation [113]. Persistent systemic inflammation due to tissue damage, environmental stressors and psychological and social stresses all influence the risk of developing many chronic diseases, including autoimmune diseases, depression, neurodegenerative disorders, accelerated cognitive decline and dementia [107,114].

4.4.1. Neuroinflammation in COVID-19

The immune system constantly communicates with the brain and spinal cord. Even in the absence of damage to the blood–brain barrier, the T- and B-lymphocytes effectors can penetrate the CNS to destroy pathogens [86,109,115,116]. Neuroinflammation is common in various CNS disease states and is characterised by microglia activation accompanied by leukocyte infiltration [117]. Microglia is highly sensitive to changes in peripheral metabolism and comorbidities as well as to external environmental influences, such as stress, diet, physical activity and environmental pollution [107,118]. Glial cells function as resident cells of the innate immune system response to clearing pathogens and damaged brain tissue, and astrocytes play a role in regulating microcirculation in the brain and regulating extracellular glutamate levels [119]. Astrocytes and microglial cells are responsible for maintaining homeostasis, including neurogenesis, synaptic formation, blood–brain barrier control, capture of reactive oxygen species, neurotransmitter uptake, ion transport and blood flow regulation [107,120,121]. Inflammation may have neurogenesis-regulating properties depending on duration and activity of microglia, astrocytes and macrophages. Proteins CD 47, CD 55 and CD 200 as well as interleukin 4 and 10 secreted by stimulated microglia have proneurogenic properties [122]. However, long-term inflammation, through the activation of microglia, increases the concentration of interleukins IL-6, IL-1β and IL-1α and TNF that are unfavourable for neurogenesis [48,123]. As a result of SARS-CoV-2 infection, brain cells, including neurons, oligodendrocytes and glial cells, may lose their physiological functions, leading to a disturbance of homeostasis in the brain. Even after a SARS-CoV-2 infection has ceased, microglia may remain excited indirectly through epigenetic changes [107,124]. Microglial dysfunction, including disorders of neuronal plasticity, synaptic function, myelination and the blood–brain barrier (BBB) maintenance, can severely impair cognitive function, which may have consequences in the short-term and long-term neuropsychiatric consequences of COVID-19 [125]. It is concluded that disturbances at the cellular and molecular level of microglia and other brain cells, along with the accompanying pandemic stress and anxiety, may contribute to the disclosure of mental disorders, including depressive disorders, psychosis and cognitive disorders such as Alzheimer's disease, Parkinson's disease and dementia [20,30,107].

4.4.2. Routes of Infection

There are several routes of infection of the nervous system with SARS-CoV-2. The SARS-CoV-2 virus can infect directly by binding to the ACE2 receptor on endothelial [126], nerve and glial cells [127–130]. In addition, it can penetrate the central nervous system (CNS) through transnasal and transsynaptic invasions [131,132] to the olfactory bulb and then the brainstem, where it can damage the respiratory centres [107,132].

4.4.3. The Effects of Neuroinflammation

As a result of systemic inflammation, circulating cytokines and chemokines can damage the blood–brain barrier and then the brain parenchyma, leading to neuroinflammation with haemorrhage, leukocyte infiltration and neurodegeneration [19,20]. In severe COVID cases, an increase in blood proinflammatory factors such as a "cytokine storm" results in an effect on the CNS and the manifestation of neuropsychiatric symptoms. [23,28,90,133,134]. Nervous system damage manifests itself through the neurological symptoms of COVID-19, such as acute ischemic stroke, meningitis, encephalopathy and Guillain-Barre syndrome as well as psychiatric disorders, including depressive disorders, delirium and

psychosis [12,13,30,135]. A number of neuropsychiatric symptoms are observed in the course of COVID-19, and research also shows the occurrence of neurological and psychiatric complications after the time of infection [136]. The studies conducted so far show the occurrence of symptoms of disturbances of consciousness and deterioration of mental state in approximately 20–30% of patients with severe COVID-19 using neuroimaging with MRI [96,137]. Moreover, in one-third of patients with acute/subacute COVID-19 referred for brain imaging, the results showed hypodense/hyperintense areas on MRI/CT and other abnormalities, such as haemorrhagic lesions, including infarcts [138]. In the study by Coolen et al. postmortem magnetic resonance imaging (MRI) results in non-survivor COVID-19 patients showed in approximately 20% olfactory bulb asymmetry and brain parenchyma abnormalities, including micro- and macro-bleeding and oedema changes [139]. An autopsy study of 21 patients with fatal COVID-19 also revealed extensive inflammation in multiple organs, with no SARS-CoV-2 present in any affected organs. In the examined brain tissue, extensive neutrophilic infiltrates with aggregates of NETs (neutrophil extracellular traps) and platelets were found, without the presence of a virus. The mainly affected areas included the olfactory bulb and medulla oblongata, which explains the symptoms of anosmia and the possible increase in hypoxia with respiratory failure during the disease [112].

5. The COVID-19 Pandemic as a Psychological Stress Factor

The global transmission of the SARS-CoV-2 virus, the lack of reliable information and disinformation fuelled by sensational headlines in the media heightened fears and social phobias [8,9,140]. A state of nationwide quarantine and additional restrictions were introduced, limiting interpersonal contacts and movement [7,141]. There was fear of uncertainty about the course of COVID-19 disease, the timing of the vaccine, the health service's ability to fight COVID-19 and government procedures to stop the virus from spreading. In addition, there was a strong stigmatisation of people infected with COVID-19 who unknowingly transmitted the infection to other people, observing symptoms of acute stress disorder, self-destructive behaviour and suicide among them [142,143]. There was widespread anxiety and other psychological problems, including the stigmatisation of people infected with the coronavirus in society, especially among medical staff [144,145]. A survey of 2200 Americans, at a time when the number of confirmed COVID-19 cases in the US was 5, with no fatalities, found that 37% of those polled were worried and concerned about the new SARS-CoV-2 virus, and 25% were more concerned in connection with the COVID-19 pandemic than the Ebola outbreak in 2004 [7]. With the exception of the immediate threat of COVID-19, the psychological impact of the pandemic was observed on the mental health of the general population, including tendencies to closely observe the functioning of the body—analysing cough, shortness of breath and constantly monitoring body temperature—and the appearance of mental disorders with a state of anxiety and panic and obsessive-compulsive disorders in connection with justified recommendations for washing and disinfecting hands [146–148]. Psychotic exacerbations or even psychosis have been reported among previously mentally unstable people who succumbed to disinformation during the pandemic [149,150]. The impact of strong anxiety accompanying the pandemic on the aggravation of the pre-existing or the emergence of new mental disorders was observed in susceptible people, deprived of natural defence mechanisms due to the lack of social support and suffering from other mental and somatic disorders and previous traumas, without access to reliable information [142,151–153]. Nonetheless, psychiatric disorders are a risk with severe COVID-19. A systematic review of studies, including 43,938 COVID-19 patients with comorbid psychiatric disorders, found that the presence of any psychiatric disorder (especially psychotic disorders and mood disorders) and exposure to anti-anxiety and antipsychotic medications were associated with an increased risk of hospitalisation and a higher risk of COVID-19 mortality. This association also applied, to a lesser extent, to intellectual disability, developmental disorders and substance use disorders, but not to anxiety disorders [154].

Furthermore, the impact of the COVID-19 pandemic and its associated social restrictions has been observed in the progression of cognitive impairment in people with dementia and in the exacerbation of neuropsychiatric symptoms in people with chronic neurological diseases [155]. One study examining the effects of quarantine in patients with Alzheimer's disease (AD), frontotemporal dementia (FTD), vascular dementia (VD) and dementia with Lewy bodies (DLB) found that approximately 60% of patients experienced changes in behavioural and psychological symptoms (BPSD) after one month of isolation, including worsening of previous symptoms (51.9%) or emergence of new symptoms (26%). The most commonly reported symptoms that worsened were irritability, agitation, apathy, depression, anxiety and sleep disturbances. Depending on the type of dementia, severity of prevalence and gender of patients, differences in the trend of reported symptoms were observed. Symptoms of anxiety and depression were more typical for the female gender, patients with AD and mild to moderate disease course. In addition, DLB was associated with a higher risk of increased sleep disturbances and hallucinations as well as FTD with changes in appetite [156]. Another cross-sectional case-control study to quantify anxiety in Parkinson's disease (PD) patients in relation to social distance restrictions compared with the general population showed the highest levels of anxiety in the PD group [157]. It is suggested that anxiety in PD patients is strongly correlated with the risk of a COVID-19 infection, the availability of the drug in a blockade situation and the perceived higher risk of disease due to chronic comorbidity [157]. In addition, a COVID-19 infection may contribute to the progression of neurodegenerative diseases, such as amyotrophic lateral sclerosis, by exacerbating inflammation, and the progression of the disease state may negatively affect patients' psychological status. [158]. Outbreaks of pandemics were invariably associated with panic states and a sense of threat to individual safety due to high mortality. Widespread health effects of the pandemic have been reported, including anxiety, insomnia, increased alcohol consumption and loss of energy [159]. Studies on the observed psychological reactions of society during previous pandemics suggest that the response to stress may be influenced by individually diverse factors, such as individual intolerance to uncertainty, perception of one's own susceptibility to illness and tendency to anxiety [142,160]. One study found that the "vulnerable group" (quarantined or relatives or suspected/ill persons) experienced depressive symptoms more frequently during the SARS pandemic compared with the "non-exposed group". Other studies have found that more than 40% of people who developed SARS experienced symptoms of post-traumatic stress disorder (PTSD) at some point during the pandemic. The respondents who were isolated worked in places with a high risk of SARS infection—e.g., individuals in infectious wards or relatives of patients who experienced contact with SARS were 2–3 times more predisposed to developing severe PTSD symptoms compared with people not exposed to the virus [161]. The above studies and the psychological impact of previous pandemics demonstrate the possible impact of the larger global COVID-19 pandemic on the increase in the incidence of PTSD in the population [162–164].

6. Depressive and Neurocognitive Disorders during a COVID-19 Pandemic

The outbreak of a pandemic and rapid changes in almost every aspect of life, social isolation, quarantines and uncertainty about the future can be treated as strong stressors dysfunctionally affecting mental health [165,166]. Studies have shown that COVID-19 patients are at high risk of stress and feelings of stigma [167,168] and are more likely than the general population to suffer from a variety of mental disorders, including depression, anxiety disorders, acute stress disorder, post-traumatic symptoms and insomnia [26,169]. An analysis of COVID-19 patients showed that 1 in 3 presented executive dysfunction and problems with attention and orientation, and areas of hypoperfusion were observed in brain imaging studies [170]. A study of survivors of COVID-19 conducted in Wuhan 6 months after recovery showed symptoms of depression among 23% of patients (367 out of 1617) [171]. One of the prospective studies concerned patients with SARS-CoV-2 admitted to the non-intensive ward, who during hospitalisation showed symptoms of

depression in 29% of the patients, while 2 weeks after discharge, in 20% of the patients, symptoms of depression were still observed. This may indicate a relatively stable severity of depression in the subjects shortly after being infected with COVID-19 [172]. Moreover, one of the studies showed that approximately 1 month after infection 31–38% of patients reported symptoms of depression [173]. Another prospective study assessing the mental state and the level of inflammatory markers in COVID-19 survivors one month and three months after discharge from the hospital showed a relationship between inflammation after COVID-19 and depression and related neurocognitive disorders. The 3-month follow-up cohort showed disorders in at least one psychopathological sphere in 35.8% of respondents. Moreover, there was a tendency to intensify depressive symptoms, especially in people with a previous history of mental disorders and in the females, as well as an association of acute infection with the manifestation of neurocognitive disorders including motor coordination and executive dysfunctions in up to 78% of the respondents. With observation, symptoms of depression persisted in contrast with symptoms of anxiety, PTSD and sleep disorders, which improved over time [19]. COVID-19 may develop prolonged inflammation, predisposing to persistent depression and related neurocognitive disorders [18,20,22,24,174]. It is associated with the SARS-CoV-2 infection itself inducing a specific inflammatory response with possible long-term elevated levels of inflammatory markers [18,19,175,176]. In a study from Ireland, approximately 25.3% of 150 patients with COVID-19 had elevated D-dimers 4 months after diagnosis, which was more common in patients requiring hospitalisation and those who were over 50 years of age [177]. A previous study of COVID-19 survivors indicates a relationship between cognitive dysfunction in maintaining attention and underlying inflammation as measured by CRP [125]. Moreover, the baseline level of SI (II) systemic immune inflammation associated with the level of lymphocytes, neutrophils and platelets was found to be related to the severity of depression symptoms and the prediction of neurocognitive impairments [19,178]. In a study by Zhou et al., higher levels of SI (II), which can be considered a marker of the low-grade inflammation observed in a mood disorder [23], have been associated with a major depressive disorder [179]. In one meta-analysis presenting results mainly from China, up to 45% of COVID-19 patients were shown to experience depression, with no gender differences found. However, other studies show that women, people with a severe history of COVID-19, those with elevated markers of inflammation, people with infected family members and patients with an earlier psychiatric diagnosis are in the risk group of developing depressive disorders [178,180].

