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Original Research Article

Inflammatory and Micronutrient Profiles in Women with Pseudomonas Aeruginosa Vaginal Infection

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Abstract: ***Background:*** Background Vaginal microbiome is a key factor in mucosal homeostasis and immune regulation in the female reproductive tract. The disturbance of the lactobacillus-dominant flora can contribute to the colonization by opportunistic pathogens such as Pseudomonas aeruginosa. Even though the P. aeruginosa is already known to be a pathogen in many anatomical locations, its contribution to vaginal infection and its systematic immuno-nutritional changes have not been adequately defined. The sustained inflammatory response after infection through therapy might help to cause changed mucosal immunity and general micronutrient deficiency. ***Aims:*** This study developed to assess local inflammatory response and systemic micronutrient profiles of women who had been diagnosed of Pseudomonas aeruginosa vaginal infection in the past, five months after standardized treatment with antimicrobials, and control group healthy women. ***Methods:*** The case-control study was a 12-month study in Thi-Qar Governorate, Iraq. Two hundred aged 35-50 years women were recruited: 100 women with known history of culture-confirmed P. aeruginosa vaginal infection diagnosed 5 months ago (Group A) and 100 age-matched healthy controls (Group B). All the cases had gone through the same antimicrobial regimens and none of them had chronic illnesses. Vaginal samples were examined by ELISA of pH, count of leukocyte (WBC/HPF), IL-1 B, IL-6, IL-8, TNF- 4 and secretion IgA. The levels of serum zinc, copper, iron, calcium, and 25-hydroxyvitamin D were determined using standard biochemical procedures. Statistical tests were performed involving parametric and non-parametric tests, odds ratios estimation, logistic regression, and principal component analysis (PCA). ***Results:*** Women in Group A showed a statistically significant higher vaginal pH, leukocyte infiltration and higher levels of IL-1B, IL-6, IL-8 and TNF-a (all $p < 0.001$) than controls. There was a significant increase in IL-8 levels, which showed that neutrophil recruitment is persistent. Group A had much lower serum zinc, iron, calcium and vitamin D concentration, and higher levels of copper ($p < 0.001$). Deficiency of vitamin D was found in 60 percent of the cases compared to 30 percent of controls. Forest plot analysis showed a high likelihood of increased odds of zinc, iron, and vitamin D deficiencies by formerly infected women. Multivariate studies indicated clear clustering distance between groups, which indicated a unique inflammatory-micronutrient signature used with antecedent P. aeruginosa vaginal infection. ***Conclusions:*** Pseudomonas aeruginosa vaginal infection history in women results in a sustained inflammatory response in the area and pronounced changes in micronutrients in the system 5 months post-standardized therapy. These results imply that there is integrated inflammatory-nutritional phenotype, which can affect the post-infectious mucosal immune restoration. Additional longitudinal and interventional research is justified to delineate the cause and effect as well as therapeutic implication.

Keywords: Pseudomonas aeruginosa; vaginal infection; inflammatory cytokines; micronutrients; zinc; vitamin D; iron metabolism; mucosal immunity; aerobic vaginitis; case–control study.

1. INTRODUCTION

The lower female genital tract is a dynamic mucosal ecosystem wherein the host factors (hormonal milieu, epithelial integrity, mucosal immunity) are in constant interaction with the resident microbial communities. Lactobacillus predominance is typical of a eubiotic vaginal microbiome in women of reproductive age that leads to colonization resistance through lactic

acid generation and antimicrobial product generation to suppress pathobionts and invading pathogens [1-4]. In addition to direct antimicrobial action, vaginal lactobacilli have the ability to tune local immune tone, which affects epithelial pathogen signaling and immune cell stimulation at the cervicovaginal mucosa [3,4]. Modern host-microbe theories highlight nutrient availability, microbial interactions, and immune-mediated control of the environment as determinants of the vaginal community stability and dysbiosis vulnerability of the environment, which must be favourable to the persistence of Lactobacillus or the proliferation of a diverse range of anaerobes/aerobes .[5,6]

Vaginal dysbiosis can develop in the event of Lactobacillus dominance, which can be broadly defined as the difference to the situation characterized by an increase in microbial diversity and the loss of protective functions and an increase in the risk of inflammation. The dysbiosis is associated with various negative effects, such as the syndrome of symptomatic vaginitis / vaginosis, acquisition of sexually transmitted infections and obstetric complications [1,2]. Notably, inflammatory vaginal diseases do not exist as one condition; aerobic vaginitis (AV) is being more and more known as a special syndrome, where lactobacilli are depleted, aerobic/enteric bacteria grow excessively and inflammation is evident with the influx of leukocytes and epithelial alterations.[7,8]

