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PERSPECTIVE

Eating Disorders in the Time of the COVID-19 Pandemic: A Perspective

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Abstract: *Background*: Due to the COVID-19 pandemic, current epidemiological conditions may exacerbate the risk of new-onset, recurrence and relapse of eating disorders. This perspective aims to better analyse the phenomenon.

ARTICLE HISTORY

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DOI: 10.2174/1871530322666220422104009 **Results:** Some data suggest that new-onset and recurrence/relapse of eating disorders are increasing due to the pandemic. Government restrictions, self-confinement, social isolation, restriction to healthcare facilities access, delayed access to diagnosis and cure, fear of contagion, distress and difficulties related to the telemedicine approach contribute to this burden. The Immune system dysfunction usually observed in undernourishment (*e.g.*, anorexia nervosa) could delay the diagnosis of respiratory infections, including COVID-19, and predispose to possible bacterial superinfections. Conversely, patients with binge eating, obesity or metabolic syndrome are susceptible to high-grade systemic inflammation and poor prognosis once the infection has occurred.

Discussion: More detailed data combining research on eating disorders and COVID-19 are required despite some evidence. Many data show that telemedicine has beneficial aspects, but its impact on long-term mental health is still poorly understood. Short- and long-term consequences of COVID-19 in patients with eating disorders are unknown, but they will likely become more apparent over time.

Conclusion: Working on emotion regulating strategies in a post-pandemic world, when people have inadequate control over the background of negative emotions, could be a future treatment strategy. Long-term studies with a larger sample size are essential to assess the long-term consequences of the blockade on patients and their healthcare providers and identify useful strategies to improve clinical management.

Keywords: Sars-cov-2, COVID-19, pandemic, eating disorders, anorexia nervosa, obesity.

1. INTRODUCTION

Feeding and eating disorders (EDs) are psychiatric syndromes associated with physical and psychological severity and maintenance factors. Epidemiological data show an increasing prevalence, between 0.3-0.9%, of anorexia nervosa (AN), especially in women, [1] and the highest mortality rate among psychiatric illnesses due to suicide [2]. Among the other foremost EDs, bulimia nervosa (BN) is estimated between 0.8-2.9%, whereas binge eating disorder (BED) has a lifespan prevalence of 2-3.5%. On the one hand, the mortality rate is lower for EDs than AN, but there are concerns about purging behaviors and metabolic disorders usually associated with EDs since they become a chronic dysfunction in around 20% of patients [3]. On the other hand, as for AN, psychiatric comorbidities are common and include mood disorders, major depressive disorders [4], anxiety disorders [5], and obsessive-compulsive disorders [6].

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Emotional and cognitive functions are impaired in EDs. There is a social behavior impairment with difficulty interacting with other people due to reduced cognitive flexibility. Additionally, many neurobiological studies report difficulties in social-emotional processing, recognition, and emotion regulation [7].

From a pathophysiological perspective, EDs typically include multifactorial causes covering genetic, psychosocial, and interpersonal risk factors, and malnutrition with neural alterations may be a maintaining factor. EDs are usually longlasting and characterized by a high risk of relapse, leading to disability and increased mortality when untreated. Thus, early intervention is essential to better manage this condition [3].

During the global epidemiological emergency of SARS-CoV-2 infection, concerns related to the fear of being infected and social isolation lead to a significant psychological consequences [8]. Among vulnerable subjects, those suffering from EDs are considered extremely frail and prone to stress [9]. This condition has become relevant during the pandemic for people with ED and their closest relatives [10]. Uncertainties caused by fear of contagion and death of family members, along with anxiety and loneliness related to social restrictions and isolation, were exacerbated in this group of individuals whose dysfunctional behavior generally tends to worsen under similar circumstances [11].

In this context, a recent social media survey [12] reported an exacerbation of EDs symptomatology in more than onethird of participants and an increase of anxiety-related symptoms in over 50% of them.

Similar results were reported by data from an Australian study evaluating self-reported ED history. The results showed that two in three respondents had an increase in restriction, one in three had an increase in binge eating, one in five started to purge more frequently, and nearly half of them experienced an increase in exercise behavior. Notably, the control group reported 28% increased food restriction and 35% increased binge eating [13].

Different explanations for explaining the phenomenon have been proposed [14]. First, public health efforts to minimize the spread of COVID-19 negatively affected access to healthcare facilities for people with EDs. Moreover, diagnosis and treatment of these disorders have been delayed, negatively impacting treatment uptake and engagement [15]. Many psychiatric patients receive a consultation and treatment through telemedicine, but both clinicians and patients expressed worries about the effectiveness of web-based therapy, as most of them consider telemedicine as a second choice, not equivalent to an in-person treatment [16].