Post-COVID Syndrome

Symptoms following COVID-19 infection may persist for up to several weeks after an acute infection. Patients with symptoms that persist more than 3 weeks after diagnosis are said to have post-COVID syndrome [181,182]. The syndrome has been suggested to result from prolonged inflammation following a SARS-CoV-2 infection, although the pathogenesis is still under investigation and is not entirely clear. Characteristic symptoms of this syndrome include dyspnoea, chest pain, myalgia, fatigue, and taste and smell disturbances, as well as mental status disorders (Figure 4) [176,183,184].

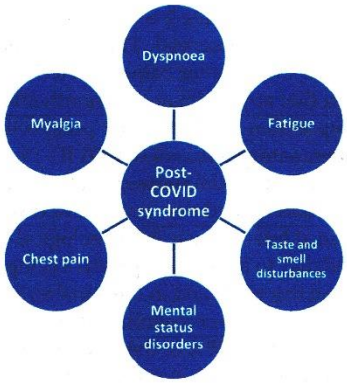

Figure 4. Symptoms of Post-COVID syndrome.

One study identified the top three symptoms of post-COVID syndrome, which included fatigue, cognitive dysfunction and general malaise [185]. The prospective observational study of patients hospitalised with COVID-19 showed that 4 months after discharge, 51% (244 of 478) had at least one symptom that was not present before the illness, including (31%) reported fatigue, (21%) cognitive symptoms and dyspnoea [184]. In non-hospitalised patients after COVID-19, without comorbidities, it is estimated that 10% to 35% may present with symptoms of post-COVID syndrome [183,186,187], and in hospitalised patients with severe COVID-19, the incidence is up to 80% [182,188,189]. An Italian study of 238 patients hospitalised with severe COVID-19, 4 months after discharge, showed prolonged pulmonary dysfunction in 53.8%, which may account for many post-COVID symptoms [190]. It seems important to follow up on patients, especially in the area of cognitive function, where neurological and cerebrovascular complications were observed during the course of the disease [19,191–193]. Direct infection of endothelial cells by SARS-CoV-2 as well as general inflammation contribute to coagulopathy and embolic/thrombotic complications, microcirculatory disorders affecting hypoxia and other symptoms in post-COVID syndrome [136,182,193]. Neurological and cerebrovascular complications are characteristic, although they are less common and may be implicated in the development of Alzheimer's disease [194]. In addition, it was indicated that in all patients after COVID-19, compared with controls, protein markers of neuronal dysfunction such as amyloid beta, total tau and p-T181, neurogranin and neurofilament light protein were increased in neuron-enriched extracellular vesicles (nEV), indicating an association with neuroinflammation and neurodegeneration [195]. Furthermore, the genetic risk factor of Alzheimer's disease (ApoE4) has been shown to increase the risk of severe COVID-19 infection, but it is still unclear [196]. It has been reported that 23 of 27 patients with Parkinson's disease and COVID-99 developed post-COVID syndrome, deterioration of motor function, increased fatigability and increased need for levodopa, as well as sleep and cognitive dysfunction [197]. In one prospective UK study, at least 4 weeks after recovery from acute COVID-19 infection, MRI in more than 70% of patients showed dysfunction in at least one organ, indicating a physiological basis for the infection and possible long-term impairment of body organs [198]. Organ failure was related to heart (systolic dysfunction, myocarditis), liver (hepatomegaly, inflammation, ectopic fat), lung (decreased vital capacity), kidney (inflammation), pancreas (inflammation, ectopic fat) and spleen (splenomegaly). Furthermore, of the incidental more severe structural MRI lesions (n = 56), three were cardiac lesions, and one was renal (hydronephrosis) [198]. Brain MRI findings of a 56-year-old previously healthy patient with neurological symptoms and depression almost 6 months after a COVID-19 infection showed multiple hyperintense areas in the white matter and semi left centres, indicating neurodegeneration and micro-vascular damage [199]. One study of plasma from patients after COVID-19 at 1–3 months found elevated levels of IL-4, which may indicate ongoing neuroinflammation [195]. Another study of 12 patients with neurological complications

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presenting with post-COVID-19 symptoms between 9 and 12 weeks post-onset found an acute inflammatory phase with significantly elevated inflammatory parameters including C-reactive protein CRP and IL-6 levels [30]. Elevated inflammatory markers may, by impairing the blood–brain barrier, contribute to neuropsychiatric complications including neurocognitive complications through alterations in neurotransmission, including gamma-aminobutyric acid (GABA) [200]. Previous studies have shown in animal models that inflammation with elevated IL-6 levels can decrease GABA receptor density [200]. Furthermore, compared with healthy individuals, evidence of altered neuronal function, neuromotor fatigue, impaired cognitive control, executive dysfunction and apathy was found in patients with post-COVID syndrome [201]. Mental status disorders, including depressive disorders, may affect 26% to 40% of patients even up to 6 months after the onset of symptoms [171,174]. In addition, based on two cases of patients with depression after COVID-19, an association between depression and interleukins, including IL-6, was demonstrated independent of other factors, which may justify the administration of cytokine-reducing drugs to prevent depression after COVID-19 [175]. Moreover, 8 patients with neurological symptoms, compared with 16 without neurological symptoms, had higher levels of anti-SARS-CoV-2 antibodies with an increase in IL-6 [176].

7. Antidepressant Treatment and COVID-19

Depression is associated with low-grade chronic inflammation and is comparable with a chronic cold [44,202]. Patients with chronic inflammatory processes and autoimmune diseases are more prone to depression [43,54,60]. In addition, the assessment of the concentrations of small molecules—metabolites that are products of changes taking place in the body—allows indirect conclusions to be made about the disturbances of specific metabolic pathways [34,203]. The antidepressant treatment used in depressive disorders has antioxidant and anti-inflammatory properties, resulting in a reduction in inflammatory cytokines including CRP and IL-6, [204], with an increase in the concentration of anti-inflammatory cytokines [205,206]. This is supported by neuroimaging studies using PET, showing less neuroinflammation in treated depressed patients compared with untreated patients, which may suggest the normalisation of TSPO expression in the brain and inhibition of microglia activity as a result of antidepressant treatment [73,207]. One study demonstrated a significant effect of antidepressant treatment as well as its duration on the total volume distribution of TSPO in patients with a history of major depressive disorder. In patients untreated for major depressive disorder for 10 years or more, TSPO volume distribution was up to 33% greater in the anterior cingulate cortex, prefrontal cortex and insula compared with participants untreated 9 years or less [208]. It is expected that, in people with a history of COVID-19, the concentration of inflammatory parameters may be higher and the response to antidepressant treatment less effective due to the possible prolonged, abnormal inflammation, with lesions at the level of the nervous system following SARS-CoV-2 infection. Differences in cytokine concentrations in patients may predict disease or resistance to treatment. Based on the current medical knowledge, it is suggested that a history of a SARS-CoV-2 infection may have a significant impact on the reduction in neurocognitive functions [19,125,174,194]. Due to its anti-inflammatory properties, antidepressant treatment may reduce the inflammatory parameters [209,210]. However, the use of antidepressants to improve neurocognitive impairment is questionable. There are studies indicating the progression of cognitive dysfunction after the inclusion of antidepressants [211,212]. Previous knowledge indicates that, among the selective serotonin reuptake inhibitors (SSRIs) group antidepressants, fluoxetine is a promising drug against COVID-19 through its effect on reducing the secretion of inflammatory cytokines/chemokines (IL-6,CCL-2,TNF-α) and immunomodulatory properties [32,209,210]. In addition, fluoxetine exhibits antiviral activity and is effective against SARS-CoV-2 in cell cultures [32]. This indicates the possible alleviation of neuropsychiatric complications after COVID-19 by fluoxetine use [32]. Such a potent inhibitory effect in both pseudovirus and authentic virus assay has also been described for vortioxetine [213].

8. Discussion

In this review, we present the current knowledge regarding the possible manifestation of depressive and neurocognitive disorders due to the inflammatory background of COVID-19. The experience of previous pandemics, including SARS-CoV, MERS, influenza of the 18th and 19th centuries and Spanish flu in the 20th century, indicates that there is an impact on the development of mental disorders with cognitive deterioration even months after the onset of the disease [18,214]. Studies of convalescents after infection with SARS-CoV and MERS coronaviruses indicate that up to 15% of respondents reported memory, attention and concentration disorders lasting from 6 weeks to 39 months from the onset of the disease [28,29].

Increasingly more studies confirm the hypothesis that inflammation caused by SARS-CoV-2 infection may, in the short term [11,19,178] and long term [2,215], have negative health consequences [182,199,216], including in the field of mental health disorders [18,148,169]. Patients who are severely affected by COVID-19 with respiratory symptoms leaving intensive care units are potentially more likely to experience long-term neuropsychiatric and neurocognitive conditions, such as depression, obsessive-compulsive disorder, psychosis and Parkinson's and Alzheimer's disease [20,30]. Studies show the correlation of inflammation with the severity of complications of post-COVID-19 syndrome, including neuropsychiatric disorders [20,30]. Studies of convalescents one month and 3 months after discharge from the hospital indicate an increase in the incidence of psychiatric disorders, including depressive disorders and a deterioration of cognitive functions [28,30,105,217]. In addition, stress during a pandemic, associated with a change in life in almost every aspect, fear of illness, death and other psychosocial factors [7,49,165], can activate the stress axis [46], affect the severity of inflammation in the brain and, consequently, its structural and functional changes [55,65,71,218]. Research confirms that females, the healthcare professionals, elderly individuals, children, college students and psychiatric patients are in the group at increased risk of developing depressive disorders during the COVID-19 pandemic [151,219–223].

An increasing number of studies of COVID-19 survivors show elevated inflammatory markers, including interleukins and CRP, indicating persistent inflammation in the body months after infection [30,175,176,184]. An interesting study found elevated parameters of D-dimers and fibrin products that may be increased during ongoing inflammation and which were observed 6 months after infection with COVID-19 [177]. In addition, observed multisystem inflammatory syndrome in children and adolescents (MIS-C) infection with elevated levels of immunoglobulins, C-reactive protein, ferritin and interleukin-6 indicate possible 4-week post-viral immunisation in the body [224]. Moreover, several cases of adults with MIS-A (multisystem inflammatory syndrome in adults), characterised by a wide spectrum of gastrointestinal, cardiovascular, dermatologic and neurologic symptoms, have been described [225]. As a result of excessive, uncontrolled inflammatory response, immune system dysfunction, including autoimmunity, may occur [18,111]. The presence of antiphospholipid antibodies has been demonstrated in patients with COVID-19, which indicates possible autoimmunity and subsequent attack of the body's own cells and a number of other complications, including a tendency to thrombosis [106,107].

The analysis of COVID-19 patients showed that every one-third of them presented with executive dysfunction with attention and orientation problems, and areas of hypoperfusion were observed in brain imaging studies [170]. There is evidence that brain hypoperfusion may accelerate amyloid-β (Aβ) accumulation, the pathology of the tau and TDP-43 proteins involved in the development of dementia [105,194]. The white matter of the brain is also very sensitive to ischemia in COVID-19, which affects cognition [194].

The SARS-CoV-2 virus enters the cell by binding ACE2, which is widely expressed on the surface of glial cells, nerve cells and endothelial cells [107]. That is why we observe a number of neuropsychiatric symptoms [12,13,137,150]. Moreover, microglia may remain in an activated state even after cessation of the infection, causing neurotransmission disorders and structural changes in the brain affecting the manifestation of neurocognitive

and depressive disorders over time [47,118,120,124,218,226,227]. Although some studies do not indicate the presence of virus in the brain in autopsy studies, the existing neuroinflammation may be the result of a strong systemic inflammatory response damaging the blood–brain barrier [112].

It has been suggested that the COVID-19-related cause of death may be induced by a specific "cytokine storm" with an elevated level of cytokines, (especially IL-1 and IL-6, systemic inflammatory response syndrome—SIRS) leading to multiple organ failure with high mortality [14–16,84,86,93]. Recent publications have shown that ACE2 expression is higher in males, which is associated with greater susceptibility to SARS-CoV-2 infection compared with females, which also explains the higher male morbidity and mortality rates [83]. The administration of interleukin 1 and 6 inhibitors in seriously ill COVID-19 patients with respiratory failure and hyperinflammation causes a significant reduction in mortality in patients with IL-1 inhibition. Interleukin 6 inhibition was effective in patients with high levels of CRP, and inhibitions of both IL-1 and IL-6 were effective in patients with low levels of lactate dehydrogenase (LDH) [228].

There are reports of improvement in post-COVID-19 symptoms due to a vaccine that may improve the immune response or reverse autoimmunity [182,229]. In addition, scientific evidence suggests the efficacy of antidepressant treatment having antiviral and anti-inflammatory properties, especially from the SSRI group of drugs, including fluoxetine [32,209,210,213].

