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USE OF BIOMARKERS IN THE DIAGNOSIS OF DEPRESSIVE DISORDERS AND SCHIZOPHRENIA

Ticiana Palhares Sampaio
Fundação Técnico Educacional Souza Marques

Lucas Marinho Coutinho Antunes
Fundação Técnico Educacional Souza Marques

Júlia Oscheneek Franca
Fundação Técnico Educacional Souza Marques

Victoria Medeiros Sasaki
Fundação Técnico Educacional Souza Marques

Gabriella Schenker Margulies
Fundação Técnico Educacional Souza Marques

Isabella Soares Netto Lisboa
Fundação Técnico Educacional Souza Marques

Abstract: Goal: to explore advances in the search for biomarkers that can improve accuracy in the diagnosis of depressive disorders and schizophrenia. **Methods:** literature review using the PUBMED, SCIELO databases and the Molecular Biology journal. Selected articles published from 2016 onwards. **Results:** Depression was widely associated with inflammatory processes, with patients showing elevation of inflammatory markers, such as IL-6, IL-2R, (CARVALHO et al, 2020), IL-4 (OSIMO et al, 2020), and other pro-inflammatory cytokines such as TNF-b, without subtype discrimination. Inflammatory dysfunction is related to the stage and severity of the disease. Furthermore, the relationship between growth factors and the pathophysiology of depression is observed. (CARVALHO et al, 2020). The increase in glutamate and cortisol, and the decrease in serotonin and noradrenaline have also been attributed as important in the development of depression. (DELL'OSSO et al, 2016). Schizophrenia has some biomarkers that can possibly help in the diagnosis of this disease. Results are obtained with the use of niacin, which indicate the existence of a subgroup of patients with common biochemical characteristics (SUN et al, 2017). These patients have a reaction to this substance, which appears in the form of redness. Certain markers are still shared with major depressive disorder and bipolar disorder, such as BNDF (Brain Derived Neutrophic Factor), IL-6 and TNFs. They are unlikely to be used as biomarkers for diagnosing schizophrenia (LAI et al, 2016) **Conclusion:** Ultimately, the use of biomarkers in the process of diagnosing psychiatric disorders is still under development. However, investment in studies on the subject is of extreme scientific importance as they may be responsible for improving the ability to make an earlier and more accurate diagnosis for cases of Depressive Disorders or Schizophrenia.

Keywords: Schizophrenia, biological markers, depression.

INTRODUCTION

A biomarker can be defined as a compound (serum protein concentrations, abnormal cardiac phenomena, etc.) that when observed in a clinical context can predict an outcome, and its observation has multiple uses, such as: diagnosis of comorbidities, exclusion of pathologies in patients, prognosis report and disease monitoring, among others (ARONSON, 2017). Biomarkers are often used for diagnostics in areas such as cardiology and endocrinology, for example, which use this resource a lot to monitor the condition of patients (GAGGIN, 2013 and D'HERBOMEZ, 2014). According to Mesquita, E. (2015), this tool is able to more accurately identify individuals at high risk of becoming ill, diagnose more quickly, as well as assist in treatment and prognosis.

Currently, the incidence of Depressive Disorder and other psychiatric disorders has increased to the point where they become major disabling causes in today's society (NOBIS et al., 2020). Therefore, progress in studies on possible biomarkers related to such comorbidities is of global interest and may change the course of their diagnoses.

The diagnosis of Depressive Disorder is based on clinical description, laboratory tests only to exclude other pathologies, follow-up studies and family history (MAIA, C. 2017). Therefore, currently, there is no more accurate method that can provide greater assertiveness for the diagnosis. This reality leaves room for a longer delay in reaching a diagnosis and, consequently, adequate management.

According to CARVALHO et al., 2020, the use of biomarkers in the diagnosis of depression has the potential to be carried

out in the future from the analysis of serum levels of various inflammatory markers and cytokines, and would have the advantage of the possibility of a considerably faster diagnosis. and more accurate.

In addition to Depressive Disorder, Schizophrenia is a difficult-to-control psychiatric disorder that is hardly diagnosed early (CARVALHO et al, 2020). According to Carteri, Randhall Bruce et al (2020), this disorder is a relevant social and economic concern worldwide. It is characterized as a cognitive, emotional and behavioral disorder that culminates in impaired mental functioning. This disorder is characterized by symptoms such as delusions, hallucinations, disorganized speech and behavior, among other symptoms that cause an individual's occupational and social dysfunction. In this context, to close a diagnosis these symptoms must be present for 6 months (Carteri, Randhall Bruce et al, 2020). Therefore, the discovery of specific biomarkers capable of more accurately identifying a condition of the disorder can accelerate the diagnosis, thus providing benefits to the treatment.