Patients with AN reported emotional distress and negative body image perception resulting from the need for video consulting by telemedicine [17]. Moreover, people with or at risk of EDs have been exposed to ED-specific media, increasing their concerns and anxiety about food intake, exercising, and weight gain [14]. More than 15,000 posts on *Instagram* referred to the so-called "quarantine-15", an expression highly related to the most common "freshman 15", used in the United States to indicate the amount of weight gained during a student's first year at college [18]. Increased social media use may incentivize binge eating attitudes, dietary restrictions and Restrictions affected not only individuals' psychological health, especially those with EDs, but also healthcare providers (HCPs). We recently hypothesized that social restrictions would negatively impact the therapeutic alliance, including influencing the frequency of dysfunctional behaviors. According to our transversal investigation, HCPs experienced a sense of therapeutic inefficiency and an impaired therapeutic alliance. Effective strategies to limit stress are needed to identify useful programs to better address these negative outcomes [20].

2. COVID-19 INFLUENCE ON EATING DISORDERS

There are similarities between previous outbreaks of SARS and Ebola and the COVID-19 pandemic. Particularly, symptoms related to post-traumatic stress disorder and adverse psychiatric sequelae could have lifelong consequences on at-risk individuals.

Many results indicate that the COVID-19 pandemic per se and public health measures adopted to tackle the spread of the infection has negatively affected psychiatric health. At-risk individuals frequently require comfort due to emotional distress by engaging in ED behaviors, exacerbated by changes in daily routine, feelings of isolation, and reduced access to healthcare and social support networks. A small number of users in this social media survey reported that the quarantine mandate allowed them to focus on ED recovery and reported a successful decrease in ED symptomatology since the onset of the pandemic [12].

A cross-sectional web-based online survey including two groups of participants, which included people selected from the general population and a second group including patients attending diet for weight loss, reported that the fear of contracting SARS-CoV-2 infection and its related clinical complaints were directly correlated with the magnitude of eating restraint, weight gain, and body image concerns in the whole sample, but more specifically in the dietitian clients' group [11].

Stressful situations are associated with various behavioral responses that have conflicting coping strategies, such as extreme eating or starvation [21]. Some individuals overeat in response to emotional triggers, which leads to more concerns and self-evaluation of body weight or shape [22].

Weight and shape concerns increased during social isolation because of higher feelings of loneliness, driving up the demand for food and, thus, contributing to disrupted eating patterns affecting nutritional status [8].

The pandemic and restrictions during the lockdown significantly impacted patients with EDs. Many people suffering from this disorder had more difficulty getting away from food when

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they were confined at home, having more family conflict, emotional arousal, depression, and anxiety [10]. The significant difficulties in accessing healthcare facilities for diagnosis and cure, changes in routinely exercising and eating, and self-isolation in a potentially triggering environment might have created additional psychological distress, which, in turn, may result in more disordered eating and clinical impairment [23].

A longitudinal study evaluating the impact of the COVID-19 epidemic on EDs patients, considering the role of pre-existing vulnerabilities (*i.e.*, psychopathology, childhood trauma, attachment style, and COVID-19-related post-traumatic symptoms), reported that patients experienced an increase in compensatory physical exercising during the lockdown. Moreover, patients with BN exacerbated binge eating attitudes, and the lockdown may have interfered with treatment outcomes. Previously remitted patients revealed new exacerbations of symptomatology after lockdown, especially in BN and AN [15].

Other reports suggested that people might have heterogeneous responses to the pandemic, also based on pre-existing psychopathological features increasing people's vulnerability to any disaster-related trauma [24]. Moreover, any improvements observed before the pandemic have been interrupted abruptly due to restrictive measures observed during the first wave of the pandemic [25].

However, an online survey in the United States and the Netherlands reported that the time spent during the pandemic resulted in positive changes in the patient's life due to a sense of connection with family and friends, the ability to focus on recovery-oriented goals, and engagement in adaptive coping skills, despite the harmful effects mentioned above [26].