Current evidence suggests that symptoms in post-COVID syndrome improve over time and patients show a good prognosis without further sequelae [230]. However, the duration and long-term effects of post-COVID syndrome are unknown and still need further study [31]. It seems important to observe patients, especially in terms of cognitive functions, in whom neurological and cerebrovascular complications were observed during the disease [138,231,232]. There is still insufficient research to establish the exact relationship between the long-term consequences of COVID-19 and the inflammation it causes [18,19,24,84,233].

9. Conclusions

It is increasingly known that, during SARS-CoV-2 infection and after recovery, patients are more likely to develop psychiatric disorders, including depressive and neurocognitive disorders. Further research is required to expand the knowledge on the impact of SARS-CoV-2 infection on the intensification or disclosure of depressive disorders and neurocognitive disorders. Research will broaden our understanding of the possible long-term neuropsychiatric consequences of a COVID-19 infection. At the same time, the studies will help to identify risk groups in terms of difficulties in treating mood disorders, as well as helping to develop potential new therapeutic methods in the future. In addition, the results of the research may increase public awareness of the serious impact of the COVID-19 pandemic on mental health, while paying attention to the need to prevent depression as a serious, potentially life-threatening disease entity. Moreover, it is predicted that, in the coming months and even years, numerous post-COVID-19 patients will seek medical attention from specialists due to complications and symptoms of post-COVID syndrome. It is important to clarify the pathogenesis of SARS-CoV-2 infection and its consequences in the body, including post-COVID-19 syndrome, and to identify markers and targeted therapy. New guidelines are needed for the diagnosis and treatment of this new clinical entity.

10. Limitations

The review did not address the aspect of the manifestation of depressive disorders during COVID-19 in specific age groups, including young adults and the elderly as well as patients with pre-existing inflammatory process. Due to the growing number of studies, only the individual and subjectively most significant results were presented to substantiate the association of inflammation after COVID-19 infection with the manifestation of

neurocognitive and depressive disorders. No clear-cut, definite theories of the effect of SARS-CoV-2 on long-term complications exist and, therefore, time for observation, research and further analysis is needed.

Author Contributions: E.D.: Conceptualisation, resources, methodology, writing original draft, review and editing; B.G.-S.: Supervision and review; N.W.: Supervision and review. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the Medical University of Bialystok, grant number SUB/1/DN/21/001/1147. The financial sponsor played no role in the design, execution, analysis or interpretation of the data.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing not applicable.

Conflicts of Interest: There are no conflicts of interest to declare.

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The Effect of Antidepressant Treatment on Neurocognitive Functions, Redox and Inflammatory Parameters in the Context of COVID-19

Eliza Samaryn [1,*], Beata Galińska-Skok [1], Aleksander Nobis [1], Daniel Zalewski [1], Mateusz Maciejczyk [2], Monika Gudowska-Sawczuk [3], Barbara Mroczko [3,4], Anna Zalewska [5] and Napoleon Waszkiewicz [1]

1 Department of Psychiatry, Medical University of Bialystok, 15-272 Bialystok, Poland; *daniel.zalewski@sd.umb.edu.pl (D.Z.)*
2 Department of Hygiene, Epidemiology, and Ergonomics, Medical University of Bialystok, 15-022 Bialystok, Poland
3 Department of Biochemical Diagnostics, Medical University of Bialystok, 15-269 Bialystok, Poland
4 Department of Neurodegeneration Diagnostics, Medical University of Bialystok, 15-269 Bialystok, Poland
5 Department of Restorative Dentistry, Medical University of Bialystok, 15-276 Bialystok, Poland
* Correspondence: eliza.samaryn@sd.umb.edu.pl

Abstract: Inflammation is an important component of the etiopathology of depression that uses oxidative and nitrosative stress (O&NS) and elevated inflammatory markers. SARS-CoV-2 infection is also associated with abnormal inflammatory processes, which may impair effective treatment of depression in COVID-19 survivors. In the presented study, thirty-three hospitalized patients with major depressive disorder (MDD) were started on antidepressant treatment, and twenty-one were re-evaluated after 4–6 weeks. The control group consisted of thirty healthy volunteers. All participants underwent neuropsychiatric evaluation, biochemical blood and urine analyses. The results of the research demonstrated positive correlations of the Hamilton Depression Rating Scale (HAM-D) scores with serum catalase (CAT) and urinary S-Nitrosothiols levels, and the Beck Depression Inventory (BDI) scores with serum reduced glutathione (GSH) and superoxide dismutase (SOD) levels. Depressed patients with a history of COVID-19 prior to the treatment had higher urinary nitric oxide (NO) levels and lower serum glutathione peroxidase (GPx) levels. In the control group, COVID-19 survivors had higher levels of urinary N-formylkynurenine (NFK). Our results suggest that the antidepressant treatment has a modulating effect on O&NS, reduces depressive symptoms and improves cognitive functions The present study does not indicate that clinical response to antidepressant treatment is associated with COVID-19 history and baseline SARS-CoV-2 antibody levels. Nevertheless, further research in this area is needed to systematize antidepressant treatment in COVID-19 survivors.

Keywords: antidepressant treatment; antidepressants; COVID-19; SARS-CoV-2; SARS-CoV-2 antibodies; depression; oxidative stress; inflammation; neurocognitive functions; CRP; D-dimers

Citation: Samaryn, E.; Galińska-Skok, B.; Nobis, A.; Zalewski, D.; Maciejczyk, M.; Gudowska-Sawczuk, M.; Mroczko, B.; Zalewska, A.; Waszkiewicz, N. The Effect of Antidepressant Treatment on Neurocognitive Functions, Redox and Inflammatory Parameters in the Context of COVID-19. *J. Clin. Med.* **2023**, *12*, 7049. https://doi.org/10.3390/jcm12227049

Academic Editor: Mauro Giovanni Carta

Received: 25 September 2023
Revised: 8 November 2023
Accepted: 9 November 2023
Published: 12 November 2023

1. Introduction

The global COVID-19 pandemic has affected society in multiple ways. In particular, it has impacted mental health through exposure to prolonged stress, anxiety and a sense of uncertainty [1,2]. It has been proven that stressful life events may cause vulnerability to depression [3]. Since the outbreak of the COVID-19 pandemic, there has been a significant increase in the prevalence of affective disorders including depression and anxiety alongside other mental disorders [4].

Currently, depressive disorder is the most common potentially life-threatening mental disorder, and a leading cause of disability [5]. Research indicates that an estimated 3.8% of the world population suffers from depression, including 5% of adults, roughly twice as many women as men [6]. The etiology of depression results from a complex

interaction between genetic, social, psychological and biological factors [7]. The following factors are all indicated to have a significant impact on the development and severity of depression: dysregulation of the hypothalamic–pituitary–adrenal axis, neurotransmission disorders including serotonin, chronic inflammation with increased inflammatory cytokines, O&NS, mitochondrial dysfunction and decreased levels of brain-derived neurotrophic factor (BDNF) [8–13].

Available data indicate that SARS-CoV-2 infection can exacerbate the symptoms of depression and even stimulate the development of this disorder. It is related to the direct pathomechanism of SARS-CoV-2 infection and coronavirus neurotropism and the indirect immune response simultaneously. It can lead to a generalized inflammatory "cytokine storm", blood–brain barrier damage, glial activation and consequent neuroinflammation with structural brain changes [14–16]. As a result of pro-inflammatory cytokines, the COVID-19 infection is accompanied by an increased activation of the kynurenine pathway and production of reactive oxygen species (ROS), which leads to oxidative damage [15,17]. A study conducted by Ahmed et al. demonstrated that O&NS contributes to the etiology and severity of COVID-19 infection. The levels of individual reactive oxygen and nitrogen species in serum, including peroxynitrite, were significantly higher in patients with COVID-19 than in healthy subjects [18]. In another study conducted on COVID-19 subjects with severe symptoms, postmortem examination revealed decreased levels of glutathione, which is the main antioxidant in all tissues. Reduced levels of this enzyme in neurons may lead to neuronal cell death [19]. In a meta-analysis, Ceban et al. showed that about one-third of individuals experienced persistent fatigue, and more than one-fifth of individuals suffered from cognitive impairment 12 or more weeks after COVID-19 diagnosis. Moreover, elevated proinflammatory markers, including elevated D-dimer levels, were also found in a subgroup of post-COVID individuals [20]. COVID-19 infection in depressed patients may exacerbate the body´s inflammation, leading to increased cognitive dysfunction and risk of developing neurodegenerative disorders [21,22].

There are studies that demonstrate several beneficial effects of antidepressants such as a reduction in inflammation, a reduction of pro-inflammatory cytokines and oxidative stress activity as well as improvements in neurocognitive functions [23–26]. Antidepressant treatment can attenuate the intensity of depression through the modulation of inflammatory pathways, brain structure transformation and synaptic plasticity [27]. It has been shown that many antidepressants reduce microglia activation and are effective in modulating the immune response [28,29]. There is growing preclinical and clinical evidence for the antioxidant effects of antidepressants. However, their mechanism of action has not been fully understood [30–33]. The research on animal models indicates that antidepressants reduce the markers of oxidative stress in the brain, the liver and peripheral tissues, and also modulate antioxidant barrier activity including SOD, CAT and GSH. The antioxidant effect has been shown to be dose-, length- and treatment-regimen-dependent [33]. Caruso et al. demonstrated that long-term treatment combined with the antidepressants fluoxetine or vortioxetine can prevent the oxidative stress associated with the depressive phenotype and memory impairment in a non-transgenic animal model of Alzheimer's disease [34]. Moreover, vortioxetine has been developed to treat cognitive dysfunctions [35]. It has been observed that antidepressants, including selective serotonin reuptake inhibitors, can mitigate the cytokine storm in COVID-19 patients [36]. Studies indicate that the drugs mentioned above may constitute a promising adjunctive treatment for COVID-19 infection [37–39] and reduce the risk of death and hospitalization in COVID-19 patients [36]. Furthermore, antidepressants in COVID-19 survivors can positively affect their mood and improve cognitive functions [20]. Nevertheless, a chronic exposure to increased inflammation may impair or diminish the effectiveness of antidepressants. It is worth mentioning that patients with high inflammation demonstrated a poor response to conventional antidepressant therapies. Studies show that a comorbid immune background of inflammatory diseases is not only a risk factor for a depressive episode but is also considered a factor in

drug resistance and recurrence of depression [40]. Therefore, the treatment of depression poses a new therapeutic challenge in the context of the COVID-19 pandemic.

The present study evaluated the effect of antidepressant treatment on the clinical and biochemical aspects of depression including changes in redox and inflammatory parameters. Moreover, another objective of the study was to examine the influence of the history of SARS-CoV-2 infection on the therapeutic effect of depression treatment, neurocognitive functions and analysis of selected inflammatory parameters.

2. Materials and Methods

This study was conducted at the Department of Psychiatry of the Medical University of Bialystok. The study participants were recruited among the patients hospitalized in the General Psychiatric Wards of the Independent Public Psychiatric Health Care Center in Choroszcz and the Department of Psychiatry at the Medical University of Bialystok. The recruitment process began in December of 2021 and was completed in February of 2023. The study was approved by the Ethics Committee of the Medical University of Bialystok (permission: APK.002.281.2021) and was carried out in accordance with the Helsinki Declaration and the Guidelines for Good Clinical Practice.

2.1. Study Design and Participants

Each participant of the study was an adult Polish citizen of the Caucasian race and presented informed consent to participate in the study. The study and control groups were selected symmetrically in terms of age (18–65 years old) and gender. Exclusion criteria included pregnancy or breastfeeding, neurocognitive diseases, serious head trauma with a history of subsequent cognitive impairment, obesity (BMI > 30 kg/m^2), steroid therapy, addiction to psychoactive substances including alcohol and active somatic comorbidity with a proven inflammatory basis. On the day of inclusion in the experiment, all study participants were physically and psychiatrically examined with the assessment of neurocognitive functions. Biological material was collected from them for analysis (the 1st measurement), and blood basic biochemical parameters were examined to assess the general health. The severity of stress associated with the COVID-19 pandemic was assessed by using a Polish version of the Impact of Event Scale—Revised (IES-R) and a self-administered questionnaire considering the respondent´s demographics. The Hamilton Depression Rating Scale (HAM-D), the Beck Depression Inventory (BDI) and the Hamilton Anxiety Rating Scale (HAM-A) were used to assess symptoms of depression and anxiety. A neuropsychological assessment was performed using the Verbal Fluency Test (VFT), WAIS-R Digit Span Test (DST), Trail Making Test (TMT) Parts A and B, Stroop Color Word Test (SCWT) and the California Verbal Learning Test (CVLT). In hospitalized patients with depression who were started on antidepressant treatment, the testing procedure (psychiatric examination with the assessment of neurocognitive functions and collection of biological material) was repeated after 4–6 weeks (the 2nd measurement).

