

# Therapeutic applications of recent advancements in insight regarding mechanisms of development of Anorexia Nervosa: implications in the management and development of biomarkers for early detection besides avoidance of neonatal malformations

Kulvinder Kochar Kaur<sup>1\*</sup>, Gautam Nand K Allahbadia<sup>2</sup>, Mandeep Singh<sup>3</sup>

<sup>1</sup>Centre For Human Reproduction Scientific Director cum Owner, G.T.B. Nagar, Jalandhar, Punjab, India.

<sup>2</sup>Ex-Rotunda-A Centre for Human Reproduction, Kalpak Garden, Perry Cross Road, Near Otter's Club, Bandra(W), Mumbai, India.

<sup>3</sup>Consultant Neurologist, Swami Satyanand Hospital, Near Nawi Kachehri, Baradri, Ladowali Road, Jalandhar, Punjab.

**\*Corresponding Author:** Kulvinder K. K., Centre for Human Reproduction Scientific Director cum Owner, G.T.B. Nagar, Jalandhar, Punjab, India.

**Received Date:** 15 October 2022; **Accepted Date:** 24 October 2022; **Published date:** 28 November 2022.

**Citation:** Kulvinder K. K., (2022). Therapeutic applications of recent advancements in insight regarding mechanisms of development of Anorexia Nervosa: implications in the management and development of biomarkers for early detection besides avoidance of neonatal malformations-A Short Communication. Journal of Internal Medicine & Health Affairs. 1(1). DOI: 10.58489/2836-2411/002

**Copyright:** © 2022 Kulvinder K. K., this is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

## Abstract

Earlier we had reviewed regarding how patients of AN who present with primary/secondary hypothalamic amenorrhoea were markedly recalcitrant to any forms of treatment besides deficiency in reward appreciation. Furthermore we concentrated on the pathophysiology of obesity along with its association with type 2 diabetes mellitus (T2DM), besides non-alcoholic fatty liver disease (NAFLD) along with other co-morbidities, like Heart Failure, adiposity, Metabolic Syndrome, role of Gut Microbiota/besides role of probiotics as well as prebiotics, with Faecal microbiota transplantation (FMT) for their treatment. Here we have focused on the latest research carried out in an eating disorder called Anorexia Nervosa (AN) which we had earlier reviewed in association with hypothalamic amenorrhoea as a psychiatric condition correlated with extreme anorexia, besides excessive exercise occasionally that usually brought young girls to us with amenorrhoea. It had been an understood condition that was markedly resistant to any treatment. Extensive research carried out recently has revealed its association with other psychiatric conditions like depression, anxiety as well as PTSD along with altered nutrition profile with lower fiber intake thus correlated with lower CRP, whereas that with high saturated Fatty Acids (FA) with greater CRP as seen with Mediterranean diet that we commonly advocate for obese patients. Here we further detail how these advancements aid in treating such patients with the knowledge that the pathophysiology behind the development of these disorders lies in the alterations in various proinflammatory cytokines besides chemokines in AN, thus the association of inflammation besides neuroinflammation explaining the coexistence of psychiatric disorders in AN. These insights aid in planning innovative treatments for such disorders besides ensuring a smooth marriage, pregnancy and child birth. FMT might aid in treating patients that are markedly resistant to any treatment.

**Keywords:** Anorexia Nervosa (AN); psychiatric conditions; altered immunity; diet composition

## Introduction

Diet composition Anorexia Nervosa (AN) represents a robust psychiatric condition possessing the properties of low body weight, eating paradigms that are restricted besides distorted body images.

It possesses the maximum standardised mortality [1], along with relapse rates [2] involving every psychiatric condition that is in general chronic [3]. No clarification exists regarding its pathophysiology with

evaluation still in progress. Meta-analysis has documented changes in the immunological profile of AN patients in particular escalated amounts of proinflammatory cytokines that **have** the probability of aiding in the generation as well as sustenance of the disorder [4]. Loss of **weight takes** place in AN patient via restriction of their caloric consumption besides in certain cases enhanced physical exercise. Of considerable