Government limitations have led to a shift in most clinical activities from face-to-face to telemedicine [27]. Although many participants acknowledged and appreciated the transition to telehealth, limitations of this treatment modality were raised for this population. The remote psychological treatment was already effectively employed in areas where geographical distance leads to inconveniences for healthcare facilities access. Nevertheless, access to adequate internet connectivity, availability of a quiet and confidential space, difficulties in weight detection, and discomfort of being filmed by a webcam represent the leading limitations of this approach [28]. Some surveys report that telemedicine may improve the effectiveness of phycological therapy in people with EDs who feel less self-conscious about their body image and more in control [29]. More research is needed to fully understand the patients' mental health impact of these resources on disease management.

3. EATING DISORDERS INFLUENCE ON COVID-19

Obesity and being underweight increase the risk of developing a viral infection [30]. In AN, gut-immune-system axis dysfunction has been described as a key regulator of systemic inflammation, cardiovascular risk, and immune system dysfunction [31]. Malnourishment induces gut microbiome changes that, in turn, increase gastrointestinal mucosal permeability, indigenous gut bacteria translocation, and systemic inflammation [32]. The neuro and immune (*i.e.*, mast cells) control of gut motility is harmed in AN [33], and it may contribute to maintaining poor nourishment in individuals with this chronic eating disorder. Chronic stress is a pivotal element in eating disorders and could be considered another cause of gut dysfunction in AN, as demonstrated by overactivity of the adrenocorticotropic axis [31, 32]. In addition, tryptophan metabolism is impaired in these patients, leading to reduced serotonin synthesis and enhanced synthesis of neurotoxic quinolinic acid that may precipitate depressive mood and further affect gut motility [32, 33]. However, controversial findings have been published in international literature. Other studies have suggested that despite severe malnourishment and impaired immune function, AN could increase the level of resilience against viral illnesses [34] for unclear reasons that are probably related to social distancing experienced by people with this eating disorder [10]. However, people with AN may be particularly vulnerable to COVID-19 because of emaciation and compromised physical health. Associations with fewer symptomatic viral infections in AN have not been studied. It is unknown whether these patients are less prone to infection or have a normal or even increased predisposition to infection, but with a greater probability of developing a less severe clinical progression [35]. In AN, a compromised capacity of cytokine response to infection has been hypothesized. This is attributable to immune exhaustion in the context of a persistent and pre-existing level of pro-inflammatory cytokines [36]. An inverse genetic correlation was found between AN and C-reactive protein (CRP), an acute phase infection biomarker [37]. Reduced or absent response of acutephase proteins, such as CRP, may delay signs and related symptoms of systemic inflammation, thus possibly postponing the time of diagnosis and fostering secondary bacterial infections [38]. Several studies confirmed that AN is associated with greater mortality because of delayed diagnosis of bacterial (often atypical) infectious diseases [39].

Patients with AN, presenting mild or no symptoms of infectious respiratory disease, often worsen clinical signs and symptoms during the recovery phase, particularly throughout the refeeding process [40]. However, a randomized controlled trial assessing the effects of refeeding therapy among mechanically ventilated adults found that caloric restriction significantly reduced the incidence of major respiratory infections [41].

Data on immune response in AN and obesity [42], and recent findings on the role of T-cells in the immune response in COVID-19 [43], show intact or increased T-cell proliferation in AN and elevated CD4-to-CD8 ratio [44] with lower expression of memory CD8 T-cell. This could be related to a perceived lack of symptomatic viral infections. And, a marked reduction in memory CD8 T-cells could lead to a reduction in lymphocytes' sub-serving recall responses. The most recent studies propose a unique immunological profile of AN, with reduced pro-inflammatory cytokines (IL-1, IL-6, and TNF), and the levels of IL-10 seem to be significantly influenced by ED diagnosis and BMI (*i.e.*, being higher in AN and normalweight individuals and lower in people suffering to binge eat-

ing disorder and obesity) [45]. The overproduction of IL-10 and the down-regulation of pro-inflammatory cytokines could explain the absence of symptoms related to infection in AN. Obesity, especially the visceral phenotype, is an independent risk factor for severe COVID-19 and has a higher mortality rate than the general population [46, 47]. Angiotensin-converting enzyme 2 (ACE2) has been identified as the host cell receptor for SARS-CoV-2, thus forming a basis for viral tropism in several tissues, including adipose tissue, and predisposing to viral entry [48]. Several mechanisms have been proposed to explain the relationship between obesity and COVID-19. These include chronic low-grade inflammation, altered memory CD8+ T-cell responses, increased circulating levels of pro-inflammatory cytokines, hyperleptinemia, and functional hypogonadism [49]. They appear to follow the opposite direction compared to AN. Adipose tissue is an immunological organ. The research identified a significant negative genetic correlation between AN and obesity linked to evolutionary adaptation and seems to be the opposite side of the same coin, involving metabolic and immunological mirror images [50]. There is a connection between the diverse response to specific infectious pathogens, cytokine biology, and fat distribution heterogeneity [51].