The study group consisted of patients with a diagnosis of unipolar depression who qualified for hospitalization and treatment due to clinical deterioration. To exclude psychiatric comorbidities, the M.I.N.I. questionnaire was used (Mini International Neuropsychiatric Interview). The diagnosis of depression was performed according to ICD-11 and SCID-1 criteria and confirmed by an experienced psychiatrist (B.G.-S.). Initially, 37 participants were recruited into the study group; however, 4 of them had to be excluded from the study due to not meeting the inclusion and exclusion criteria (BMI > 30 kg/m^2). Finally, 33 patients (women = 20, men = 13, mean age = 40.7) were included in the study group, among whom 15 participants confirmed a positive history of COVID-19 and a symptomatic course of the disease. The mean time between COVID-19 infection and study examination was 15 months. After conducting the verification by testing IgG anti-protein N and IgG anti-protein S-RBD antibodies to the SARS-CoV-2 virus, past contact with the virus was confirmed in 21 subjects. Participants subjectively rated the severity of SARS-CoV-2 infection on a scale of 1 to 10 points. In addition, they graded taste and olfactory impairment

during COVID-19 using a three-point scale: 0 points—unchanged, 1 point—weakened, 2 points—loss, 3 points—altered.

Twenty-one patients, among them 13 women and 8 men, (including 15 with a confirmed history of SARS-CoV-2) were re-evaluated after a period of the antidepressant treatment with serotonergic transmitter modulating properties. The drug was chosen by the treating physician based on the clinical picture, previous response to treatment and possible side effects. The antidepressant treatment was initiated at the start of hospitalization and included selective serotonin reuptake inhibitors (SSRIs) (escitalopram $n = 1$, fluoxetine $n = 1$, sertraline $n = 3$), serotonin and norepinephrine reuptake inhibitors (SNRIs) (duloxetine $n = 7$, venlafaxine $n = 3$), amitriptyline ($n = 1$), vortioxetine ($n = 1$), mirtazapine ($n = 1$) and combination therapy of duloxetine + bupropion ($n = 3$). Drug dosages were used according to individual clinical response and tolerance to treatment. Escitalopram dosing was started at 5 mg per day and increased to a maximum of 10 mg per day. Fluoxetine dosing was started at 10 mg per day and increased to a maximum of 40 mg per day. Sertraline dosing was started at 25 mg per day and increased to a maximum of 100 mg per day. Duloxetine dosing was started at 30 mg and increased to a maximum of 90 mg per day. The dose of bupropion in combination treatment with duloxetine was up to a maximum of 300 mg per day. Venlafaxine dosing was started at 75 mg per day and increased to a maximum of 225 mg per day. Amitriptyline dosing was started at 25 mg and increased to a maximum of 150 mg per day. Mirtazapine dosing was started at 10 mg and increased to a maximum dose of 45 mg per day. Lastly, vortioxetine dosing was started at 5 mg and increased to a maximum dose of 10 mg per day (Table 1). The response to the antidepressant treatment was measured as improvements in scores on the HAM-D, BDI and HAM-A scales before and after the treatment.

Table 1. The antidepressant treatment used during the study.

Antidepressant Treatment	*n*	%	Maximum Dose (mg)
Escitalopram	1	3.0	10
Fluoxetine	1	3.0	40
Sertraline	3	9.1	100
Duloxetine	7	21.2	90
Venlafaxine	3	9.1	225
Amitriptyline	1	3.0	150
Vortioxetine	1	3.0	10
Mirtazapine	1	3.0	45
Duloxetine + bupropion	3	9.1	60 + 150

The control group consisted of 30 healthy volunteers (women = 20, men = 10, mean age = 42.5) with no former history of psychiatric disorders who met the inclusion and exclusion criteria. The M.I.N.I. (Mini International Neuropsychiatric Interview) questionnaire was used to identify the control group. The mean time between COVID-19 infection and examination was 9.2 months. Among these individuals, 21 out of 30 confirmed a positive history of COVID-19, but after a verification of antibodies to SARS-CoV-2, contact with the virus was found in 23 study participants.

2.2. Blood and Urine Collection

The biological material tested consisted of 10 mL of blood and 10–15 mL of urine. Venous blood was collected from each fasting participant in the morning by qualified staff using sterile disposable equipment. In the next step, a fraction of the collected material was analyzed for basic biochemical parameters (complete blood count, potassium, sodium, creatinine, alanine transaminase, aspartate transaminase, C-reactive protein, thyroid-stimulating hormone, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides and D-dimers) using an MPW M-DIAGNOSTIC centrifuge and a Cobas Integra 400+ analyzer (Roche, Basel, Switzerland).

Subsequently, the rest of the serum was frozen in Eppendorf tubes (Eppendorf, Germany, Hamburg) and stored at −80 °C for other assays including anti-SARS-CoV-2 antibodies (anti-N IgG and anti-S-RBD IgG) and redox parameters.

Urine samples were collected from the midstream of the first-morning urine and centrifuged at 1300× *g* for 10 min at 4 °C. (MPW 351, MPW Med. Instruments, Warsaw, Poland). Subsequently, the supernatant was collected, frozen and stored in Eppendorf tubes at −80 °C until biochemical analysis was performed.

2.3. C-Reactive Protein and D-Dimer Assays

The method used to determine C-reactive protein (CRP) and D-dimer parameters was the immunoturbidimetric method.

2.4. SARS-CoV-2 Antibody Assays

IgG antibodies to the nucleocapsid protein (anti-N IgG) and the receptor-binding domain (RBD) of the S1 subunit of the spike protein (anti-S-RBD IgG) of SARS-CoV-2 were measured on an Alinity analyzer (Abbott, Chicago, IL, USA) according to the manufacturer's guidelines using a chemiluminescent microparticle immunoassay (CMIA). The measurements for anti-N IgG antibodies, titers $\geq$ 1.4 and for anti-S-RBD IgG antibodies $\geq$ 50 AU/mL were positive.

2.5. Redox Assays

The parameters determined in serum and urine were the following: kynurenine (KN), N-formylkynurenine (NFK), dityrosine (DT), tryptophan (TRY), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH), 4-hydroxynonenal (4-HNE), nitric oxide (NO), S-Nitrosothiols and peroxynitrite.

All reagents for redox assays were purchased from the company Sigma-Aldrich (Nümbrecht, Germany/Saint Louis, MO, USA). Antioxidant enzymes were detected in serum and urine. A BioTek Synergy H1 96-well microplate reader (Winooski, VT, USA) was used to measure absorbance and/or fluorescence. Determinations were carried out in duplicate samples and normalized to 1 mg of total protein. Total protein content was determined colorimetrically using the bicinchoninic acid (BCA) method (Thermo Scientific PIERCE BCA Protein Assay (Rockford, IL, USA)). Bovine serum albumin (BSA) was used as a standard.

2.6. Protein Glycoxidation Products

The content of KN, NFK, DT and TRY were assessed fluorometrically, measuring fluorescence at 365/480, 325/434, 330/415 and 295/340 nm, respectively. Following this, urine and serum samples were diluted in 0.1 M H_2SO_4 (1:5, *v*/*v*) directly before determination. Later, the results were normalized to the fluorescence of 0.1 mg/mL quinine sulfate (in 0.1 M H_2SO_4) and expressed in arbitrary fluorescence units (AFU)/mg protein [41].

2.7. Antioxidant Assays

Cu-Zn superoxide dismutase (SOD) activity in serum and urine was assessed spectrophotometrically at 480 nm, measuring the rate of inhibition of epinephrine oxidation. One unit of SOD activity was defined as the amount of enzyme that inhibits 50% of the epinephrine oxidation [42].

Serum and urine catalase (CAT) activity was determined spectrophotometrically at 240 nm by assessing the distribution of hydrogen peroxide (H_2O_2). One unit of CAT activity was described as the amount of enzyme catalyzing the breakdown of 1 mM H_2O_2 per min [43].

Serum glutathione peroxidase (GPx) activity was assessed spectrophotometrically at 340 nm, based on the reduction reaction of organic peroxides by GPx in the presence of decreased nicotinamide adenine dinucleotide phosphate (NADPH) [44].

Reduced glutathione (GSH) concentration was measured by a colorimetric method developed by Ellman using 5,5-dithio-bis-(2-nitrobenzoic acid) DTNB, whereas the absorbance was measured at 412 nm [45].

2.8. Oxidative and Nitrosative Stress Markers

The end product of oxidation 4-Hydroxynonenal (4-HNE) was determined using a colorimetric lipid peroxidation assay. For that purpose, a methasulfonic-acid-based medium at 586 nm was used [46].

The levels of total nitric oxide (NO), peroxynitrite and S-Nitrosothiols in serum and urine were measured spectrophotometrically at 490, 320 and 490 nm, respectively. Total NO was determined using sulfanilamide and N-(1-naphthyl)-ethylenediamine dihydrochloride (NEDA·2 HCl). Peroxynitrite concentration in serum and urine was assessed by peroxynitrite-mediated nitration, resulting in the formation of nitrophenol. The level of S-nitrosothiols in serum and urine was determined by the reaction of Griess reagent with Cu^{2+} ions [47,48].

2.9. Statistical Analysis

The data were presented as a number of cases with a certain percentage for the qualitative data and a median with an interquartile range for the quantitative data. The normality of data distribution was assessed using the Shapiro–Wilk test. Differences in quantitative variables between groups were assessed using the Mann–Whitney test for variables with non-normal distribution and the *t*-test for data with normal distribution. The Wilcoxon–Mann–Whitney test was used in paired comparisons. The differences in qualitative variable distributions were assessed using the Chi-square test. The Spearman's rank correlation coefficient was employed to evaluate the correlations. The analyses were performed using the R programming language in the RStudio environment (R 3.3.0+). The p values < 0.05 were considered significant for the study.

3. Results

3.1. Demographics

The study and control groups were compatible in terms of age, gender, relationship status and BMI, but the depressed subjects were more prone to be smokers and had lower education levels. The study group consisted of 33 patients with depression, including 21 with a positive history of COVID-19. After the antidepressant treatment of 4–6 weeks, a reassessment was performed on 21 patients, 15 of whom had a history of COVID-19. Twelve patients did not undergo the second examination due to various reasons (faster discharge, lack of cooperation or contact, discontinuation of the study). The control group consisted of 30 patients, 23 of whom had been infected with COVID-19 in the past (Table 2). Due to the small number of smokers in control group (n = 3), we conducted a statistical analysis only for the patients. The application of the Mann–Whitney test did not reveal significant differences between smoking and non-smoking patients in O&NS and kynurenine pathway parameters, CRP and D-dimers.

Table 2. Demographic and clinical characteristics of all subjects.

	Controls (n = 30)	MDD Patients (n = 33)	p-Value	Treatment Response Evaluation (n = 21)
Demographic Information				
Age (median, Q1–Q3)	42 (34.5–54)	44 (26–55)	0.746	43 (21–50)
BMI (median, Q1–Q3)	23.8 (21.7–26.4)	24.7 (21.2–27.5)	0.449	24.2 (20.8–26.9)
Sex (% female)	66.60%	60.60%	0.8126	61.90%
Education (%)				
6–9 years	0 (0.0)	4 (12.1)		2 (9.5)
10–14 years	7 (23.3)	25 (75.8)	<0.001	16 (76.2)
>15 years	23 (76.7)	4 (12.1)		3 (14.3)
Relationship status (%)				
Single	8 (26.7)	16 (48.4)	0.126	13 (61.9)
In a relationship	22 (73.3)	17 (51.5)		8 (38.1)
Smoking status (%smokers)	3 (10)	15 (45.4)	0.003	8 (38.1)
Clinical Information				
COVID-19 confirmed history (%)	23 (76.6)	21(63.6)	0.395	15 (71.4)
Severity of symptoms	4 (2.25–5.78)	2 (0–5)	0.248	2 (0–5)
Taste disorders (%)	*15 (50)*	*8 (24.2)*	*0.1894*	*6 (28.5)*
Smell disorders (%)	16 (53.3)	7 (21.2)	0.4005	6 (28.5)
Episodes (%)				
1	0	6 (18.1)	<0.0001	6 (28.5)
2 or more	0	27 (81.8)		15 (71.5)
Hamilton Depression Rating Scale (HAM-D) median (Q1–Q3)	0 (0–0)	22 (18–27)	<0.001	5 (3–10)
Beck Depression Inventory (BDI) median (Q1–Q3)	4 (1–6.75)	29 (21–41)	<0.001	11 (6–22)
Hamilton Anxiety Rating Scale (HAM-A) median (Q1–Q3)	0 (0–0)	22 (14–26)	<0.001	4 (1.5–9.5)
Impact of Event Scale—Revised (IES-R) median (Q1–Q3)	19.5 (7–30.2)	22.5 (12.2–48.5)	0.2156	23 (14–18)

3.2. Comparison between Study and Control Groups

3.2.1. O&NS and Kynurenine Pathway Parameters, CRP and D-Dimers

Significantly increased concentration of TRY was observed in the study group before treatment compared to the control group. Moreover, a significant difference was observed in serum peroxynitrite, TRY and DT concentrations between the study group at the second measurement and the controls. Peroxynitrite concentrations were significantly lower, while DT and TRY were characterized by higher concentrations in the study group after undergoing the antidepressant treatment (Table 3).