Thus, according to ZHANG et al, 2016 and SUN et al, 2017, the diagnosis of psychiatric disorders has the potential to be carried out in the future with the help of a serum analysis of proteins related to immunity, growth factors and metabolic reactions. The objective of the present work was to explore advances and difficulties in the search for biomarkers that can improve the accuracy in the diagnosis of depressive disorders and schizophrenia.

METHOD

Literature review by the PUBMED and SCIELO databases, with the search for the descriptors "biomarker", "schizophrenia", "mental disorders", "psychiatry" and "depression" joined by the AND connector and "depressive disorder" and "pharmacogenetics" also joined by the AND connector. Thirty articles were found, discarding those that did not address the use of biomarkers for the therapeutic choice in cases of depressive disorder and schizophrenia. The selected articles were published in the last 5 years (2016-2021), had the full text available for reading and were filtered by the English language. Of those found, 22 were selected for data extraction and carrying out the work.

RESULTS AND DISCUSSION

DEPRESSION MARKERS

The link between depression and inflammation has been proven through scientific studies (KOHLER et al, 2016), and patients with inflammatory disorders have higher rates of depression. Elevation of inflammatory markers is continuous in depression, without subtype discrimination. (OSIMO et al, 2020). It was observed that inflammatory dysfunction is more related to the stage and severity of the disease. (DUBOIS et al, 2018). However, the presence of inflammation is also an indicator of schizophrenia and bipolar disorder. Regarding cytokines, we can mention some of relevance.

The increased concentration of IL-6, among the inflammatory cytokines, is the most increased and reported in depression and can be used as an early marker for cognitive decline in depression. Tumor necrosis factor alpha is also constantly increased in depression relative to healthy individuals. (CARVALHO et al, 2020). However, this marker for depression is still inconclusive.

Regarding interleukins, an increase in IL-2R in the blood has been reported in patients with depression and bipolar disorder. (CARVALHO et al, 2020) Interleukin-4 (IL-4), one of the most important anti-inflammatory cytokines, on the other hand, was recently found to be down-regulated in depression. (OSIMO et al, 2020)

Regarding the decrease in bone mineral density in depressive patients, altered levels of bone markers, osteoprotegerin, osteopontin and RANK-RANKL were observed. (KADRIU et al, 2018).

Upregulation of malonic dialdehyde (MDA) - the end product of lipid peroxidation that contributes to the activation of pro-inflammatory cytokines, such as TNF-ß and IL-8 - is reported in major depressive disorder. (OGLODEK, 2018).

Another relationship seen was growth factors as promising markers for depression. Brain-derived neurotrophic factor (BDNF), endothelial growth factor, fibroblast growth factor (FGF) and nerve growth factor (VGF) are involved in the pathophysiology of depression and modulated with the use of antidepressants. Baseline levels of BDNF are decreased in patients with depressive disorder, with the magnitude of its decrease being negatively related to the severity of depression. Another growth factor, FGF-2, has been reported to be elevated in depressed patients. (CARVALHO et al, 2020).

Increased peripheral glutamate concentration and cortical hyperglutamatergy were associated with depression (CARVALHO et al, 2020). The increase in glutamate is related to the decrease in serotonin and norepinephrine and can generate excitotoxicity, which contributes to the development of depression. Decreased levels of dopamine in the striatum and cortex have also been reported. Furthermore, reduced plasma tryptophan may be a marker for depression. (DELL'OSSO et al, 2016).

Regarding cortisol, a difference was observed between healthy individuals and those with depression. Evidence supports the diagnosis of elevated serum cortisol concentrations. (JIA et al, 2019).

Despite the links between the aforementioned markers and patients with depression, there is still difficulty in the scientific field to establish associations between biochemical alterations and the diagnosis of depression.

SCHIZOPHRENIA MARKERS

In schizophrenia, the redness that appears on the skin with the use of niacin may be a biomarker that helps in the diagnosis of this disease (MAROUFI et al, 2016). However, in a subgroup of patients, homogeneous biochemical characteristics are noted, allowing researchers to understand more about the disease (SUN et al, 2017). These defects in phospholipid signaling allow niacin to be used as a bioindicator.