The field of research in ED may provide the opportunity to integrate the "metabolic and microbiome bookends" hypothesis of AN and obesity [52] to answer critical questions crucial to our understanding of the predisposition to clinical manifestation, progression, and outcomes of COVID-19 in AN and EDs.

The first step requires more clinical and laboratory studies on this topic and an epistemological perspective.

CONCLUSION

Our knowledge about COVID-19 is still advancing, but various hypotheses should inspire further research. Combining research in the field of EDs and COVID-19 may provide a unique opportunity to study the predisposition to COVID-19 in patients with EDs.

As obesity appears to be an epidemic and represents an independent risk factor for severe COVID-19, we need to address both pandemics in the context of genetic predisposition and obesogenic niche by applying modern evolutionary thinking [49].

Many data show that online treatment has some beneficial aspects, but work is still lacking to fully understand its impact on patients' mental health. Working on emotion regulating strategies as part of treatment in a post-pandemic world at a time when people have limited control over the antecedents of negative emotions may be a strategy for treatment in the future [30].

Short- and long-term consequences of simultaneously having EDs and COVID-19 are unknown, but this is likely to become more apparent over time. Long-term studies that consider a larger sample size are essential to assess the long-term effects of the blockade on ED patients and their healthcare providers and identify useful strategies to improve clinical management.

LIST OF ABBREVIATIONS

EDs	=	Eating Disorders
BN	=	Bulimia Nervosa
BED	=	Binge Eating Disorder

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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REFERENCES

- Smink, F.R.; van Hoeken, D.; Hoek, H.W. Epidemiology of eating disorders: incidence, prevalence and mortality rates. *Curr. Psychiatry Rep.*, 2012, 14(4), 406-414.
 http://dx.doi.org/10.1007/s11920-012-0282-v PMID: 22644309
- Harris, E.C.; Barraclough, B. Excess mortality of mental disorder. Br. J. Psychiatry, 1998, 173(1), 11-53. http://dx.doi.org/10.1192/bjp.173.1.11 PMID: 9850203
- [3] Marucci, S.; Ragione, L.D.; De Iaco, G.; Mococci, T.; Vicini, M.; Guastamacchia, E.; Triggiani, V. Anorexia nervosa and comorbid psychopathology. *Endocr. Metab. Immune Disord. Drug Targets*, 2018, 18(4), 316-324. http://dx.doi.org/10.2174/1871530318666180213111637 PMID: 29437020
- [4] Fernandez-Aranda, F.; Pinheiro, A.P.; Tozzi, F.; Thornton, L.M.; Fichter, M.M.; Halmi, K.A.; Kaplan, A.S.; Klump, K.L.; Strober, M.; Woodside, D.B.; Crow, S.; Mitchell, J.; Rotondo, A.; Keel, P.; Plotnicov, K.H.; Berrettini, W.H.; Kaye, W.H.; Crawford, S.F.; Johnson, C.; Brandt, H.; La Via, M.; Bulik, C.M. Symptom profile of major depressive disorder in women with eating disorders. *Aust. N. Z. J. Psychiatry*, **2007**, *41*(1), 24-31.

http://dx.doi.org/10.1080/00048670601057718 PMID: 17464678

[5] Swinbourne, J.M.; Touyz, S.W. The co-morbidity of eating disorders and anxiety disorders: a review. *Eur. Eat. Disord. Rev.*, 2007, 15(4), 253-274.

http://dx.doi.org/10.1002/erv.784 PMID: 17676696

[6] Halmi, K.A.; Sunday, S.R.; Klump, K.L.; Strober, M.; Leckman, J.F.; Fichter, M.; Kaplan, A.; Woodside, B.; Treasure, J.; Berrettini, W.H.; Al Shabboat, M.; Bulik, C.M.; Kaye, W.H. Obsessions and compulsions in anorexia nervosa subtypes. *Int. J. Eat. Disord.*, 2003, 33(3), 308-319.