There were no significant differences in the study group between the concentrations of CRP and D-dimers in measurements before and after the treatment and the controls (Table 3). Furthermore, no significant differences were observed in relation to COVID-19 between the study group in the first measurement and the control group.

Table 3. O&NS and kynurenine pathway parameters, CRP, D-dimers in study and control groups.

Serum/Urine	Variable	Control Group (n = 30)			Pre-Treatment Group (n = 33)			p *	Post-Treatment Group (n = 21)			p **
		Median	Q1	Q3	Median	Q1	Q3		Median	Q1	Q3	
Serum	CAT, nmol H_2O_2/min/mg protein	1.55	1.26	1.74	1.39	1.06	1.76	0.561	1.54	1.43	1.72	0.563
	DT, AFU/mg protein	11.1	8.05	12.5	11.8	10.3	13.6	0.095	12.6	10.6	14.6	0.02
	GSH, µg/mg protein	1.02	0.894	1.13	0.892	0.818	1.05	0.054	1.09	0.932	1.14	0.438
	4-HNE, umol/mg protein	6.21	5.7	6.43	6.22	5.82	6.55	0.77	5.94	5.06	6.47	0.447
	KN, AFU/mg protein	15	9.23	18.1	16.3	11.5	18.9	0.299	16	14.5	17.8	0.306
	NFK, AFU/mg protein	8.6	5.51	11.8	10.8	7.95	11.9	0.149	9.43	8.68	11.7	0.283
	NO, nmol/mg protein	5.37	2.2	15.7	7.19	1.13	19.6	0.453	10.4	2.95	23.3	0.547
	Peroxynitrite, nmol/mg protein	30.1	18.8	40.5	24.7	16.7	41.6	0.522	12.9	11.9	15.1	0.000
	GPx, mU/mg protein	1.43	1.34	1.55	1.49	1.4	1.55	0.189	1.47	1.38	1.5	0.572
	S-Nitrosothiols, nmol/mg protein	3.51	3.12	3.93	3.54	3.28	3.94	0.373	3.47	3.11	3.75	0.915
	SOD, mL/mg protein	0.287	0.211	0.359	0.288	0.22	0.349	0.778	0.193	0.041	0.365	0.106
	TRY, AFU/mg protein	137	108	158	160	145	170	0.008	158	139	171	0.026
Urine	CAT, nmol/H_2O_2/min/mg protein	0.881	0.746	1.27	0.94	0.766	1.46	0.416	0.975	0.851	1.22	0.337
	DT, AFU/mg protein	48.2	29.7	65.6	50.9	34.8	76.4	0.69	57.1	40.8	77.2	0.302
	GSH, µg/mg protein	1.21	0.914	1.6	1.27	1.13	1.84	0.215	1.44	1.16	1.72	0.059
	4-HNE, umol/mg protein	5.02	3.79	7.04	5.31	3.69	8.88	0.79	5.36	4.17	7.17	0.711
	KN, AFU/mg protein	37	30.7	47.4	43.1	33.9	53	0.431	46.4	35.8	61.6	0.073
	NFK, AFU/mg protein	17.4	11.4	24.7	18.3	12.2	29.7	0.647	22.6	15.3	32.5	0.179
	NO, nmol/mg protein	2.64	1.42	3.96	2.38	1.07	3.21	0.516	2.39	1.27	3.59	0.628
	Peroxynitrite, nmol/mg protein	7.49	5.73	9.06	7.46	6.32	11.8	0.431	7.47	6.64	9.96	0.827
	GPx, mU/mg protein	1.37	0.973	1.96	1.51	0.988	2.38	0.599	1.4	1.18	2.1	0.628
	S-Nitrosothiols, nmol/mg protein	4.84	3.98	6.34	5.68	4.75	6.81	0.072	5.57	4.94	6.25	0.049
	SOD, mL/mg protein	0.119	0.074	0.253	0.209	0.098	0.338	0.205	0.225	0.134	0.401	0.051
	TRY, AFU/mg protein	5.81	4.01	8.41	6.63	4.93	12	0.247	7.04	5.17	12.7	0.124
Serum	CRP, mg/L	0.8	0.525	1.45	0.6	0.3	1.7	0.313	0.75	0.4	1.25	0.626
	D-dimers, ng/mL	401	349	509	456	387	530	0.072	457	338	524	0.558

p *—control group vs. pre-treatment group; p **—control group vs. post-treatment group. Abbreviations: CAT, catalase; DT, dityrosine; GSH, reduced glutathione; 4-HNE, 4-hydroxynonenal; KN, kynurenine; NFK, N-formylkynurenine; NO, nitric oxide; GPx, glutathione peroxidase; SOD, superoxide dismutase; TRY, tryptophan; CRP, C-reactive protein

Additionally, in depressed patients with a history of COVID-19, we observed lower levels of GPx in serum (p = 0.008) and significantly higher levels of NO in urine (p = 0.033) in the first measurement. Meanwhile in the second measurement, higher levels of S-Nitrosothiols (p = 0.045) in serum were found. In the control group, significantly higher levels of NFK in urine were determined in COVID-19 survivors (p = 0.048) (Table 4).

Table 4. O&NS and kynurenine pathway parameters of participants with and without COVID-19 history.

Variable	Non-COVID			COVID			p
	Median	Q1	Q3	Median	Q1	Q3	
	First measurement (COVID n = 21, non-COVID n = 12)						
NO urine, nmol/mg protein	1.33	0.93	2.15	3.06	1.77	4.96	0.033
GPx serum, mU/mg protein	1.54	1.51	1.64	1.46	1.39	1.51	0.008
	Second measurement (COVID n = 15, non-COVID n = 6)						
S-Nitrosothiols serum, nmol/mg protein	3.13	2.86	3.42	3.66	3.21	3.92	0.045
	Control group (COVID n = 23, non-COVID n = 7)						
NFK urine, AFU/mg protein	13.4	11.3	14	20.6	12.5	27.8	0.048

Abbreviations: NO, nitric oxide; GPx, glutathione peroxidase; NFK, N-formylkynurenine.

3.2.2. Scales Assessing Severity of Depression and Anxiety, Results of Cognitive Tests and Stress Related to the COVID-19 Pandemic

In the study group, the scores of scales assessing the severity of depression and anxiety were significantly higher before and after the antidepressant treatment compared to the control group. No significant differences were observed between the pre-treatment depressed patients and the control group in IES-R scores (Table 2), also in relation to COVID-19 history. Significantly lower scores in tests of cognitive functions (VFT, TMT Parts A&B, DST, SCWT and CVLT) were observed in the depressed patients before treatment than in the control group. However, after undergoing the antidepressant treatment, significantly lower scores in depressed patients were limited to the Stroop Color Word Test (Table 5).

Table 5. Results of cognitive tests and clinical scales in study and control groups.

Variable	Control Group (n = 30)			Pre-Treatment Group (n = 33)			p *	Post-Treatment Group (n = 21)			p **
	Median	Q1	Q3	Median	Q1	Q3		Median	Q1	Q3	
VFT Animals Category	24.5	21	29	20	17	23.2	0.012	20	16	24.5	0.116
VFT Letter "K"	18	17	20	13	8	18	0.001	17	12	20.5	0.284
VFT Letter "S"	14	11.2	19	10	8.5	13	0.002	12	10	14.5	0.085
Digital Span Task WAIS-R	11	10.2	15	10	8	12.5	0.027	11	9	15.5	0.451
TMT A	20	17.2	25.5	25.5	2.5	36.2	0.001	21	17.5	33	0.271
TMT B	42	38.2	56.8	65	51.8	94.5	0.001	56	41	86	0.121
SCWT word-reading	21	19	22.8	24.5	22.8	27	0	23	22	27	0.004
SCWT color-naming	50	43	55.8	59	50	80.2	0.006	58	50	64.5	0.051
Trials 1–5	7	5	8	5	3	6	0.004	7	6	8	0.312
Trial 1	6	4.25	7	4	3	5	0.001	7	6	8	0.145
List B	6	5	7.75	6	4	7	0.508	6	5	8.5	0.461
Short-Delay Free Recall	7	6	9	5.5	4	7	0.009	7	5.5	8	0.654
Short-Delay Cued Recall	8	6.25	10	4.5	4	7.25	0.003	7	5.5	10	0.565
Long-Delay Free Recall	8	5.25	10	5	4	8	0.01	8	6	8.5	0.867
Long-Delay Cued Recall	7	5.25	10	5	4	6	0	6	5.5	9	0.636
HAM-D	0	0	0	22	18	27	0	5	3	10	0
BDI	4	1	6.75	29	21	41	0	13	6.25	22.8	0
HAM-A	0	0	0	22	14	26	0	4	1.5	9.5	0

p *—control group vs. pre-treatment group; p **—control group vs. post-treatment group. Abbreviations: VFT, the Verbal Fluency Test; TMT, Trail Making Test; SCWT, Stroop Color Word Test; HAM-D, the Hamilton Depression Rating Scale; BDI, the Beck Depression Inventory; HAM-A, the Hamilton Anxiety Rating Scale.

3.3. Comparison of the Results of the First and Second (before and after Antidepressant Treatment) Measurements in the Study Group

3.3.1. O&NS and Kynurenine Pathway Parameters, CRP, and D-Dimers

A significant decrease in serum peroxynitrite levels ($p < 0.000$) and an elevation of GSH levels ($p = 0.046$) were observed in serum after the antidepressant treatment. Other than that, no significant differences were observed. No statistically significant differences in inflammatory parameters CRP and D-dimers were detected (Table 6).

3.3.2. Scales Assessing Severity of Depression and Anxiety and Results of Cognitive Tests

After the treatment, there was a significant decrease in the severity of depression and anxiety assessed by HAM-D ($p = 0$), BDI ($p = 0$) and HAM-A ($p = 0$), and an increase in the scores of individual CVLT tasks (Trial 1, Trials 1–5, List B, Short-Delay Free Recall, Short-Delay Cued Recall, Long-Delay Free Recall) assessing memory processes (Table 7).

Table 6. O&NS and kynurenine pathway parameters, CRP, D-dimers in study group: pre- and post-treatment.

Serum/Urine	Variable	Pre-Treatment Group (n = 21 *)			Post-Treatment Group (n = 21)			p
		Median	Q1	Q3	Median	Q1	Q3	
Serum	CAT, nmol H_2O_2/min/mg protein	1.39	1.12	1.76	1.54	1.43	1.72	0.473
	DT, AFU/mg protein	11.7	10.3	13.5	12.6	10.6	14.6	0.153
	GSH, µg/mg protein	0.892	0.818	1.05	1.09	0.932	1.14	0.046
	4-HNE, umol/mg protein	6.06	5.58	6.48	5.94	5.06	6.47	0.946
	KN, AFU/mg protein	17.1	11.1	19.1	16	14.5	17.8	0.869
	NFK, AFU/mg protein	10.8	7.95	11.8	9.43	8.68	11.7	0.661
	NO, nmol/mg protein	6.14	1.07	15.1	10.4	2.95	23.3	0.609
	Peroxynitrite, nmol/mg protein	36.8	16.6	56.8	12.9	11.9	15.1	0.000
	GPx, mU/mg protein	1.48	1.42	1.51	1.47	1.38	1.5	0.785
	S-Nitrosothiols, nmol/mg protein	3.55	3.07	3.93	3.47	3.11	3.75	0.681
	SOD, mL/mg protein	0.291	0.203	0.351	0.193	0.041	0.365	0.055
	TRY, AFU/mg protein	160	143	172	158	139	171	0.812
Urine	CAT, nmol H_2O_2/min/mg protein	1.01	0.75	1.59	0.975	0.851	1.22	0.901
	DT, AFU/mg protein	55.2	35.6	81.6	57.1	40.8	77.2	0.767
	GSH, µg/mg protein	1.27	1.13	1.84	1.44	1.16	1.72	0.452
	4-HNE, umol/mg protein	495	3.69	10.1	5.36	4.17	7.17	0.946
	KN, AFU/mg protein	44.2	34.4	53.4	46.4	35.8	61.6	0.338
	NFK, AFU/mg protein	19.2	12.3	33.1	22.6	15.3	32.5	0.412
	NO, nmol/mg protein	2.07	1.04	4.96	2.39	1.27	3.59	0.609
	Peroxynitrite, nmol/mg protein	7.46	6.21	12.1	7.47	6.64	9.96	0.973
	GPx, mU/mg protein	1.56	1.01	2.65	1.4	1.18	2.1	0.946
	S-Nitrosothiols, nmol/mg protein	5.68	4.72	7.17	5.57	4.94	6.25	0.892
	SOD, mL/mg protein	0.172	0.072	0.362	0.225	0.134	0.401	0.432
	TRY, AFU/mg protein	6.84	4.93	14.7	7.04	5.17	12.7	0.946
Serum	CRP, mg/L	0.5	0.3	1.7	0.8	0.4	1.3	0.943
	D-dimers, ng/mL	456	383	551	457	338	524	0.225

* Matched cases only. Abbreviations: CAT, catalase; DT, dityrosine; GSH, reduced glutathione; 4-HNE, 4-hydroxynonenal; KN, kynurenine; NFK, N-formylkynurenine; NO, nitric oxide; GPx, glutathione peroxidase; SOD, superoxide dismutase; TRY, tryptophan; CRP, C-reactive protein.