significance besides the reduction in caloric consumption the macronutrients constituents of their diets is considerably different in lean along with healthy or normal weight individuals [5]. It has been demonstrated that AN patients have lesser consumption of fat, proteins as well as carbohydrates however greater fiber contrasted to their healthy peers [6]. Moreover, it has been documented that despite treatment along with weight correction AN patients keep on displaying subideal dietary consumption of micronutrients as well as Vitamins [7] besides restricted food variations [8]. Diet has a significant impact on the control of inflammation [9], along with is correlated with dietary paradigms besides inflammatory status has been documented [10]. Like consumption of dietary fiber have been correlated with lesser C Reactive Protein (CRP), whereas saturated fatty acids have been correlated with greater CRP amounts [11]. It is well known that Mediterranean diets, that is usually plant dependent possessing greater fiber, lesser saturated fatty acids possess anti-inflammatory capacity besides conferring lesser health risks contrasted to western style diets [12]. Furthermore, if poor nutrition is present, it considerably influences the immune functions in association with micronutrients deficiencies that **pointed** those remarkable changes in the control of the immune system [13]. With the information regarding eating aberrations in the form of eating not orderly along with inadequate nutrition consumption, AN patient in general has manifestation of numerous nutrients deficiency [14]. Like zinc deficiency has been persistently seen in AN patient with this deficiency is considerably correlated with robust immune impairment that has maximum impact on T helper cells that is associated with delayed healing of wounds [15]. Besides that, the nutrients of considerable significance are cholesterol; hypercholesterolemia that has been exhaustively evaluated regarding cardiovascular disease (CVD) is usually **demonstrated** by AN patient's population that have broad variation in action inclusive of facilitation of inflammatory events along with the generation of monocyte as well as neutrophils [16]. Of key importance is that sterols binding directly impacts numerous **immune** receptors controlling cytokines expression [17]. It is feasible hence that the immunological changes seen in AN patients might be secondary to eating aberrations besides inadequate nutrition consumption.

Over the last decade considerable focus has been regarding the part of the immune system, in particular the part of cytokines in

psychiatric conditions inclusive of depression [8,19], anxiety [20]. post-traumatic stress conditions [21], all of which in general co-exist with AN patient. Cytokines represent small messenger molecules of the immune system that might be implicated in the autocrine, paracrine along with endocrine signalling in addition to functions of brain [22]. They are generated by variable cells inclusive of macrophage, along with astrocytes as well as microglia [18] besides have been illustrated to gain entry through humoral, neural, cellular pathways [22]. in addition to that they have been illustrated to possess a part in appetite besides controlling of feeding via impacting the metabolic pathways along with neurotransmitter signal transduction, as well as modulation of hypothalamo-pituitary-adrenal (H-P-A) axis as illustrated by Himmerich et al [19]. in contrast to healthy control group it was recently demonstrated, changes in the cytokine's amounts have been found in AN patient [23]. Furthermore, on contrasting patients with present AN with the ones that have undergone recovery significant variation in amounts of different inflammatory markers have been documented, pointing that certain markers might represent state markers of this condition, while others in the form of trait markers of AN [24].

Having the knowledge regarding changes in the cytokines in AN, the documented actions of diet on inflammatory status as well as vice versa along with eating aberrations in people presenting with AN, Pataslos et al. posited that the reported inflammatory profile might be at minimum secondary to their diet. Thus, their primary aim was contrasting the consumption of enrolled AN from those who had recovered from AN (rec AN) along with healthy controls (HC) besides estimate if these groups varied in their inflammatory probability of their diet with the utilization of Dietary Inflammatory Index (DII (R)) [25]. Thus, they enrolled patients with present AN (n=51), those who had recovered from AN (n=23) along with healthy controls (n=49). Utilization of Food Frequency Questionnaire (FFQ) to calculate DII (R) score as well as determination of serum inflammatory markers from the blood drawn. In case of present AN enrolled they found lesser consumption of cholesterol contrasted to HC along with rec AN. A one-way ANOVA illustrated no significant group variations in DII (R) score. Multivariate regression analysis demonstrated a significant correlation with Tumour necrosis factor alpha (TNF $\alpha$ ) amounts in their present AN sample. Thus, their observations on nutrients consumption are partly in agreement with prior work. The absence of group variations on DII (R) scores probably

pointed that diet does not crucially aid in changes in the inflammatory markers amounts in present AN along with recovered AN. Further research would be advantageous by having larger samples besides utilization of 24h dietary recalling for evaluation of dietary consumption [26].

Furthermore, it is clear that cytokines work as signalling proteins that are generated by a variety of immune cells in the periphery as well as brain (astrocytes as well as microglia) [27]. They possess a key part in the control of immune system, in the pathophysiology of autoimmune conditions as well as generation of brain besides their function [28]. Till date no clarification regarding state or trait inflammatory markers exist with occasional studies have tried to evaluate the association of inflammatory markers along with clinical properties correlated with this condition.