http://dx.doi.org/10.1002/eat.10138 PMID: 12655628

- [7] Caglar-Nazali, H.P.; Corfield, F.; Cardi, V.; Ambwani, S.; Leppanen, J.; Olabintan, O.; Deriziotis, S.; Hadjimichalis, A.; Scognamiglio, P.; Eshkevari, E.; Micali, N.; Treasure, J. A systematic review and meta-analysis of 'Systems for Social Processes' in eating disorders. *Neurosci. Biobehav. Rev.*, **2014**, *42*, 55-92. http://dx.doi.org/10.1016/j.neubiorev.2013.12.002
 PMID: 24333650
- Brooks, S.K.; Webster, R.K.; Smith, L.E.; Woodland, L.; Wessely, S.; Greenberg, N.; Rubin, G.J. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet*, 2020, 395(10227), 912-920. http://dx.doi.org/10.1016/S0140-6736(20)30460-8 PMID: 32112714
- [9] Todisco, P.; Donini, L.M. Eating disorders and obesity (ED&O) in the COVID-19 storm. *Eat. Weight Disord.*, **2021**, *26*(3), 747-750. http://dx.doi.org/10.1007/s40519-020-00938-z PMID: 32488728
- [10] Touyz, S.; Lacey, H.; Hay, P. Eating disorders in the time of COVID-19. J. Eat. Disord., 2020, 8(1), 19.
 http://dxia.org/10.118/c/40227_000_00205_2_DMID: 20227045
 - http://dx.doi.org/10.1186/s40337-020-00295-3 PMID: 32337045
- [11] Haddad, C.; Zakhour, M.; Bou Kheir, M.; Haddad, R.; Al Hachach, M.; Sacre, H.; Salameh, P. Association between eating behavior and

quarantine/confinement stressors during the coronavirus disease 2019 outbreak. *J. Eat. Disord.*, **2020**, *8*(1), 40. http://dx.doi.org/10.1186/s40337-020-00317-0 PMID: 32879730

- [12] Nutley, S.K.; Falise, M.A.; Henderson, R.; Apostolou, V.; Mathews, C.A.; Striley, C.W. Impact of the COVID-19 Pandemic on Disordered Eating Behavior: Qualitative Analysis of Social Media Posts. *JMIR Ment Health*, **2021**, 8(1), e26011.
- [13] Phillipou, A.; Meyer, D.; Neill, E.; Tan, E.J.; Toh, W.L.; Van Rheenen, T.E.; Rossell, S.L. Eating and exercise behaviors in eating disorders and the general population during the COVID-19 pandemic in Australia: Initial results from the COLLATE project. *Int. J. Eat. Disord.*, **2020**, *53*(7), 1158-1165. http://dx.doi.org/10.1002/eat.23317 PMID: 32476163
- [14] Rodgers, R.F.; Lombardo, C.; Cerolini, S.; Franko, D.L.; Omori, M.; Fuller-Tyszkiewicz, M.; Linardon, J.; Courtet, P.; Guillaume, S. The impact of the COVID-19 pandemic on eating disorder risk and symptoms. *Int. J. Eat. Disord.*, **2020**, *53*(7), 1166-1170. http://dx.doi.org/10.1002/eat.23318 PMID: 32476175
- Weissman, R.S.; Bauer, S.; Thomas, J.J. Access to evidence-based care for eating disorders during the COVID-19 crisis. *Int. J. Eat. Disord.*, 2020, 53(5), 369-376. http://dx.doi.org/10.1002/eat.23279 PMID: 32338400
- [16] Clark Bryan, D.; Macdonald, P.; Ambwani, S.; Cardi, V.; Rowlands, K.; Willmott, D.; Treasure, J. Exploring the ways in which COVID-19 and lockdown has affected the lives of adult patients with anorexia nervosa and their carers. *Eur. Eat. Disord. Rev.*, 2020, 28(6), 826-835. http://dx.doi.org/10.1002/erv.2762 PMID: 32643844
- [17] Schlegl, S.; Maier, J.; Meule, A.; Voderholzer, U. Eating disorders in times of the COVID-19 pandemic-Results from an online survey of patients with anorexia nervosa. *Int. J. Eat. Disord.*, 2020, 53(11), 1791-1800. http://dx.doi.org/10.1002/eat.23374 PMID: 32841413
- [18] Pearl, R.L. Weight Stigma and the "Quarantine-15". Obesity (Silver Spring), 2020, 28(7), 1180-1181.
- http://dx.doi.org/10.1002/oby.22850 PMID: 32324954
 [19] Khosravi, M. The challenges ahead for patients with feeding and eating disorders during the COVID-19 pandemic. *J. Eat. Disord.*, **2020**, 8(1), 43.
- http://dx.doi.org/10.1186/s40337-020-00322-3 PMID: 32922783
 [20] Colleluori, G.; Goria, I.; Zillanti, C.; Marucci, S.; Dalla Ragione, L. Eating disorders during COVID-19 pandemic: the experience of Italian healthcare providers. *Eat. Weight Disord.*, **2021**, 26(8), 2787-2793.
- http://dx.doi.org/10.1007/s40519-021-01116-5 PMID: 33560511
 [21] NIH US National Library of Medicine, Eating Habits of Adults During the Quarantine. Clinical trials 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04339842 [Last accessed 25 Apr 2020].
- [22] Braden, A.; Musher-Eizenman, D.; Watford, T.; Emley, E. Eating when depressed, anxious, bored, or happy: Are emotional eating types associated with unique psychological and physical health correlates? *Appetite*, **2018**, *125*, 410-417. http://dx.doi.org/10.1016/j.appet.2018.02.022 PMID: 29476800
- [23] Machado, P.P.P.; Pinto-Bastos, A.; Ramos, R.; Rodrigues, T.F.; Louro, E.; Gonçalves, S.; Brandão, I.; Vaz, A. Impact of COVID-19 lockdown measures on a cohort of eating disorders patients. *J. Eat. Disord.*, **2020**, 8(1), 57. http://dx.doi.org/10.1186/s40337-020-00340-1 PMID: 33292539
- [24] Castellini, G.; Cassioli, E.; Rossi, E.; Innocenti, M.; Gironi, V.; Sanfilippo, G.; Felciai, F.; Monteleone, A.M.; Ricca, V. The impact of COVID-19 epidemic on eating disorders: A longitudinal observation of pre *versus* post psychopathological features in a sample of patients with eating disorders and a group of healthy controls. *Int. J. Eat. Disord.*, 2020, 53(11), 1855-1862. http://dx.doi.org/10.1002/eat.23368 PMID: 32856333
- [25] Fiorillo, A.; Gorwood, P. The consequences of the COVID-19 pandemic on mental health and implications for clinical practice. *Eur. Psychiatry*, **2020**, *63*(1), e32. http://dx.doi.org/10.1192/j.eurpsy.2020.35 PMID: 32234102
- [26] Fernández-Aranda, F.; Casas, M.; Claes, L.; Bryan, D.C.; Favaro, A.; Granero, R.; Gudiol, C.; Jiménez-Murcia, S.; Karwautz, A.; Le Grange, D.; Menchón, J.M.; Tchanturia, K.; Treasure, J. COVID-19 and implications for eating disorders. *Eur. Eat. Disord. Rev.*, 2020, 28(3), 239-245.