Unlike bacterial vaginosis, which is characterized by minimal inflammation, AV is usually accompanied by erythema/edema, and microscopy is characterized by leukocytes and parabasal/immature epithelial cells [7,8]. More recent studies have also attempted to augment AV diagnostics with the use of microscopic and clinical criteria which are more practical in practice, highlighting the clinical significance of the ability to discriminate among AV-like inflammatory phenotypes and other causes of vaginitis .[9,10]

Pseudomonas aeruginosa is a Gram-negative pathogen and has an unusually broad ecological range with a well-established presence in hard-to-treat infections in all body locations. Though vaginal infection with P. aeruginosa is rare when compared to classical causes of vaginitis, the culture-based study of the vulvovaginitis and vaginal discharge syndrome reveal that a wide spectrum of bacterial agents can be isolated, which is why it is plausible to consider such nontraditional pathogens as the cause of vaginitis in particular clinical settings, and why microbiological confirmation is valuable in cases that are persistent and/or atypical [11,12]. The biologic plausibility of P. aeruginosa as a pathogen of the genital tract is based upon its set of virulence factors, as well as the ability to multiply on wet surfaces and resist antimicrobial pressure.

The key characteristic of the pathobiology of P. aeruginosa is the capacity of the bacteria to organize virulence via regulation networks and develop strong biofilms that may help to protect bacteria against host defenses and enhance antimicrobial tolerance. Detailed analyses point to the fact that motility and adhesion (flagella, pili), extracellular polymeric structures (e.g., alginate), and quorum-sensing-regulated pathways promote the formation of biofilms and combine environmental signals with host signals [1318]. Infection related to biofilms has the potential to maintain the inflammatory response and prevent eradication, which extends the activation of the mucosal immunity. Moreover, P. aeruginosa expresses various effectors and toxins, including the elements of the type III secretion system, exotoxin A, elastase/proteins, and redox-active pigments that may harm the epithelial tissues, regulate the immune signaling and facilitate immune evasion [13-16]. The reasons why these properties are clinically relevant are that ongoing mucosal inflammation may be potentiated by innate immune mechanisms, such as cytokine cascades that attract neutrophils and condition barrier activity.

Recruitment of leukocytes and elevated levels of pro-inflammatory mediators are usually the manifestations of innate immune activation at the mucosal surface. Mucosal immunity in the female reproductive tract entails an integrated system of epithelial defenses, antimicrobial peptides and resident/recruited immune cells which in combination to achieve rapid responses to microbial assault and tissue homeostasis [19,20]. Recent summaries of female reproductive tract mucosal immunity place importance on the hormonally and epithelial physiologically tuned local immune responses, and the potential impact of immune-microbe feedback on community structure and stability [21,22]. Cytokines like IL-1 0 -6 -8 -TNF- -A are often investigated in inflammatory vaginitis phenotypes, and IL-8 plays a key role as a neutrophil chemotaxis factor, an anticipated constituent of inflammatory diseases with high leukocyte counts on a microscope.

Systemic host factors can also mediate susceptibility and recovery in combination with local inflammation. Micronutrients are known to play a role in immune capability, barrier stability and inflammatory control. Zinc is an essential trace element that is needed to perform normal activity of both innate and adaptive immune cells; it influences neutrophil and natural killer cells, has an impact on cytokine production, and harmonization of signaling pathways involved in the regulation of inflammation [23,24]. Endocrine and nutritional factors also shape the female reproductive tract mucosa that may change epithelial and immune functionality and, as a result, colonization resistance and inflammatory responsiveness [21,22]. Outside skeletal functions, vitamin D has been studied in immunomodulatory functions, such as inherent defense

regulation and inflammatory processes; systematic reviews are ongoing to assess its more widespread immune functions as well as outcomes in relation to infections in populations [25,26]. Although effects are different according to baseline status and context, vitamin D biology can still be used in mucosal immunity studies since it does have a regulatory effect in immune response.

Mineral metabolism is also disturbed by inflammation using acute-phase pathways. During infection and inflammation, iron homeostasis is stringently controlled and hepcidin helps to decrease the supply of this mineral to the blood, which is an innate defense mechanism but also leads to hypoferremia [26,27]. During inflammatory conditions, copper inflammation can also occur due to the increase in the levels of ceruloplasmin, the main copper carrier in the plasma, an acute-phase reactant, whose production can be stimulated by inflammatory cytokines [15-23]. Therefore, micronutrient patterns of inflammation in the context of infection can be indicative of nutritional condition and redistribution under the influence of inflammation.