Broadly cytokines classification is feasible as per their immunological functions into Th1 Cytokines [interferon gamma (IFN $\gamma$ ) interleukin-(IL)-2 along with IL 12], Th2 Cytokines (IL -4, IL 5 as well as IL 13), proinflammatory cytokines (IL -1, IL -6, IL -8, IL -17, IL -21, IL -22, IFN $\alpha$  along with Tumor necrosis factor alpha (TNF $\alpha$ ), as well as anti inflammatory cytokines (IL -10 as well as transforming growth factor beta (TGF- $\beta$ )) [29]. In addition to that chemokines represent a family of small cytokines whose function is to synchronize the function of immune cells to attract them towards the area of inflammation. Concentration has been laid on proinflammatory cytokines, implicated in upregulation of the inflammatory reaction in case of AN.

Meta-analysis of in vivo studies have found proof regarding enhancement of some proinflammatory cytokines like TNF $\alpha$ , IL-1 $\beta$  as well as IL-6, in AN [30]. Some pointers of robustness like body mass index (BMI) influence cytokine amounts with extremes of enhanced or repressed BMI causing escalated amounts of proinflammatory cytokines [30]. Proof exists regarding changes in the cytokine amounts get partly reverted with weight enhancement like IL -6, as well as IL -7 have been demonstrated to get back to normal subsequent to escalation BMI to >18.5kg/m<sup>2</sup> [23,30]. In a longitudinal study reduction of IL -6 coexisted with little recovery in psychological symptoms of eating aberrations [23], that pointed the probability of a state biomarker in AN. Nevertheless, in spite of weight enhancement some cytokines persist to be changed in these cases (like TNF $\alpha$  as well as IL-1 $\beta$  [30], pointing to probable trait markers regarding this disorder. Clarification regarding other

cytokines being implicated at the time of acute stages of AN is (like TNF $\alpha$  as well as IL-15) [31] not existent if they are state or trait markers in AN. In a recent cross-sectional study by Nilsson et al. [32], where assessment of inflammatory markers in present AN recovered AN (rec AN) along with healthy controls (HC) was performed [32]. Their outcomes pointed a variation in numerous inflammatory markers in AN contrasted to controls ((like lesser amounts of constituents of TNF, IL -12 $\beta$ , IL -18 receptor $\beta$ , IL -10 receptor $\beta$ ), however no variations rec AN along with HC. Numerous of the inflammatory markers observed to be changed in the acute AN were associated with Milhous their conclusions were that the abnormal inflammatory profiles observed in acute AN were a state marker whose rectification occurred following recovery from this disorder [32]. Nevertheless, assessment was not conducted regarding clinical symptoms or other kinds of psychopathology (like depression) that probably might aid in the changed inflammatory profiles of acute AN patient. Enhanced rates of other have been demonstrated in a study observing greater than 2/3rd individuals possessing a co-morbid axis 1 disorder like major depressive disorder or an anxiety disorder [33]. Moreover, childhood traumatic experiences serve in the form of a risk factor for the generation of an eating disorder [34] along with post TNF $\alpha$ , IL-6 traumatic stress disorder (PTSD) exists in 15-25% of AN individual's [35]. Escalation of the proinflammatory cytokines (like TNF $\alpha$ , IL-6 as well as IL-1 $\beta$ ) are believed to be implicated in the pathogenesis of numerous psychiatry conditions, inclusive of depression, schizophrenia, addiction besides PTSD [36]. Additionally anti psychotic as well as anti-depressant medicines whose utilization is done regarding treatment of these co-morbidities have been illustrated to result in alterations of cytokines formation besides signalling in vivo [37], along with in vitro [38].

Assessment of the part of psychiatric symptoms in particular the ones correlated with changes in the cytokine amounts (like injury, depression. Stress as well as anxiety [39] might reveal the association amongst psychological variables besides cytokines amounts in AN [31] with identification of association amongst the BMI psychopathology of eating disorders clinical variables besides inflammatory markers (like IFN $\gamma$  – inducible protein 10 (IP10), placental growth factor) in addition to general psychopathology along with other inflammatory markers (like

eotaxin, IL -7, IL -8, IP10, monocyte chemoattractant protein 1 (MCP1), thymus along with activation-regulated chemokines (TARC). Nevertheless, this study did not consider the recovered AN (rec AN), along with it further found crucial confounding variables (like age along with BMI) that was not controlled for in the assessment.