The subgroup is about 30.67% of the total population of schizophrenic patients, with a specificity of 88.37% for men and 83.75% for women. This reaction, shown in this subgroup, is due to abnormalities in the fatty acid composition of the membrane, which may be caused by increased phospholipase A2 activity, oxidative stress or dysregulation of lipid metabolism in patients with schizophrenia. (SUN et al, 2017).

According to Zhang et al (2016), patients with schizophrenia had significantly low levels of BNDF. However, this finding is also present in major depressive disorder and bipolar disorder, making it less likely to be used as a bioindicator (LAI et al, 2016). Patients also showed a positive correlation of BNDF with levels of IL-2 and IL-8, while low levels of BNDF and TNF-α together are associated with poor performance on the PANSS (Positive and Negative Syndrome Scale) regarding questions cognitive. (ZHANG et al, 2016).

Other markers that call attention to schizophrenia are those involved with inflammatory processes, where, through them, it is possible to diagnose neuroatypicals, who have schizophrenia, in the control group. This is because more than 70% of bioindicators for

this disease are involved in the response of the inflammatory process. These are: S100B, IL-6, IL-2 and TNFs. (LAI et al, 2016).

Furthermore, according to Pandurangi and Buckley (2020), the use of antipsychotic drugs such as clozapine is associated with a decrease in these cells involved in the response of inflammatory processes, cytokines.

Monoamines such as dopamine, norepinephrine and serotonin are also directly associated with the pathogenesis of schizophrenia, which are modulated pharmacologically through the use of antipsychotics to treat the disease.

Finally, according to Lai et al (2016), some studies have shown that peripheral bioindicators are more useful as indicators of patient status. Changes in these same markers appear to be associated with how the patient appears clinically, responses to treatments, and clinical changes in symptoms, suggesting that these are specific to certain clinical events.

CONCLUSION

Ultimately, the use of biomarkers in the process of diagnosing psychiatric disorders is still under development. However, investment in studies on the subject is of extreme scientific importance as they may be responsible for improving the ability to make an earlier and more accurate diagnosis for cases of Depressive Disorders or Schizophrenia. Therefore, the existence of biomarkers associated with the aforementioned disorders may, in the future, enable greater effectiveness in psychiatric treatment. After all, there is currently no more accurate method that can provide greater assertiveness for diagnosis. Given the complex nature of the process, there is a long way to go in search of scientific data that prove the efficiency of biomarkers for performing diagnoses in psychiatry, however, as presented in the present review, relevant studies have presented solid results on the subject. This way, the development of new scientific studies that can enrich the current knowledge on the subject are of paramount importance.

REFERENCES

ARONSON JK, et al. Biomarkers-A General Review. *Curr Protoc Pharmacol*. 2017; 76:9.23.1-9.23.17. doi:10.1002/cpph.19

BRAND S.J, et al. A review of biomarkers in mood and psychotic disorders: A dissection of clinical vs. preclinical correlates. *Curr. Neuropharmacol.* 2015; 13:324–368. doi: 10.2174/1570159X13666150307004545.

Carteri, Randhall Bruce et al. A closer look at the epidemiology of schizophrenia and common mental disorders in Brazil. Dementia & Neuropsychologia [online]. 2020, v. 14, n. 03 [Accessed 10 June 2021] , pp. 283-289. Available from: <https://doi.org/10.1590/1980-57642020dn14-030009>. Epub 18 Sept 2020. ISSN 1980-5764. https://doi.org/10.1590/1980-57642020dn14-030009.

CARVALHO AF, et al. Revisão abrangente baseada em evidências de 162 biomarcadores periféricos para os principais transtornos mentais. *Tradução Psiquiatria.* 2020; 10: 1-13. doi: 10.1038 / s41398-020-0835-5.

DELL'OSSO L, Carmassi C, Mucci F, Marazziti D. Depression, Serotonin and Tryptophan. *Curr Pharm Des*. 2016;22(8):949-54. doi: 10.2174/1381612822666151214104826. PMID: 26654774.

D'HERBOMEZ M, et al. Biomarqueurs en endocrinologie [Biomarkers in endocrinology]. *Presse Med*. 2014; 43(1):40-56. doi:10.1016/j.lpm.2013.11.003

DUBOIS T., et. al. Immunity and psychiatric disorders: variabilities of immunity biomarkers are they specific? *Psychiatr. Danub.* 2018; 30: 447–451. PMID: 30439824

Expert Group on BiomarkersBiomarkers in Cardiology - Part 2: In Coronary Heart Disease, Valve Disease and Special Situations. Arquivos Brasileiros de Cardiologia [online]. 2015, v. 104, n. 5 [Acessado 10 Junho 2021] , pp. 337-346. Disponível em: <https://doi.org/10.5935/abc.20150061>. Epub Maio 2015. ISSN 1678-4170. https://doi.org/10.5935/abc.20150061.