http://dx.doi.org/10.1002/erv.2738 PMID: 32346977

[27] Termorshuizen, J.D.; Watson, H.J.; Thornton, L.M.; Borg, S.; Flatt, R.E.; MacDermod, C.M.; Harper, L.E.; van Furth, E.F.; Peat, C.M.; Bulik, C.M. Early impact of COVID-19 on individuals with self-reported eating disorders: A survey of ~1,000 individuals in the United States and the Netherlands. *Int. J. Eat. Disord.*, **2020**, *53*(11), 1780-1790.

http://dx.doi.org/10.1002/eat.23353 PMID: 32720399

[28] Tuerk, P.W.; Keller, S.M.; Acierno, R. Treatment for anxiety and depression *via* clinical videoconferencing: evidence base and barriers to expanded access in practice. *Focus Am. Psychiatr. Publ.*, 2018, 16(4), 363-369.

http://dx.doi.org/10.1176/appi.focus.20180027 PMID: 31975928

- [29] Simpson, S.; Bell, L.; Knox, J.; Mitchell, D. Therapy via videoconferencing: a route to client empowerment? *Clin. Psychol. Psychother.*, 2005, 12(2), 156-165. http://dx.doi.org/10.1002/cpp.436
- [30] Simeunovic Ostojic, M.; Maas, J.; Bodde, N.M.G. COVID-19, anorexia nervosa and obese patients with an eating disorder - some considerations for practitioners and researchers. *J. Eat. Disord.*, **2021**, 9(1), 15.