Besides the concentration on proinflammatory cytokines in the literature pointed that the assessment of other group of cytokines had not been pursued. Like minimum highlighting of cytokines expression by the T helper type (Th17) cells that is inclusive of IL -17 $\alpha$ , IL -21, as well as IL -22[40]. These cytokines are responsible for autoimmune conditions besides inflammatory events, where their formation can result in exacerbated inflammation (IL -17 $\alpha$ ) [41], besides aid in the pathogenesis of autoimmune diseases [42]. Autoimmune diseases are believed to possess bidirectional association with eating disorders, with diagnosis of one escalating the probability of the diagnosis of the other [43] despite the modulating factors are not clarified. IL -17 has been correlated with the existence of anxiety symptoms in the patients with autoimmune diseases [44] besides the pathogenesis along with sustenance of other psychiatric disorders [38,45]. Akin to that there have been minimum assessment regarding the part of chemokines in AN. Chemokines like MCP1, macrophage inflammatory protein-1 alpha (MIP-1 $\alpha$ ), MIP-1 $\beta$ , RANTES) are believed to be generally implicated in variation of psychiatric conditions [46] besides possess the neuromodulator action which possessing the capacity of changing cognition [47]. Furthermore, changes in the chemokine's functions have been correlated with depression via their part in control of adult hippocampal neurogenesis besides neuroplasticity [48], as well as is believed to be changed in AN [49].

In total whereas there is corroborated proof regarding changes in the cytokines in particular in AN (like TNF $\alpha$ , IL-6 as well as IL-1 $\beta$ ), assessment of other cytokines besides chemokines have not been attempted as comprehensively in this population (like IL -17, IL -12, IL -17 $\alpha$ , IL -21, IL -22, as well as MCP1, MIP-1 $\alpha$ , MIP-1 $\beta$ ) or there is absence of a study confirming their part. Additionally, the degree to which the amounts of **inflammatory** markers are correlated with the properties related to the clinical presentation of AN of not been fully assessed. Changed amounts of **inflammatory** markers might be besides of scientific interest in the form of

biomarkers or key messenger molecules implicated in the pathophysiology of AN. They might be working as future drug targets as hampering of some cytokine pathways are accessible along with received approval regarding treatment of autoimmune diseases, besides might have illustrated to impact body weight in meta-analysis results[50]. Extra treatments like nonsteroidal anti-inflammatory agents, omega 3-FA, statins along with minocycline's have illustrated anti-inflammatory actions in major depressive disorders[51]. Hence repurposing of these agents might work for AN. Thus, Keeler et al. [24] conducted a cross sectional study with determination of serum amounts of 36 inflammatory markers in presentation of patients with acute AN (n=56), recovered AN (rec AN, n=24), along with healthy controls (HCs) (n=51). The association amongst BMI as well as psychopathology of eating disorders, symptoms of depression along with inflammatory markers were evaluated. Statistical models regulated with realization of variables impacting cytokine amounts (like age, ethnicity, smoking status, along with medicine utilization). Totally maximum inflammatory markers inclusive of proinflammatory cytokines remained unaltered in acute AN along with rec AN. Nevertheless, in acute AN along with rec AN amount of MIP-1 $\beta$  were lesser contrasted to HCs. IL -7, IL -12/ IL -23p40 were decreased in AN as well as macrophages obtained chemokines, MIP-1 $\alpha$  along with TNF $\alpha$  amounts were decreased in rec AN contrasted to HCs. Thus, their conclusions pointed that decreased MIP-1 $\beta$  might be a trait marker of the illness while IL -7, as well as IL -12/ IL -23p40 were state markers. The lack of escalated **proinflammatory** cytokines in AN contradicts with the broader literature though covariates inclusions might reason their different observations [24].

Prochazkova et al. [52], in a study regarding bacterial alpha-diversity parameter evaluation illustrated that only Chao 1 index escalated in patients with AN prior to the realimentation pointed to interpersonal variability. Following that core microbiota elimination signs were seen in patients with AN. Overrepresented OTUs (operation taxonomic units) in patients with AN taxonomically belonged to *Alistipes*, *Clostridiales*, *Christensenellaceae*, in addition to *Ruminococcaceae*. Underrepresented OTUs in patients with AN were *Faecalibacterium*, *Agathobacter*, *Bacteroides*, *Blautia* in addition to, *Lachnospira*. Patients illustrated greater inter

personal variability in the gut bacteriome, along with in metagenome component in contrast to controls, pointing to changed bacteriome functions. Patients had reduction in quantities of serotonin, GABA, dopamine, butyrate as well as acetate in their stool samples in contrast to controls.

