Short Communication

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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

Kulvinder Kochar Kaur*, Gautam Nand K Allahbadia , Mandeep Singh

1. Scientific Director, Kulvinder Kaur Centre for Human Reproduction, Punjab, India
2. Scientific Director, Ex-Rotunda-A Centre for Human Reproduction, Mumbai, India
3. Consultant Neurologist, Swami Satyanand Hospital, Punjab, India

***Correspondence:**
Kulvinder Kochar Kaur
Email: **kulvinder.dr@gmail.com**

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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 type2 diabetes mellitus(T2DM) besides non-alcoholic fatty liver disease(NAFLD)along with other co-morbidities, like heart failure, adiposity, Metabolic Syndrome&role of GutMicrobiota/besides role of pro 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 amenorrhea as a psychiatric condition correlated with extreme anorexia, besides excessive exercise occasionally that usually brought young girls to us with amenorrhea. It had been an illunderstood 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 post-traumatic stress disorder (PTSD) along with altered nutrition profile with lower fiber intake thus correlated with lower CRP, whereas that with high saturated FattyAcids(FA) with greater CRP as seen with the Mediterranean diet that we commonly advocatefor obese patients. Here we further detail how these advancement 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 in view of the presence of altered gut microbiotain AN like in obesity.

Key words: Anorexia Nervosa(AN) ; psychiatric conditions; altered immunity; diet composition

INTRODUCTION:

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 have 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 patients via restriction of their caloric consumption besides in certain cases enhanced physical exercise.Of considerable significance besides the reduction in caloric consumption the macronutrients constitutents 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 that 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 patients in general have manifestation of numerous nutrients deficiency[14].Like zinc deficiency has been persistently seen in AN patients 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 is cholesterol; hypercholesterolemia that has been exhaustively evaluated regarding cardiovascular disease (CVD) is usually demonstrated by AN patients 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 patients. 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 etal.[19]. in contrast to healthy control group it was recently demonstrated, changes in the cytokines amounts have been found in AN patients[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(FF□□ to calculate DII $^{(R)}$ score as well as determination of serum inflammatory markers from the blood drawn.In case of present AN enrolled theyfound 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 Tumor necrosis factor alpha(TNFα) amounts in their present AN samples .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(IFNγ) 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, IFNα along with Tumor necrosis factor alpha(TNFα), as well as anti inflammatory cytokines(IL -10 as well as transforming growth factor beta(TGF-β) [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 TNFα, IL-1β 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^2 [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 inspite of weight enhancement some cytokines persist to be changed in these cases(like TNFα as well as IL-1β[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 TNFα 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 -12β, IL -18 receptorβ , IL -10 receptorβ), however no variations rec AN along with HC. Numerous of the inflammatory markers observed to be changed in the acute AN were associated with BMI. Hence 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 1disorder 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 TNFα,IL-6 traumatic stress disorder (PTSD) exists in 15-25% of AN individuals [[35]. Escalation of the proinflammatory cytokines(like TNFα,IL-6 as well as IL-1β)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 IFNγ – 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 chempoattractant 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 -17α, 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 -17α)[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-1α),MIP-1β,RANTES)are believed to be generally implicated in variation of psychiatric conditions[46] besides possess the neuromodulatory action which possessing the capacity of changing cognition[47]. Furthermore changes in the chemokines 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 TNFα,IL-6 as well as IL-1β), assessment of other cytokines besides chemokines have not been attempted as comprehensively in this population(like IL -17 , IL -12, IL -17α , IL -21, IL -22, as well as MCP1, MIP-1α,MIP-1β)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 antiinflammatory agents, omega 3-FA,statins along minicyclines have illustrated anti inflammatory actions in major depressive disorders[51].Hence repurposing of these agents might work for AN.

Thus Keeler etal.[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 amounts of MIP-1β were lesser contrasted to HCs . IL -7 , IL -12/ IL -23p40 were decreased in AN as well as macrophages obtained chemokines, MIP-1α along with TNFα amounts were decreased in rec AN contrasted to HCs . Thus their conclusions pointed that decreased MIP-1β 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 etal.[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 constitutents amongst patients with AN along with healthy controls nor any association of the fungal constitutents 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 inescalated body mass index(BMI) along with recovery of psychometric parameters, Short chain fatty acids (SCFA) in addition to neurotransmitter profiles along with microbial community constitutents 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 patients with attractive outcomes obtained in a single studyof an AN patient possessing significant dysfunctions in the gut barrier function in addition to low alpha diversity demonstrated considerably significant enhancements in both measures subsequentto 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 in weight was driven maximum times by a 55% enhancement in body fat inspite 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 haven been utilized toevaluate 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/secondaryhypothalamic 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 antinflammatory agents, certain minerals like zinc seen to be deficient along with omega 3-FA,statins along 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

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