http://dx.doi.org/10.1186/s40337-021-00369-w PMID: 33472682

- [31] Achamrah, N.; Déchelotte, P.; Coëffierabc, M. New therapeutic approaches to target gut-brain axis dysfunction during anorexia nervosa. *Clin. Nutr. Exp.*, **2019**, *28*, 33-41. http://dx.doi.org/10.1016/j.yclnex.2019.01.006
- [32] Roubalová, R.; Procházková, P.; Papežová, H.; Smitka, K.; Bilej, M.; Tlaskalová-Hogenová, H. Anorexia nervosa: Gut microbiotaimmune-brain interactions. *Clin. Nutr.*, **2020**, *39*(3), 676-684. http://dx.doi.org/10.1016/j.clnu.2019.03.023 PMID: 30952533
- [33] Hart, A.; Kamm, M.A. Review article: mechanisms of initiation and perpetuation of gut inflammation by stress. *Aliment. Pharmacol. Ther.*, 2002, *16*(12), 2017-2028. http://dx.doi.org/10.1046/j.1365-2036.2002.01359.x
 PMID: 12452934
- [34] Dobner, J.; Kaser, S. Body mass index and the risk of infection from underweight to obesity. *Clin. Microbiol. Infect.*, 2018, 24(1), 24-28.

http://dx.doi.org/10.1016/j.cmi.2017.02.013 PMID: 28232162

- [35] Brown, R.F.; Bartrop, R.; Beumont, P.; Birmingham, C.L. Bacterial infections in anorexia nervosa: delayed recognition increases complications. *Int. J. Eat. Disord.*, 2005, 37(3), 261-265. http://dx.doi.org/10.1002/eat.20135 PMID: 15822085
- [36] Nova, E.; Samartín, S.; Gómez, S.; Morandé, G.; Marcos, A. The adaptive response of the immune system to the particular malnutrition of eating disorders. *Eur. J. Clin. Nutr.*, **2002**, *56*(S3)(Suppl. 3), S34-S37.

http://dx.doi.org/10.1038/sj.ejcn.1601482 PMID: 12142959

- [37] Tylee, D.S.; Sun, J.; Hess, J.L.; Tahir, M.A.; Sharma, E.; Malik, R.; Worrall, B.B.; Levine, A.J.; Martinson, J.J.; Nejentsev, S.; Speed, D.; Fischer, A.; Mick, E.; Walker, B.R.; Crawford, A.; Grant, S.F.A.; Polychronakos, C.; Bradfield, J.P.; Sleiman, P.M.A.; Hakonarson, H.; Ellinghaus, E.; Elder, J.T.; Tsoi, L.C.; Trembath, R.C.; Barker, J.N.; Franke, A.; Dehghan, A. 23 and Me Research Team. Inflammation Working Group of the CHARGE Consortium; METASTROKE Consortium of the International Stroke Genetics Consortium; Netherlands Twin Registry; neuroCHARGE Working Group; Obsessive Compulsive and Tourette Syndrome Working Group of the Psychiatric Genomics Consortium, Faraone SV, Glatt SJ. Genetic correlations among psychiatric and immune-related phenotypes based on genome-wide association data. Am. J. Med. Genet. B. Neuropsychiatr. Genet., 2018, 177(7), 641-657. http://dx.doi.org/10.1002/ajmg.b.32652 PMID: 30325587
- [38] Guinhut, M.; Melchior, J.; Godart, N.; Hanachi, M. Extremely severe anorexia nervosa: hospital course of 354 adult patients in a clinical nutrition-eating disorders-unit. *Clin. Nutr.*, **2020**, *6*, 9-11. http://dx.doi.org/10.1016/j.clnu.2020.09.0113 PMID: 33023762
- [39] Nilsson, I.A.K.; Millischer, V.; Göteson, A.; Hübel, C.; Thornton, L.M.; Bulik, C.M.; Schalling, M.; Landén, M. Aberrant inflammatory profile in acute but not recovered anorexia nervosa. *Brain Behav. Immun.*, **2020**, *88*, 718-724.
 - http://dx.doi.org/10.1016/j.bbi.2020.05.024 PMID: 32389698
- [40] Doig, G.S.; Simpson, F.; Heighes, P.T.; Bellomo, R.; Chesher, D.; Caterson, I.D.; Reade, M.C.; Harrigan, P.W. Refeeding Syndrome

Trial Investigators Group. Restricted *versus* continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, singleblind controlled trial. *Lancet Respir. Med.*, **2015**, *3*(12), 943-952. http://dx.doi.org/10.1016/S2213-2600(15)00418-X PMID: 26597128