Mycobiome evaluation did not document important alterations in alpha diversity and fungal profile constituents amongst patients with AN along with healthy controls nor any association of the fungal constituents with the bacterial profile. Their outcomes illustrated the presence of altered profile of the gut microbiome in addition to its metabolites in patients with robust AN. Despite therapeutic partial renourishment resulting in escalated body mass index (BMI) along with recovery of psychometric parameters, short chain fatty acids (SCFA) in addition to neurotransmitter profiles along with microbial community constituents did not alter considerably at the time of hospitalization duration that can possess the probability of a result just by partial weight recuperation [52].

Furthermore, as with animal studies it got corroborated by fecal microbiome transplantation in AN patient with attractive outcomes obtained in a single study of an AN patient possessing significant dysfunctions in the gut barrier function in addition to low alpha diversity demonstrated considerably significant enhancements in both measures subsequent to the fecal microbiome transplant from a healthy, first-degree relative [53]. SCFA were further escalated subsequent to fecal microbiome transplant, besides serotonin quantities [53]. In a different study a patient with AN illustrated considerably significant escalation in weight accrual subsequent to fecal microbiome transplant from an unrelated healthy female donor [54]. This escalation in weight was driven maximum times by a 55% enhancement in body fat in spite of a documented stable caloric consumption [54]. The capacity of fecal microbiome transplants to enhance body weight/adiposity without a simultaneous escalation of food consumption has significant treatment implications for those suffering from severe AN, as refeeding is often tough in these populations. Knowing that these are case reports and no large-scale, randomized controlled trials have been utilized to evaluate the influence of fecal microbiome transplant in AN, interpretation of these observations need to be done cautiously. However provision of proof-of-concept regarding treatment of gut dysbiosis in AN might be an

attractive therapeutic strategy [rev in ref55].

## Conclusions

Earlier we had reviewed regarding how patients of AN who present with primary/secondary hypothalamic amenorrhoea were markedly recalcitrant to any forms of treatment [56,57]. Here we have updated the newer research regarding the eating habits, proinflammatory cytokines as well as chemokines besides associated psychiatric disorders that are associated with these besides how they might respond to various anti-inflammatory agents, certain minerals like zinc seen to be deficient along with omega 3-FA, statins along with minicyclines. Further more they have been observed to be associated with imbalance in gut microbiota as is seen with patients with obesity [58]. In addition to that these eating disorders patients besides showing improvement in weight amenorrhea patients with AN now have started getting married and becoming pregnant with main problems encountered being if poor diet intake occurs in early pregnancy neonatal brain development is impacted besides not much other influence of mode of deliveries, LSCS rates observed other than correlation with poor consumption of nutrients along with calories as they want to preserve the original body figure [rev in 59,60]. Moreover students who faced food Insecurity have been shown to generate such ED in latter part of life [61].

## Conflict of Interest-nil

## References

1. Papadopoulos, F. C., Ekbom, A., Brandt, L., & Ekselius, L. (2009). Excess mortality, causes of death and prognostic factors in anorexia nervosa. *The British Journal of Psychiatry*, 194(1), 10-17.
2. Berends, T., Boonstra, N., & Van Elburg, A. (2018). Relapse in anorexia nervosa: a systematic review and meta-analysis. *Current opinion in psychiatry*, 31(6), 445-455.
3. Steinhausen, H. C. (2002). The outcome of anorexia nervosa in the 20th century. *American journal of Psychiatry*, 159(8), 1284-1293.
4. Dalton, B., Bartholdy, S., Robinson, L., Solmi, M., Ibrahim, M. A., Breen, G., ... & Himmerich, H. (2018). A meta-analysis of cytokine concentrations in eating disorders. *Journal of psychiatric research*, 103, 252-264.
5. Van Binsbergen, C. J., Hulshof, K. F., Wedel, M., Odink, J., & HJ, C. B. (1988). Food preferences and aversions and dietary pattern in anorexia