Table 7. Results of cognitive test and clinical scales in study group: pre- and post-treatment.

Variable	Pre-Treatment Group (n = 21 *)			Post-Treatment Group (n = 21)			p
	Median	Q1	Q3	Median	Q1	Q3	
VFT Animals Category	20	18	23	20	16	24.5	0.600
VFT Letter "K"	14	10	18	17	12	20.5	0.190
VFT Letter "S"	11	10	13,5	12	10	14.5	0.757
Digital Span Task WAIS-R	10	8	12,5	11	9	15.5	0.090
TMT A	24	21	34,5	21	17.5	33	0.111
TMT B	65	49	98	56	41	86	0.421
SCWT word-reading	23	22	27	23	22	27	0.473
SCWT color-naming	58	49.5	73.5	58	50	64.5	0.230
Trial 1	4	3	5	7	6	8	0
Trials 1–5	5	3	6	7	6	8	0.001
List B	6	4	7	6	5	8.5	0.026
Short-Delay Free Recall	5	4	7	7	5.5	8	0.015
Short-Delay Cued Recall	4	4	7	7	5.5	10	0.008
Long-Delay Free Recall	4	4	7.5	8	6	8.5	0.005
Long-Delay Cued Recall	5	4	6	6	5.5	9	0.001
HAM-D	20	19	27	5	3	10	0
BDI	28	21	43	11	6	22	0
HAM-A	22	14	26	4	1.5	9.5	0

* Matched cases only. Abbreviations: VFT, the Verbal Fluency Test; TMT, Trail Making Test; SCWT, Stroop Color Word Test; HAM-D, the Hamilton Depression Rating Scale; BDI, the Beck Depression Inventory; HAM-A, the Hamilton Anxiety Rating Scale.

3.4. Correlations of Oxidative Stress, CRP and D-Dimers with Individual Parameters

In the study group, there was no significant correlation of the concentrations of oxidative stress parameters from the first measurement to be performed alternating in HAM-D, HAM-A and BDI scores after the treatment. We observed a positive correlation of CRP values with a reduction of depression severity assessed by BDI after the antidepressant treatment ($r = 0.5$; $p = 0.0169$).

In the depressed patients before the treatment, we observed positive correlations of HAM-D scale scores with serum CAT and urinary S-Nitrosothiols levels, as well as positive correlations of BDI scores with serum GSH and SOD levels. In addition, there was a positive correlation of IES-R scores with serum GSH levels before treatment in the study group (Table 8).

Table 8. Statistically significant correlations between oxidative stress parameters and clinical variables in study group before treatment.

First Variable	Second Variable	r	p	Method
HAM-D	CAT serum, nmol H_2O_2/min/mg protein	0.38	0.0289	Spearman
HAM-D	S-Nitrosothiols urine, nmol/mg protein	0.38	0.027	Spearman
BDI	*GSH serum, µg/mg protein*	*0.39*	*0.0251*	*Spearman*
BDI	SOD serum, ml/mg protein	0.42	0.0154	Spearman
IES-R	GSH serum, µg/mg protein	0.52	0.00424	Spearman

Abbreviations: HAM-D, the Hamilton Depression Rating Scale; BDI, the Beck Depression Inventory; IES-R, the Impact of Event Scale—Revised; CAT, catalase; GSH, reduced glutathione; SOD, superoxide dismutase.

3.5. Correlations of SARS-CoV-2 Antibodies with Individual Parameters

In the study group before and after antidepressant treatment, no significant correlations were found between the levels of SARS-CoV-2 antibodies and the severity of depression and anxiety, the change in the scores of the HAM-D, HAM-A, BDI scales and the severity of general symptoms during SARS-CoV-2 infection.

On the other hand, a significant correlation was observed in the control group between the levels of anti-N IgG antibodies and the severity of taste disorders during SARS-CoV-2 infection ($r = 0.44$; $p = 0.0182$). The observed correlation was positive, meaning that those with higher levels of antibodies had more severe symptoms during their COVID-19 infection.

4. Discussion

A growing number of studies point to the relevance of inflammation in the pathomechanism of the development of depression, which is accompanied by an increase in O&NS causing impaired brain function and modulation of neurotransmission [49,50]. Depression is associated with altered levels of oxidative stress markers and impaired total antioxidant status. This includes usually decreased concentrations of certain antioxidant compounds, such as glutathione (GSH), or enzymes, including glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) [51,52]. However, some sources report either an increase or no change in the concentration of antioxidant enzymes [53–56]. A study by Bilici et al. indicates that increased severity of depression is characterized by significantly higher levels of certain antioxidant enzymes, including erythrocyte SOD and GPx [49]. Other studies confirm the linkage between oxidative stress and depression as well as the significant positive correlation between disease severity and SOD activity [50,57]. The results of this study indicate that O&NS and an increase in antioxidant enzymes are associated with the severity of depression. In the patients with depression before treatment, we observed positive correlations of HAM-D scale scores with serum CAT and urinary S-Nitrosothiols, as well as positive correlations of BDI scores with serum GSH and SOD. Increased levels of antioxidant enzymes may be the result of a compensatory effect [58]. During oxidative stress and inflammation, GSH synthesis is upregulated [59], which may

explain our results of the correlation between the severity of the Beck Depression Inventory and higher GSH. S-Nitrosothiols as antioxidants protect against oxidative damage [60]. Therefore, their increase may also indicate the body's response to stress. It is worth mentioning that, in this group of patients, we found a positive correlation between IES-R scores and serum GSH levels in the first measurement. Research indicates reduced GSH levels in depression and other conditions associated with oxidative stress [56,61–63]. However, increased levels of the main antioxidant GSH may indicate antioxidant protection against cell death [64,65], which may also appear in the case of severe emotional stress related to COVID-19. In addition, we observed higher TRY levels in the group of depressed patients before antidepressant treatment versus the control group. However, these data are not consistent with numerous studies showing reduced TRY levels in depressed patients. It is related to the excessive activation of the enzyme indole 2,3-dioxygenase (IDO) catabolizing tryptophan to kynurenine and its metabolites [17]. Nevertheless, a study presented by Nobis et al. showed similar results to the current study [66]. It can be only theorized that the increased levels of TRY in depressed patients may derive from the catabolic degradation of body proteins at the onset of depression/inflammation and TRY release. This leads to the conclusion that protein and TRY reserves may be depleted in the chronic stage of the disorder. Similarly, the activity of antioxidant enzymes may initially increase during the inflammatory phase, but their reserves may be depleted during depression.

Oxidative stress is associated with the neurodegenerative process characteristic of depression and cognitive decline [49,57,67]. Several studies prove the presence of deficits in the areas of memory, attention, executive functions and psychomotor speed in depressed patients compared to healthy individuals and their symmetrical correlation with the severity of depression and the number of episodes [68]. We confirmed reports of reduced cognitive functions in depressed individuals in comparison to healthy individuals, as evidenced by significantly lower scores in tests assessing cognitive functions (VFT, TMT Part A&B, DST, SCWT and CVLT).

A meta-analysis by Osimo et al. found that more than half of depressed patients present slightly elevated CRP levels, and about a quarter of patients show signs of low-grade inflammation [69]. This indicates the impact of inflammation in the course of depression. In addition, psychological stress caused the symptoms of depression and anxiety and induced a chronic low-grade hypercoagulable state, which may be linked to elevated D-dimers in the aforementioned group of depressed patients [70]. The survival of COVID-19 may be associated with persistent increases in CRP and D-dimer levels, indicating long-lasting inflammation in the body, even up to several months after combating the virus. This has been demonstrated by a growing number of studies [71–74]. Therefore, one would expect that in patients with depression and after COVID-19, persistent inflammation would be expressed by higher CRP and D-dimer parameters. However, in our study, we did not confirm these hypotheses. We did not observe statistically significant differences in CRP and D-dimer parameters between the control group and the study group, in patients before and after the antidepressant treatment as well as their history of COVID-19.

A study by Saleh et al. showed continued oxidative stress in the brain with decreased gray matter glutathione (GSH) levels several months after infection in subjects with a history of COVID-19 [75]. In their study, Stufano et al. reported that oxidative damage persists in subjects with prior COVID-19 infection even four months after SARS-CoV-2 infection [76]. This suggests a possible role of oxidative stress mediators in the pathogenesis of long COVID, meaning long-term symptoms after the infection. In our study, we found higher urinary NO levels and lower serum GPx levels in depressed patients with a history of COVID-19 before the antidepressant treatment. Higher levels of nitrosative stress biomarkers and lower levels of GPx, which is involved in protecting cells from toxicity, may indicate a greater contribution of inflammation in patients with depression and a history of COVID-19. In healthy controls with a history of COVID-19, significantly higher levels of NFK, a biomarker of protein damage, were observed.

In their study, Hampshire et al. supported the hypothesis that post-COVID-19 individuals (both hospitalized and non-hospitalized cases) may have permanent and significant cognitive deficits [77]. In addition, based on an analysis of a 2-year retrospective cohort study of individuals diagnosed with COVID-19, Taquet et al. found an increased risk of cognitive deficits, dementia and other neuropsychiatric disorders [78]. Moreover, in their study, Latronico et al. observed an improvement in cognitive functions over time from SARS-CoV-2 infection, while symptoms of depression, anxiety and post-traumatic stress disorder, present after 3 months, remained unchanged [79]. However, in this study, we did not confirm the hypothesis of a significant effect of COVID-19 infection on cognitive functions scores in healthy controls, and we did not find differences in subjects with depression before and after treatment in the context of COVID-19. No correlation was found between the level of anti-SARS-CoV-2 antibodies and the individual results of cognitive tests. This may be dependent on the number of studied subjects and the time passed since the illness, which also indicates a questionable effect of COVID-19 intercourse on cognitive functions in people with depression.

So far, the results of studies demonstrating an increased risk of psychological distress after COVID-19 are mixed, due to evidence of mitigating the effects of infection over time [80]. However, a large study analyzing data from over 50,000 participants found an association between COVID-19 exposure and later mental distress, depression, anxiety and overall lower life satisfaction, showing no evidence for a link between COVID-19 and gender, education and pre-pandemic mental health [81]. Even so, our study did not support this hypothesis since there was no greater severity of depression and anxiety found in both the study group and the control group due to the COVID-19 illness. There was also no correlation found between the results in the HAM-D, HAM-A and BDI scales and levels of antibodies to SARS-CoV-2. Although some studies indicate that the level of SARS-CoV-2 antibodies depends on the severity of COVID-19 infection [82], in our study among study participants, we did not observe a correlation of SARS-CoV-2 levels with the severity of general symptoms during SARS-CoV-2 infection. However, we observed a significant correlation between the level of anti-N IgG antibodies indicating past COVID-19 and the severity of taste disorders during SARS-CoV-2 infection. This may indicate that a stronger immune response leads to more pronounced taste disorder symptoms. In their study, Kwasniewska et al. verified that taste and olfactory symptoms in younger patients correlated with lower antibodies levels [83]. These results are not consistent with our evidence but may be due to the consideration of combining taste and olfactory disorders as opposed to our considerations.

Antidepressant treatment has immunomodulatory properties. It can normalize oxidative stress parameters and increase the activity of some neuroprotective antioxidant enzymes [51,84]. However, there are studies indicating an ambiguous effect of antidepressant treatment on the modulation of oxidative stress. In the brain, antioxidant properties were most frequently demonstrated, but in the liver and testicular cells, most studies showed pro-oxidant effects. Studies show that effective antidepressant treatment reduces inflammation, and higher inflammation inhibits the response to antidepressants [85]. In a meta-analysis by Gasparini et al., patients who did not respond to antidepressants had higher baseline levels of C-reactive protein and interleukin-8, which indicated an abnormal inflammatory process [86]. Our study does not support this hypothesis, as we observed an association between higher CRP values and an improvement in BDI scores after the antidepressant treatment. However, after the inclusion of the antidepressant treatment (lasting 4–6 weeks), significantly decreased levels of peroxynitrite, a byproduct of NO synthesis and a key oxidant in redox processes in pathological conditions, were observed in patients in the study group. In addition, there were significantly increased serum levels of GSH, which is the most important peroxynitrite scavenging antioxidant. Moreover, higher levels of DT, a marker of oxidative protein damage, were observed after the antidepressant treatment, differently to the control group. This may cast doubt on the exclusively antioxidant effects of this group of drugs. However, it could also be due to a small study group or too short

duration of the treatment, as Sarandol et al. indicate that 6-week antidepressant treatment has no effect on oxidative systems [50]. In addition, significant reductions in depression and anxiety severity and improvements in cognitive functions (CVLT tasks -Trials 1–5, Trial 1, List B, Short-Delay Free Recall, Short-Delay Cued Recall, Long-Delay Free Recall) were observed in depressed patients after antidepressant treatment. So far, several studies have confirmed the positive effect on cognitive functions after antidepressant treatment [87–90].