- [41] Dalton, B.; Bartholdy, S.; Robinson, L.; Solmi, M.; Ibrahim, M.A.A.; Breen, G.; Schmidt, U.; Himmerich, H. A meta-analysis of cytokine concentrations in eating disorders. *J. Psychiatr. Res.*, 2018, 103, 252-264. http://dx.doi.org/10.1016/j.jpsychires.2018.06.002
 PMID: 29906710
- [42] Grifoni, A.; Weiskopf, D.; Ramirez, S.I.; Mateus, J.; Dan, J.M.; Moderbacher, C.R.; Rawlings, S.A.; Sutherland, A.; Premkumar, L.; Jadi, R.S.; Marrama, D.; de Silva, A.M.; Frazier, A.; Carlin, A.F.; Greenbaum, J.A.; Peters, B.; Krammer, F.; Smith, D.M.; Crotty, S.; Sette, A. Targets of T cell responses to sars-cov-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell*, **2020**, *181*(7), 1489-1501.e15.
- http://dx.doi.org/10.1016/j.cell.2020.05.015 PMID: 32473127
 [43] Gibson, D.; Mehler, P.S. Anorexia nervosa and the immune system: a narrative review. J. Clin. Med., 2019, 8(11), 1915.
- http://dx.doi.org/10.3390/jcm8111915 PMID: 31717370
 [44] Caroleo, M.; Carbone, E.A.; Greco, M.; Corigliano, D.M.; Arcidiacono, B.; Fazia, G.; Rania, M.; Aloi, M.; Gallelli, L.; Segura-Garcia, C.; Foti, D.P.; Brunetti, A. brain-behavior-immune interaction: serum cytokines and growth factors in patients with eating disorders at extremes of the body mass index (BMI) spectrum. *Nutrients*, 2019, *11*(9), 1995.
- http://dx.doi.org/10.3390/nu11091995 PMID: 31450770
 [45] Huang, Y.; Lu, Y.; Huang, Y.M.; Wang, M.; Ling, W.; Sui, Y.; Zhao, H.L. Obesity in patients with COVID-19: a systematic review and meta-analysis. *Metabolism*, 2020, 113, 154378. http://dx.doi.org/10.1016/j.metabol.2020.154378 PMID: 33002478

- [46] Giagulli, V.A.; Guastamacchia, E.; Magrone, T.; Jirillo, E.; Lisco, G.; De Pergola, G.; Triggiani, V. Worse progression of COVID-19 in men: Is testosterone a key factor? *Andrology*, **2021**, 9(1), 53-64. http://dx.doi.org/10.1111/andr.12836 PMID: 32524732
- [47] Radzikowska, U.; Ding, M.; Tan, G.; Zhakparov, D.; Peng, Y.; Wawrzyniak, P.; Wang, M.; Li, S.; Morita, H.; Altunbulakli, C.; Reiger, M.; Neumann, A.U.; Lunjani, N.; Traidl-Hoffmann, C.; Nadeau, K.C.; O'Mahony, L.; Akdis, C.; Sokolowska, M. Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. *Allergy*, **2020**, *75*(11), 2829-2845. http://dx.doi.org/10.1111/all.14429 PMID: 32496587

[48] Lisco, G.; Giagulli, V.A.; De Pergola, G.; De Tullio, A.; Guastamacchia, E.; Triggiani, V. COVID-19 IN MAN: A VERY DANGER-OUS AFFAIR. *Endocr. Metab. Immune Disord. Drug Targets*, 2021, 21(9), 1544-1554. http://dx.doi.org/10.2174/1871530321666210101123801 PMID: 33388025

- [49] Mahon, P.B.; Hildebrandt, T.B.; Burdick, K.E. New genetic discoveries in anorexia nervosa: implications for the field. Am. J. Psychiatry, 2017, 174(9), 821-822.
- http://dx.doi.org/10.1176/appi.ajp.2017.17050574 PMID: 28859512
 [50] Wells, J.C. Ethnic variability in adiposity and cardiovascular risk: the variable disease selection hypothesis. *Int. J. Epidemiol.*, 2009, 38(1), 63-71.

http://dx.doi.org/10.1093/ije/dyn183 PMID: 18820320

- [51] Bulik, C.M.; Flatt, R.; Abbaspour, A.; Carroll, I. Reconceptualizing anorexia nervosa. *Psychiatry Clin. Neurosci.*, **2019**, *73*(9), 518-525. http://dx.doi.org/10.1111/pcn.12857 PMID: 31056797
- [52] Vuillier, L.; May, L.; Greville-Harris, M.; Surman, R.; Moseley, R.L. The impact of the COVID-19 pandemic on individuals with eating disorders: the role of emotion regulation and exploration of online treatment experiences. *J. Eat. Disord.*, **2021**, *9*(1), 10. http://dx.doi.org/10.1186/s40337-020-00362-9 PMID: 33436064

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