- nervosa patients. *European Journal of Clinical Nutrition*, 42(8), 671-678.
6. Chiurazzi, C., Cioffi, I., De Caprio, C., De Filippo, E., Marra, M., Sammarco, R., ... & Pasanisi, F. (2017). Adequacy of nutrient intake in women with restrictive anorexia nervosa. *Nutrition*, 38, 80-84.
  7. Pettersson C, Svedlund A, Wallergren O, Swolin-Eide D, Paulson-Karlsson G, Ellegard L. (2021), Dietary intake and nutritional status in adolescent and young adults with Anorexia Nervosa: a 3 year follow up study. *Clin Nutr*; 40:5391-8.
  8. Schebendach, J. E., Mayer, L. E., Devlin, M. J., Attia, E., Contento, I. R., Wolf, R. L., & Walsh, B. T. (2011). Food choice and diet variety in weight-restored patients with anorexia nervosa. *Journal of the American Dietetic Association*, 111(5), 732-736.
  9. Smidowicz, A., & Regula, J. (2015). Effect of nutritional status and dietary patterns on human serum C-reactive protein and interleukin-6 concentrations. *Advances in nutrition*, 6(6), 738-747.
  10. Wood, A. D., Strachan, A. A., Thies, F., Aucott, L. S., Reid, D. M., Hardcastle, A. C., ... & Macdonald, H. M. (2014). Patterns of dietary intake and serum carotenoid and tocopherol status are associated with biomarkers of chronic low-grade systemic inflammation and cardiovascular risk. *British journal of nutrition*, 112(8), 1341-1352.
  11. Ma, Y., Griffith, J. A., Chasan-Taber, L., Olendzki, B. C., Jackson, E., Stanek III, E. J., ... & Ockene, I. S. (2006). Association between dietary fiber and serum C-reactive protein. *The American journal of clinical nutrition*, 83(4), 760-766.
  12. Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C., Das, U. N., & Stefanadis, C. (2004). Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: The ATTICA Study. *Journal of the American College of Cardiology*, 44(1), 152-158.
  13. Childs, C. E., Calder, P. C., & Miles, E. A. (2019). Diet and immune function. *Nutrients*, 11(8), 1933.
  14. Palla, B., & Litt, I. F. (1988). Medical complications of eating disorders in adolescents. *Pediatrics*, 81(5), 613-623.
  15. Prasad, A. S. (2008). Zinc in human health: effect of zinc on immune cells. *Molecular medicine*, 14(5), 353-357.
  16. Tall, A. R., & Yvan-Charvet, L. (2015). Cholesterol, inflammation and innate immunity. *Nature Reviews Immunology*, 15(2), 104-116.
  17. Fessler, M. B. (2016). The intracellular cholesterol landscape: dynamic integrator of the immune response. *Trends in immunology*, 37(12), 819-830.
  18. Dantzer R. (2009), Cytokines sickness behaviour, and depression. *Immunol Allergy Clin North Am*; 29:247-64.
  19. Himmerich, H., Fulda, S., Linseisen, J., Seiler, H., Wolfram, G., Himmerich, S., ... & Pollmächer, T. (2008). Depression, comorbidities and the TNF- $\alpha$  system. *European Psychiatry*, 23(6), 421-429.
  20. Tang Z, Ye G, Chen X, Pan M, Fu J, Fu T, et al. (2008), Peripheral proinflammatory patients with generalized post traumatic stress disorder anxiety disorder. *J Affect Disord* X;225:593-8.
  21. Speer, K., Upton, D., Semple, S., & McKune, A. (2018). Systemic low-grade inflammation in post-traumatic stress disorder: a systematic review. *Journal of inflammation research*, 111-121.
  22. Capuron, L., & Miller, A. H. (2011). Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacology & therapeutics*, 130(2), 226-238.
  23. Dalton, B., Leppanen, J., Campbell, I. C., Chung, R., Breen, G., Schmidt, U., & Himmerich, H. (2020). A longitudinal analysis of cytokines in anorexia nervosa. *Brain, Behavior, and Immunity*, 85, 88-95.
  24. Keeler, J. L., Patsalos, O., Chung, R., Schmidt, U., Breen, G., Treasure, J., ... & Dalton, B. (2021). Reduced mip-1 $\beta$  as a trait marker and reduced il-7 and il-12 as state markers of anorexia nervosa. *Journal of Personalized Medicine*, 11(8), 814.
  25. Shivappa, N., Steck, S. E., Hurley, T. G., Hussey, J. R., & Hébert, J. R. (2014). Designing and developing a literature-derived, population-based dietary inflammatory index. *Public health nutrition*, 17(8), 1689-1696.
  26. Patsalos, O., Dalton, B., Kyprianou, C., Firth, J., Shivappa, N., Hébert, J. R., ... & Himmerich, H. (2021). Nutrient intake and dietary inflammatory potential in current and recovered anorexia nervosa. *Nutrients*, 13(12), 4400.
  27. Oppenheim, J. J. (2001). Cytokines: past, present, and future. *International journal of*