In the context of COVID-19 history, no association was observed between the level of SARS-CoV-2 antibodies and the response to antidepressant treatment expressed by changes in the HAM-D, HAM-A and BDI scales. Moreover, in the second measurement, depressed patients with a history of COVID-19 had higher serum levels of S-Nitrosothiols, which may indicate that the limited effect of the antidepressant therapy in these patients, due to the initial higher inflammation, is limited.

5. Conclusions

In our study, in line with existing knowledge, we confirmed that depression is closely related to increased inflammation, including O&NS, and is accompanied by a cognitive decline. We noted the correlation of depression severity with oxidative stress (CAT, GSH and SOD in serum, S-Nitrosothiols in urine). We also indicated that an effective antidepressant treatment has a modulating effect on oxidative stress parameters, clinical improvement of depressive symptoms and cognitive function scores. Even though we did not confirm the hypothesis that COVID-19 history could affect the clinical response to the antidepressant treatment in depressed patients, we did observe reduced levels of the antioxidant enzyme GPx in biochemical parameters and elevated levels of NO in urine, indicating increased oxidative stress. Moreover, in subjects with depression and a history of COVID-19, significantly higher serum levels of S-Nitrosothiols were noted in the second measurement, which may point to a limited biochemical response to antidepressant treatment. Perhaps in additional studies, an association could be discovered between the level of SARS-CoV-2 antibodies and the response to treatment as expressed by changes in depression and anxiety scales in depressed individuals. Studies indicate that the higher the inflammation, the weaker the response to antidepressant treatment, which can be a source of treatment ineffectiveness and resistance.

Therefore, it is important to search for new therapeutic solutions and potentiation of antidepressant treatments in patients in the context of a history of SARS-CoV-2 infection. In the era of the COVID-19 pandemic and its consequences, it is important to conduct further research in this area, especially since depression is a potentially life-threatening disease.

6. Limitations

The limitations of this study include the small group size in the pre- and post-treatment antidepressant measurements as well as the heterogeneity of the groups in terms of education, smoking history and antidepressant treatment used during the study. Due to the different pharmacodynamic profiles, antidepressants may affect the parameters evaluated in our study differently. Moreover, the study does not include a comparison of depressed patients on antidepressant treatment with depressed patients without treatment, which is a limitation of the study. Furthermore, due to the hindered cooperation with depressed patients or technical difficulties, some data are incomplete.

Author Contributions: Conceptualization, B.G.-S. and E.S.; methodology, B.G.-S., N.W., E.S., M.M., M.G.-S., B.M. and A.Z.; formal analysis, E.S.; investigation, E.S., A.N. and D.Z.; resources, A.Z. and M.M.; writing—original draft preparation, E.S.; writing—review and editing, B.G.-S. and N.W.; visualization, E.S.; supervision, B.G.-S. and N.W.; project administration, B.G.-S. and N.W.; funding acquisition, N.W. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the Medical University of Bialystok, grant number B.SUB.23. 353.01. I. The financial sponsor played no role in the design, execution and interpretation of the data.

Institutional Review Board Statement: The study was approved by the Ethics Committee of the Medical University of Bialystok (permission: APK.002.281.2021) and was carried out in accordance with the Helsinki Declaration and the Guidelines for Good Clinical Practice.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.

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8. Streszczenie w języku polskim

Wstęp

Pandemia COVID-19 przyczyniła się do znacznego wzrostu częstości występowania zaburzeń psychicznych, w tym zaburzeń depresyjno-lękowych. Dotychczasowe badania naukowe wskazują na wpływ przebytego zakażenia SARS-CoV-2 na ujawnianie się lub nasilenie objawów zaburzeń depresyjnych. Infekcja COVID-19 może prowadzić do dysfunkcji układu odpornościowego i przedłużającego się stanu zapalnego nawet kilka miesięcy po infekcji, co może przyczyniać się do trudności w leczeniu zaburzeń depresyjnych. Przegląd literatury wskazuje, że pacjenci z wysokim wyjściowym stanem zapalnym wykazują słabszą odpowiedź na konwencjonalne terapie przeciwdepresyjne, a współwystępujące podłoże immunologiczne chorób zapalnych jest czynnikiem ryzyka epizodu depresyjnego, lekooporności i nawrotowości depresji. Leczenie przeciwdepresyjne wykazuje szereg korzystnych efektów, takich jak łagodzenie nasilenia objawów depresji, poprawa funkcji poznawczych oraz redukcja stanu zapalnego ze zmniejszeniem poziomu prozapalnych cytokin i stresu oksydacyjno-nitrozacyjnego. Zaobserwowano, że niektóre leki przeciwdepresyjne mogą łagodzić objawy depresyjne u pacjentów z COVID-19. Wobec rosnącej częstości zaburzeń depresyjnych i specyfiki ich leczenia w okresie postpandemicznym COVID-19 konieczne są dalsze badania naukowe celem opracowania nowych strategii terapeutycznych.

Cel pracy doktorskiej

Celem pracy doktorskiej była ocena wpływu przebytego zakażenia SARS-CoV-2 na skuteczność leczenia przeciwdepresyjnego z oceną funkcji neuropoznawczych oraz analizą wybranych parametrów zapalnych u osób z depresją.

Materiał i metody

Zbadano 33 hospitalizowanych pacjentów z rozpoznaniem zaburzeń depresyjnych i 30 osób zdrowych, bez zaburzeń psychicznych. W grupie badanej kontakt z wirusem SARS-CoV-2 potwierdzono u 21 osób, natomiast w grupie kontrolnej u 23 uczestników badania. Wszyscy uczestnicy zostali poddani badaniu fizycznemu i psychiatrycznemu, ocenie funkcji neuropoznawczych oraz pobrano od nich materiał biologiczny do analizy

(pierwszy pomiar). Nasilenie stresu związanego z pandemią COVID-19 oceniano za pomocą polskiej wersji Skali Wpływu Zdarzeń—Revised (IES-R). Powtórnej procedury testowej (drugi pomiar) dokonano po 4-6 tyg od włączenia leczenia przeciwdepresyjnego u 21 osób, w tym u 15 osób z potwierdzonym wywiadem SARS-CoV-2. Odpowiedź na lek przeciwdepresyjny mierzono jako poprawę wyników w zakresie skal HAM-D, BDI i HAM-A przed- i po- włączeniu leczenia. U wszystkich uczestników zbadano podstawowe parametry biochemiczne z krwi, a w próbkach pobranej surowicy i moczu oznaczono parametry szlaku kynureninowego oraz stresu oksydacyjnego i nitrozacyjnego: kynurenina (KN), N-formylokynurenina (NFK), dityrozyna (DT), tryptofan (TRY), dysmutaza ponadtlenkowa (SOD), katalaza (CAT), peroksydaza glutationowa (GPx), zredukowany glutation (GSH), 4-hydroksynonenal (4-HNE), tlenek azotu (NO), S-nitrozotiole i nadtlenoazotyny.

Wyniki

U osób z depresją po leczeniu przeciwdepresyjnym zaobserwowano istotny spadek stężenia nadtlenoazotynu w surowicy oraz istotny wzrost stężenia GSH w surowicy. U pacjentów z depresją i przebytym COVID-19 zaobserwowano istotnie niższą aktywność GPx w surowicy oraz istotnie wyższe stężenie NO w moczu w pierwszym pomiarze, a w drugim pomiarze stwierdzono istotnie wyższe stężenia S-Nitrozotioli w surowicy. U pacjentów z depresją przed leczeniem zaobserwowano pozytywne korelacje wyników skali HAM-D z aktywnością CAT w surowicy i stężeniem S-nitrozotioli w moczu, a także pozytywne korelacje wyników BDI ze stężeniem GSH i aktywnością SOD w surowicy. Nie zaobserwowano istotnej korelacji w zakresie parametrów stresu oksydacyjnego z pierwszego pomiaru ze zmianami wyników skal HAM-D, HAM-A i BDI przed i po leczeniu przeciwdepresyjnym. Nie obserwowano istotnych różnic w stężeniach CRP i D-dimerów u osób z depresją w porównaniu do grupy kontrolnej, ani wpływu leczenia przeciwdepresyjnego na stężenia CRP i D-dimerów. Nie obserwowano wpływu przechorowania COVID-19 na zmiany stężeń CRP i D-dimerów. Wykazano pozytywną korelację wartości CRP ze zmniejszeniem nasilenia depresji według skali BDI po leczeniu przeciwdepresyjnym. Po leczeniu zaobserwowano istotne zmniejszenie nasilenia depresji i lęku ocenianego za pomocą skal HAM-D, BDI i HAM-A, oraz podwyższenie wyników w poszczególnych zadaniach CVLT oceniających procesy

pamięciowe. Nie zaobserwowano istotnych różnic w wynikach IES-R między pacjentami z depresją przed leczeniem, a grupą kontrolną, a także w odniesieniu do historii COVID-19. W grupie badanej przed i po leczeniu przeciwdepresyjnym nie stwierdzono istotnych korelacji między stężeniami przeciwciał SARS-CoV-2, a nasileniem depresji i lęku, zmianą wyników skal HAM-D, HAM-A, BDI oraz nasileniem ogólnych objawów podczas zakażenia SARS-CoV-2. W grupie kontrolnej zaobserwowano istotną korelację między stężeniami przeciwciał anty-N IgG, a nasileniem zaburzeń smaku podczas zakażenia SARS-CoV-2.

Wnioski

1. Chociaż doniesienia z przeglądu literatury sugerują, że procesy zapalne występujące w zakażeniu SARS-CoV-2 mogą wpływać na skuteczność leczenia osób z depresją, niniejsze badanie nie potwierdza, że odpowiedź kliniczna na leczenie przeciwdepresyjne może być związana z przechorowaniem COVID-19 i wyjściowym stężeniem przeciwciał SARS-CoV-2.
2. Poziom odczuwanego stresu związanego z pandemią COVID-19 nie różnił się między osobami z depresją, a osobami bez depresji oraz w zależności od przechorowania COVID-19.
3. Przebycie COVID-19 wśród osób z depresją wiąże się z nasilonym stresem oksydacyjnym w porównaniu do grupy kontrolnej (niższa aktywność GPx i wyższe stężenie NO).
4. Leczenie przeciwdepresyjne wpływa na parametry stresu oksydacyjnego i nitrozacyjnego (wzrost stężenia GSH, spadek stężenia nadtlenoazotynu).
5. Leczenie przeciwdepresyjne wpływa na redukcję objawów depresji i poprawę funkcji poznawczych.
6. Nasilenie depresji koreluje z parametrami stresu oksydacyjnego i nitrozacyjnego (aktywnością CAT i SOD, stężeniem GSH, stężeniem S-nitrozotioli).
7. Dalsze badania są niezbędne do oceny wpływu przebycia COVID-19 na skuteczność terapii przeciwdepresyjnej. Ich wyniki mogą pogłębić wiedzę i świadomość wśród klinicystów, wspierać poszukiwanie nowych metod optymalizacji leczenia zaburzeń depresyjnych w okresie po pandemicznym oraz umożliwić lepszą identyfikację pacjentów z grup podwyższonego ryzyka, w tym z zespołem post-COVID-19.

9. Streszczenie w języku angielskim

Introduction

The COVID-19 pandemic has contributed to a significant increase in the incidence of mental disorders, including depressive and anxiety disorders. Previous scientific research indicates that a history of SARS-CoV-2 infection may trigger or exacerbate symptoms of depressive disorders. COVID-19 infection can lead to immune system dysfunction and prolonged inflammation lasting even several months post-infection, which may contribute to difficulties in treating depressive disorders. The literature review indicates that patients with elevated baseline inflammation show a weaker response to conventional antidepressant therapies and that coexisting immunological underpinnings of inflammatory diseases are a risk factor for a depressive episode, treatment resistance, and recurrence of depression. Antidepressant treatment has several beneficial effects, such as alleviating depressive symptom severity, improving cognitive functions and reducing inflammation by lowering levels of pro-inflammatory cytokines and oxidative-nitrosative stress. It has been observed that some antidepressants may alleviate depressive symptoms in patients with COVID-19. Given the increasing frequency of depressive disorders and the specificity of their treatment in the post-pandemic COVID-19 period, further research is necessary to develop new therapeutic strategies.

Aim of the study

The doctoral dissertation aimed to evaluate the impact of previous SARS-CoV-2 infection on the effectiveness of antidepressant treatment with an assessment of neurocognitive functions and an analysis of selected inflammatory parameters in individuals with depression.