GAGGIN HK, et al. Biomarkers and diagnostics in heart failure. *Biochim Biophys Acta*. 2013; 1832(12):2442-2450. doi:10.1016/j.bbadis.2012.12.014

JIA Y, LIU L, et al. Increased Serum Levels of Cortisol and Inflammatory Cytokines in People With Depression. *J Nerv Ment Dis*. 2019 Apr;207(4):271-276. doi: 10.1097/NMD.0000000000000957. Erratum in: J Nerv Ment Dis. 2019 Jul;207(7):610. PMID: 30844940.

KADRIU B, et al. A administração aguda de cetamina corrige marcadores ósseos inflamatórios anormais no transtorno depressivo maior. *Mol. Psiquiatria*. 2018; 23: 1626–1631. doi: 10.1038 / mp.2017.109.

KOHLER O, KROGH J, MORS O, BENROS ME. Inflammation in Depression and the Potential for Anti-Inflammatory Treatment. *Curr Neuropharmacol.* 2016;14(7):732-42. doi: 10.2174/1570159x14666151208113700. PMID: 27640518; PMCID: PMC5050394.

LAI, Chi-Yu *et al*. Biomarkers in schizophrenia: A focus on blood based diagnostics and theranostics. *World J Psychiatry*, [*s. l.*], ano 2016, v. 6, 2016.

LIU T, et al. Uma meta-análise de marcadores de estresse oxidativo na depressão. *PLos ONE*. 2015; 10:e0138904. doi:10.1371/journal.pone.0138904.

Maia, Caio & Campos, Eugênio. (2017). Estado da arte da nosologia psiquiátrica: RDoC em debate. Revista de Medicina da UFC. 57. 36. 10.20513/2447-6595.2017v57n1p36-42.

NOBIS, Aleksander; ZALEWSKI, Daniel; WASZKIEWICZ, Napoleon. Peripheral Markers of Depression. 2020, *J. Clin. Med.* 9, no. 12: 3793. doi:10.3390/jcm9123793

OGLODEK EA. Changes in the concentrations of inflammatory and oxidative status biomediators (MIP-1 α, PMN elastase, MDA, and IL-12) in depressed patients with and without posttraumatic stress disorder. *Pharmacol Rep.* 2018 Feb;70(1):110-118. doi: 10.1016/j.pharep.2017.08.008. Epub 2017 Aug 26. PMID: 29339257.

OSIMO, E.F, PILLINGER, T, RODRIGUEZ, I.M, KHANDAKER G.M, PARIANTE C.M, HOWES, O.D. Marcadores inflamatórios em depressão: Uma meta-análise de diferenças médias e variabilidade em 5166 pacientes e 5083 controles. 2020, *Brain Behav. Imun.* 2020:901–909. doi: 10.1016/j.bbi.2020.02.010.

PANDURANGI, Ananda K; BUCKLEY, Peter F. Inflammation, Antipsychotic Drugs, and Evidence for Effectiveness of Anti-inflammatory Agents in Schizophrenia. *Curr Top Behav Neurosci.,* [*s. l.*], ano 2019, v. 44, p. 227-244, 2019.

SUN, Liya; YANG, Xuhan; JIANG, Jie; *et al*. Identification of the Niacin-Blunted Subgroup of Schizophrenia Patients from Mood Disorders and Healthy Individuals in Chinese Population. Schizophrenia Bulletin, v. 44, n. 4, p. 896–907, 2017. Disponível em: <https://academic.oup.com/schizophreniabulletin/article/44/4/896/4564459>. Acesso em: 5 Jun. 2021.

YAO, Jeffrey K.; DOUGHERTY, George G.; GAUTIER, Clara H.; *et al*. Prevalence and Specificity of the Abnormal Niacin Response: A Potential Endophenotype Marker in Schizophrenia. *Schizophrenia Bulletin*, v. 42, n. 2, p. 369–376, 2015. https://doi.org/10.1093/schbul/sbv130

ZHANG, Xiang Yang; TAN, Yun-Long; CHEN, Da-Chun; *et al*. Interaction of BDNF with cytokines in chronic schizophrenia. Brain, Behavior, and Immunity, v. 51, p. 169–175, 2016. Disponível em: <https://www.sciencedirect.com/science/article/abs/pii/S0889159115300210#!>. Acesso em: 5 Jun. 2021.