- hematology, 74, 3-8.
28. Kronfol, Z., & Remick, D. G. (2000). Cytokines and the brain: implications for clinical psychiatry. *American Journal of Psychiatry*, 157(5), 683-694.
  29. Himmerich, H., Patsalos, O., Lichtblau, N., Ibrahim, M. A., & Dalton, B. (2019). Cytokine research in depression: principles, challenges, and open questions. *Frontiers in psychiatry*, 10, 30.
  30. Solmi, M., Veronese, N., Favaro, A., Santonastaso, P., Manzano, E., Sergi, G., & Correll, C. U. (2015). Inflammatory cytokines and anorexia nervosa: A meta-analysis of cross-sectional and longitudinal studies. *Psychoneuroendocrinology*, 51, 237-252.
  31. Dalton, B., Campbell, I. C., Chung, R., Breen, G., Schmidt, U., & Himmerich, H. (2018). Inflammatory markers in anorexia nervosa: an exploratory study. *Nutrients*, 10(11), 1573.
  32. Nilsson, I. A., Millischer, V., Göteson, A., Hübel, C., Thornton, L. M., Bulik, C. M., ... & Landén, M. (2020). Aberrant inflammatory profile in acute but not recovered anorexia nervosa. *Brain, behavior, and immunity*, 88, 718-724.
  33. Ulfvenrand S,Brigegard A,Norring C,HgdahlL,vonHauuwolf -JuhlinY . Psychiatric co-morbidity in women with eating disorders: results from a clinical larger database. *Psychiatry Res* 2015; 230: 294-99.
  34. Kong, S., & Bernstein, K. (2009). Childhood trauma as a predictor of eating psychopathology and its mediating variables in patients with eating disorders. *Journal of Clinical Nursing*, 18(13), 1897-1907.
  35. Tagay, S., Schlottbohm, E., Reyes-Rodriguez, M. L., Repic, N., & Senf, W. (2014). Eating disorders, trauma, PTSD, and psychosocial resources. *Eating disorders*, 22(1), 33-49.
  36. Kim, Y. K., Amidfar, M., & Won, E. (2019). A review on inflammatory cytokine-induced alterations of the brain as potential neural biomarkers in post-traumatic stress disorder. *Progress in Neuro-psychopharmacology and biological Psychiatry*, 91, 103-112.
  37. Kluge, M., Schuld, A., Schacht, A., Himmerich, H., Dalal, M. A., Wehmeier, P. M., ... & Pollmächer, T. (2009). Effects of clozapine and olanzapine on cytokine systems are closely linked to weight gain and drug-induced fever. *Psychoneuroendocrinology*, 34(1), 118-128.
  38. Himmerich H, Schonher K,Fulda S,Shedrick AJ,Bauer K,Sack U. (2011), Impact of anti-psychotics on cytokines production. *J Psychiatry Res*; 45:1358-65
  39. Gill, J., Vythilingam, M., & Page, G. G. (2008). Low cortisol, high DHEA, and high levels of stimulated TNF- $\alpha$ , and IL-6 in women with PTSD. *Journal of Traumatic Stress: Official Publication of The International Society for Traumatic Stress Studies*, 21(6), 530-539.
  40. Guglani, L., & Khader, S. A. (2010). Th17 cytokines in mucosal immunity and inflammation. *Current Opinion in HIV and AIDS*, 5(2), 120.
  41. Song, X., & Qian, Y. (2013). IL-17 family cytokines mediated signaling in the pathogenesis of inflammatory diseases. *Cellular signalling*, 25(12), 2335-2347.
  42. Pan, H. F., Li, X. P., Zheng, S. G., & Ye, D. Q. (2013). Emerging role of interleukin-22 in autoimmune diseases. *Cytokine & growth factor reviews*, 24(1), 51-57.
  43. Hedman A, Breithaupt L, HubelC, Thornton LM, Tilander A, Norring C, et al. (2019), Bidirectional relationship between eating disorders and autoimmune diseases. *J Child Psychol Psychiatry*; 60: 803-12.
  44. Liu, Y., HO, R. C. M., & Mak, A. (2012). The role of interleukin (IL)-17 in anxiety and depression of patients with rheumatoid arthritis. *International journal of rheumatic diseases*, 15(2), 183-187.
  45. Davami, M. H., Baharlou, R., Vasmehjani, A. A., Ghanizadeh, A., Keshtkar, M., Dezhkam, I., & Atashzar, M. R. (2016). Elevated IL-17 and TGF- $\beta$  serum levels: a positive correlation between T-helper 17 cell-related pro-inflammatory responses with major depressive disorder. *Basic and clinical neuroscience*, 7(2), 137.
  46. Stuart MJ,Baune BT. (2014), Chemokines and chemokines receptor in mood disorders , schizophrenia and cognitive impairment:a systematic review of Biomarker studies . *Neurosis Biobehav Rev*; 42:93-115.
  47. Leighton, S. P., Nerurkar, L., Krishnadas, R., Johnman, C., Graham, G. J., & Cavanagh, J. (2018). Chemokines in depression in health and in inflammatory illness: a systematic review and meta-analysis. *Molecular psychiatry*, 23(1), 48-