Material and Methods

A total of 33 hospitalised patients diagnosed with depressive disorders and 30 healthy individuals without mental disorders were examined. In the study group, contact with the SARS-CoV-2 virus was confirmed in 21 individuals, while in the control group, it was confirmed in 23 study participants. At the beginning of the study, all participants underwent a physical and psychiatric examination, an assessment of neurocognitive

functions, and biological material was collected for analysis (first measurement). The second test procedure (second measurement) was performed 4-6 weeks after initiating antidepressant treatment in 21 individuals, including 15 persons with a confirmed history of SARS-CoV-2. Response to antidepressants was measured as an improvement in scores on the HAM-D, BDI, and HAM-A scales before and after treatment. Basic biochemical parameters of blood were examined in all participants, and parameters of the kynurenine pathway and oxidative and nitrosative stress were determined in serum and urine samples: kynurenine (KN), N-formylkynurenine (NFK), dityrosine (DT), tryptophan (TRY), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH), 4-hydroxynonenal (4-HNE), nitric oxide (NO), S-nitrosothiols and peroxynitrites.

Results

A significant decrease in serum peroxynitrite concentration and a significant increase in serum GSH concentration were observed in depressed individuals after antidepressant treatment. In patients with depression and a history of COVID-19, significantly lower serum GPx activity and significantly higher urinary NO concentration were observed in the first measurement, and significantly higher serum S-nitrosothiol concentrations were found in the second measurement. In patients with depression before treatment, positive correlations of HAM-D scale results with serum CAT activity and urinary S-nitrosothiol concentration were observed, as well as positive correlations of BDI results with serum GSH concentration and SOD activity. No significant correlation was observed in oxidative stress parameters from the first measurement with changes in HAM-D, HAM-A and BDI scale results before and after antidepressant treatment. No significant differences were observed in CRP and D-dimer concentrations in people with depression compared to the control group, nor was there an effect of antidepressant treatment on CRP and D-dimer concentrations. No impact of COVID-19 on changes in CRP and D-dimer concentrations was observed. A positive correlation between CRP values and a reduction in the severity of depression according to the BDI scale after antidepressant treatment was demonstrated. After treatment, a significant decrease in the severity of depression and anxiety was observed using the HAM-D, BDI, and HAM-A scales, as well as an increase in the scores for individual CVLT tasks assessing memory processes. No significant differences were observed in the IES-R scores between patients with

depression before treatment and the control group, as well as to the history of COVID-19. In the study group, before and after antidepressant treatment, no significant correlations were found between the concentrations of SARS-CoV-2 antibodies and the severity of depression and anxiety, the change in the results of the HAM-D, HAM-A, BDI scales and the severity of general symptoms during SARS-CoV-2 infection. In the control group, a significant correlation was observed between the concentrations of anti-N IgG antibodies and the severity of taste disorders during SARS-CoV-2 infection.

Conclusions

1. Although reports from the literature review suggest that inflammatory processes occurring in SARS-CoV-2 infection may affect the effectiveness of treatment in people with depression, this study does not confirm that the clinical response to antidepressant therapy may be associated with having had COVID-19 and the initial concentration of SARS-CoV-2 antibodies.
2. The level of perceived stress related to the COVID-19 pandemic did not differ between people with depression and those without depression, depending on whether they had COVID-19.
3. Having had COVID-19 among people with depression is associated with increased oxidative stress compared to the control group (lower GPx activity and higher NO concentration).
4. Antidepressant treatment affects the parameters of oxidative and nitrosative stress (increased GSH concentration, decreased peroxynitrite concentration).
5. Antidepressant treatment reduces the symptoms of depression and improves cognitive functions.
6. Depression severity correlates with oxidative and nitrosative stress parameters (CAT and SOD activity, GSH concentration, S-nitrosothiol concentration).
7. Further studies are necessary to assess the impact of COVID-19 on the effectiveness of antidepressant therapy. Their results may deepen the knowledge and awareness among clinicians, support the search for new methods to optimise the treatment of depressive disorders in the post-pandemic period, and enable better identification of patients from high-risk groups, including those with post-COVID-19 syndrome

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11. Oświadczenia współautorów

Informacja o charakterze udziału współautorów w publikacjach (praca przeglądowa)

Eliza Dąbrowska, Beata Galińska-Skok, Napoleon Waszkiewicz: *Depressive and Neurocognitive Disorders in the Context of the Inflammatory Background of COVID-19.* Life 2021, 11, 1056. Doi: 10.3390/ life11101056

Imię i nazwisko współautora	*Charakter udziału*
doktorant – lek. Eliza Samaryn	Stworzenie koncepcji manuskryptu, analiza dostępnych materiałów źródłowych, przygotowanie manuskryptu, w tym tabel i rycin wchodzących w skład manuskryptu
dr hab. n. med. Beata Galińska-Skok	konsultacja merytoryczna, korekta manuskryptu
prof. dr hab. n. med. Napoleon Waszkiewicz	konsultacja merytoryczna, korekta manuskryptu

Oświadczam, że wszyscy współautorzy wyrazili zgodę na wykorzystanie powyższej publikacji w pracy doktorskiej lek. Elizy Samaryn

Podpis doktoranta

Eliza Samaryn

Potwierdzam opisany powyżej merytoryczny wkład kandydata w powstanie publikacji wchodzącej w skład rozprawy doktorskiej.

Podpis promotora

Beata Galińska-Skok

Informacja o charakterze udziału współautorów w publikacjach (praca oryginalna)

Eliza Samaryn, Beata Galińska-Skok, Aleksander Nobis, Daniel Zalewski, Mateusz Maciejczyk, Monika Gudowska-Sawczuk, Barbara Mroczko, Anna Zalewska, Napoleon Waszkiewicz: *The Effect of Antidepressant Treatment on Neurocognitive Functions, Redox and Inflammatory Parameters in the Context of COVID-19.* Journal of Clinical Medicine 2023. 12(22), 7049. Doi: 10.3390/jcm12227049

Imię i nazwisko współautora	*Charakter udziału*
doktorant – lek. Eliza Samaryn	Udział w planowaniu eksperymentów, przeprowadzanie eksperymentów prezentowanych w pracy, opracowanie i analiza wyników, analiza statystyczna, przygotowanie manuskryptu, przygotowanie tabel i rycin wchodzących w skład manuskryptu
dr hab. n. med. Beata Galińska-Skok	stworzenie koncepcji pracy, nadzór nad powstawaniem pracy, konsultacja merytoryczna, korekta manuskryptu
lek. Aleksander Nobis	Pomoc przy rekrutowaniu pacjentów do badania i tworzeniu bazy danych
lek. Daniel Zalewski	Pomoc przy rekrutowaniu pacjentów do badania i tworzeniu bazy danych
dr hab. n. med. Mateusz Maciejczyk	Przeprowadzenie oznaczeń biochemicznych, konsultacja merytoryczna
dr. n. med. Monika Gudowska-Sawczuk	Współuczestnictwo w przeprowadzeniu oznaczeń biochemicznych, konsultacja merytoryczna
prof. dr hab. n. med. Barbara Mroczko	Współuczestnictwo w przeprowadzeniu oznaczeń biochemicznych, konsultacja merytoryczna
prof. dr hab. n. med. Anna Zalewska	Współuczestnictwo w przeprowadzeniu oznaczeń biochemicznych, konsultacja merytoryczna
prof. dr hab. n. med. Napoleon Waszkiewicz	nadzór nad powstawaniem pracy, konsultacja merytoryczna, korekta manuskryptu

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Podpis promotora

Beata Galińska-Skok

Białystok, 26.09.2024r.

dr hab. n. med. Beata Galińska-Skok
Klinika Psychiatrii

Uniwersytet Medyczny w Białymstoku
ul. J. Kilińskiego 1
15-089 Białystok

Oświadczenie

Oświadczam, iż mój udział w przygotowaniu publikacji:

Eliza Dąbrowska, Beata Galińska-Skok, Napoleon Waszkiewicz: Depressive and Neurocognitive Disorders in the Context of the Inflammatory Background of COVID-19. Life 2021, 11, 1056. Doi: 10.3390/ life11101056 , wchodzącej w skład rozprawy doktorskiej *lek. Elizy Samaryn „Wpływ przebytego zakażenia SARS-CoV-2 na skuteczność leczenia przeciwdepresyjnego z oceną funkcji neuropoznawczych oraz analizą wybranych parametrów zapalnych u osób z depresją"* polegał na konsultacji merytorycznej i korekcie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie przez lek. Elizę Samaryn publikacji w postępowaniu o nadanie stopnia doktora w dziedzinie nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne.

dr hab. n. med. Beata Galińska-Skok
lekarz medycyny
specjalista psychiatra
3472837

Białystok, 26.09.2024r.

prof. dr hab. n. med. Napoleon Waszkiewicz
Klinika Psychiatrii

Uniwersytet Medyczny w Białymstoku
ul. J. Kilińskiego 1
15-089 Białystok

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KIEROWNIK
Kliniki Psychiatrii
Prof. dr hab. n. med. Napoleon Waszkiewicz

Białystok, 26.09.2024r.

dr hab. n. med. Beata Galińska-Skok
Klinika Psychiatrii

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dr hab. n. med. Beata Galińska-Skok
lekarz medycyny
specjalista psychiatra
3472837

Białystok, 26.09.2024r.

dr n. med. Aleksander Nobis
Klinika Psychiatrii

Uniwersytet Medyczny w Białymstoku
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dr n. med. Aleksander Nobis
LEKARZ
3707807

Białystok, 26.09.2024r.

lek. Daniel Zalewski
Klinika Psychiatrii UMB

Uniwersytet Medyczny w Białymstoku
ul. J. Kilińskiego 1
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Wyrażam zgodę
Daniel Zalewski
26/09/2024

Białystok, 26.09.2024r.

dr hab. n. med. Mateusz Maciejczyk
Zakład Higieny, Epidemiologii i Ergonomii

Uniwersytet Medyczny w Białymstoku
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dr hab. n. med.
Mateusz Maciejczyk

Białystok, 26.09.2024r.

dr hab. n. med. Monika Gudowska-Sawczuk
Zakład Diagnostyki Biochemicznej

Uniwersytet Medyczny w Białymstoku
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Monika Gudowska-Sawczuk

Białystok, 26.09.2024r.

prof. dr hab. n. med. Barbara Mroczko
Zakład Diagnostyki Biochemicznej

Uniwersytet Medyczny w Białymstoku
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KIEROWNIK
Zakładu Diagnostyki Biochemicznej
prof. dr hab. Barbara Mroczko

Białystok, 26.09.2024r.

prof. dr hab. n. med. Anna Zalewska
Zakład Stomatologii Zachowawczej

Uniwersytet Medyczny w Białymstoku
ul. J. Kilińskiego 1
15-089 Białystok

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Jednocześnie wyrażam zgodę na wykorzystanie przez lek. Elizę Samaryn publikacji w postępowaniu o nadanie stopnia doktora w dziedzinie nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne.

Prof. dr hab. Anna Zalewska
specjalista stomatologii dziecięcej
8897157

Białystok, 26.09.2024r.

prof. dr hab. n. med. Napoleon Waszkiewicz
Klinika Psychiatrii

Uniwersytet Medyczny w Białymstoku
ul. J. Kilińskiego 1
15-089 Białystok

Oświadczenie

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KIEROWNIK
Kliniki Psychiatrii
Prof. dr hab. n. med. Napoleon Waszkiewicz

12. Zgoda Komisji Bioetycznej

Projekt badania został zaakceptowany przez Komisję Bioetyczną Uniwersytetu Medycznego w Białymstoku

KOMISJA BIOETYCZNA
PRZY UNIWERSYTECIE MEDYCZNYM W BIAŁYMSTOKU
ul. Jana Kilińskiego 1
15-089 Białystok
tel. 85 748 54 07, fax 85 748 55 08
komisjabioetyczna@umb.edu.pl

Białystok, 27.05.2021 r.

Uchwała nr: APK.002.281.2021

Na podstawie art. 29 ust. 2 i 14 ustawy dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (t.j. Dz. U z 2020, poz. 514 ze zm.), Komisja Bioetyczna przy Uniwersytecie Medycznym w Białymstoku, po zapoznaniu się z projektem badania zgodnie z zasadami GCP/ Guidelines for Good Clinical Practice /- **w y r a ż a z g o d ę** na prowadzenie tematu badawczego: „Wpływ przebytego zakażenia SARS-CoV-2 na skuteczność leczenia przeciwdepresyjnego z oceną funkcji neuropoznawczych oraz analizą wybranych parametrów zapalnych u osób z depresją" przez dr hab. Beatę Galińską-Skok wraz z zespołem badawczym z UMB.

Planowany okres realizacji od 27.05.2021 r. do 31.12.2023 r.

Przewodnicząca Komisji Bioetycznej przy UMB

prof. dr hab. Otylia Kowal-Bielecka

Pouczenie:
1. Odwołanie od uchwały komisji bioetycznej wyrażającej opinię może wnieść:
1) wnioskodawca;
2) kierownik podmiotu, w którym eksperyment medyczny ma być przeprowadzony;
3) komisja bioetyczna właściwa dla ośrodka, który ma uczestniczyć w wieloośrodkowym eksperymencie medycznym.
2. Odwołanie, o którym mowa w ust. 1, wnosi się za pośrednictwem komisji bioetycznej, która podjęła uchwałę, do Odwoławczej Komisji Bioetycznej w terminie 14 dni od dnia doręczenia uchwały wyrażającej opinię.