- 58.
48. Milenkovic VM, StantonEH, Nothdurter C, Ruupprecht R, Wetzal CH. (2019), The role of chemokines in major depressive disorder. *Int J Mol Sci*; 20:2283.
49. Keeler, J., Patsalos, O., Thuret, S., Ehrlich, S., Tchanturia, K., Himmerich, H., & Treasure, J. (2020). Hippocampal volume, function, and related molecular activity in anorexia nervosa: A scoping review. *Expert review of clinical pharmacology*, 13(12), 1367-1387.
50. Patsalos, O., Dalton, B., & Himmerich, H. (2020). Effects of IL-6 signaling pathway inhibition on weight and BMI: a systematic review and meta-analysis. *International journal of molecular sciences*, 21(17), 6290.
51. Bai, S., Guo, W., Feng, Y., Deng, H., Li, G., Nie, H., ... & Tang, Z. (2020). Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials. *Journal of Neurology, Neurosurgery & Psychiatry*, 91(1), 21-32.
52. ProchazkovaP, Roubalova R, DvorakJ, KreisingerJ, HillM, Tlaskalova-HogenovaH, etal. (2021), The intestinal microbiota and metabolites in patients with Anorexia Nervosa. *Gut Microbes*;13(1):1-25.
53. Prochazkova, P., Roubalova, R., Dvorak, J., Tlaskalova-Hogenova, H., Cermakova, M., Tomasova, P., ... & Papezova, H. (2019). Microbiota, microbial metabolites, and barrier function in a patient with anorexia nervosa after fecal microbiota transplantation. *Microorganisms*, 7(9), 338.
54. de Clercq, N. C., Frissen, M. N., Davids, M., Groen, A. K., & Nieuwdorp, M. (2019). Weight gain after fecal microbiota transplantation in a patient with recurrent underweight following clinical recovery from anorexia nervosa. *Psychotherapy and psychosomatics*, 88(1), 58-60.
55. Butler, M. J., Perrini, A. A., & Eckel, L. A. (2021). The role of the gut microbiome, immunity, and neuroinflammation in the pathophysiology of eating disorders. *Nutrients*, 13(2), 500.
56. Kulvinder Kochar Kaur, Allahbadia GN, Singh M. (2016), Hypothalamic Amenorrhoea-an Update on Aetiopathogenesis, Endocrine Profile and Management- *Open Access Journal of Gynecology*;1:1.
57. Kaur, K. K., Allahbadia, G., & Singh, M. (2017). Therapeutic Impact of Dysfunction in Reward Processing in Anorexia Nervosa-A Mini Review. *Ann Nutr Disord & Ther*, 4(2), 1045.
58. Kaur, K. K., Allahbadia, G. N., & Singh, M. (2020). The association of dietary fatty acids and gut microbiota alterations in the development of neuropsychiatric diseases: A systematic review. *Obes Res Open J*, 7(1), 19-45.
59. das Neves, M. D. C., Teixeira, A. A., Garcia, F. M., Rennó, J., da Silva, A. G., Cantilino, A., ... & Garcia, F. D. (2021). Eating disorders are associated with adverse obstetric and perinatal outcomes: a systematic review. *Brazilian Journal of Psychiatry*, 44, 201-214.
60. Janas-Kozik, M., Żmijowska, A., Zasada, I., Jelonek, I., Cichoń, L., Siwiec, A., & Wilczyński, K. M. (2021). Systematic Review of Literature on Eating Disorders During Pregnancy—Risk and Consequences for Mother and Child. *Frontiers in Psychiatry*, 12, 777529.
61. Barry, M. R., Sonnevile, K. R., & Leung, C. W. (2021). Students with food insecurity are more likely to screen positive for an eating disorder at a large, public university in the Midwest. *Journal of the Academy of Nutrition and Dietetics*, 121(6), 1115-1124.