All of these ideas give the justification to examine women with established P. aeruginosa vaginal infection in an integrated approach which incorporates (i) local inflammatory response measurements (e.g., vaginal pH, leukocyte infiltration, cytokine infiltration, and mucosal immunoglobulins), and (ii) systemic micronutrient concentrations (zinc, copper, iron, calcium, and vitamin D). Moreover, it was also proposed to use multivariate methods to answer the question of whether combined inflammatory and micronutrient indicators are a characteristic biological indicator among women who had previously developed Pseudomonas aeruginosa vaginal infection, five months following conventional antimicrobial therapy, in comparison with healthy controls.

2. MATERIALS AND METHODS

2.1. Study Design and Population

The study is a retrospective case-control study that will be performed during the period between January and December of the year 2024, in Thi-Qar Governorate, Iraq. Two hundred married women, aged 3550 years were enrolled. Group A (cases) consisted of 100 women who had the culture-confirmed Pseudomonas aeruginosa vaginal infection diagnosis five months before the enrollment. Group B (controls) comprised of 100 age matched healthy women who had no history of vaginal infection in the previous six months and negative vaginal culture at the time of enrolment.

The eligible cases had undergone a standardized antimicrobial treatment of 710 days under the direction of susceptibility tests, and no other antimicrobial treatment had been administered within eight weeks of the sampling. The medical records were consulted to ensure that treatment was adhered to and treatment uniformity. To exclude confounding factors, the women that had chronic systemic diseases, endocrine disorders, diabetes, autoimmune conditions, immunosuppressive therapy, recent corticosteroid use, menstruating, or recent micronutrient supplementation were excluded.

2.2. Clinical and Sample Collection Procedures.

All the participants were examined at enrollment (five months after diagnosis of cases) through gynecological examination, vaginal pH examination, microscopic examination of white blood cells (WBC) and repeat vaginal culture to determine whether the bacteria had been cleared or not. Asymptomatic women were recruited only to be observed to define the post-infection inflammatory condition and not acute disease.

Vaginal swabs were taken to measure the pH, the number of WBC (cells/HPF) and cytokines. Five milliliters of venous serum were obtained, centrifuged (3000 rpm, 10 minutes), and stored at a low temperature of -20C in serum. Sampling was done during 8: 00-10: 00 AM to minimize circadian variation.

2.3. Laboratory Measurements

Vaginal inflammatory cytokines (IL-1, IL-6, IL-8, TNF-1) and secretory IgA were assessed by ELISA kits validated and the test was repeated twice (inter, intra-assay coefficient <10%). Serum micronutrient (zinc, copper, iron, calcium) measurement was done by spectrophotometric colorimetric assays and the measurement of 25-hydroxyvitamin D was done by ELISA. Each batch was having internal quality controls.

2.4. Statistical and Ethical Concerns.

The analysis of data was done with SPSS v10. Shapiro Wilk was used to test normalcy. The right parametric or non-parametric tests were used and odds ratios with 95% confidence interval were obtained. Vitamin D could be served as a predictor using the logistic regression and principal component analysis could be used to evaluate the multivariate patterns. A p of below 0.05 was deemed as significant in a two-tailed manner. They were granted with ethical approval and a written informed consent as per the Declaration of Helsinki.

3. RESULTS

There was no significant difference between groups in age distribution (Table 1; $p = 0.64$), and future differences in the parameters of inflammatory and biochemical are hardly expected to be age-related. Women infected one month before with Pseudomonas aeruginosa vaginal infection (Group A) had a significantly different local vaginal environment of healthy controls (Group B). Since Table 2 and Figure 1 indicate that all values are significantly different, Group A demonstrated a greater vaginal pH, stronger leukocyte invasion (median WBC 24 vs 4 cells/HPF), and a greater pro-inflammatory cytokine concentration, including IL-

1B, IL-6, IL-8, and TNF- 2 (all $p < 0.001$). The excessive rise in IL-8 (median 901 pg/mL) is in line with improved neutrophil recruitment, whereas the high values of IL-1B and TNF-alpha suggest the activation of innate inflammatory response pathways. All these findings are an indication of long term mucosal immune activation and not a short-term inflammatory reaction. There were also evident systemic biochemical differences (Table 3; Figure 2). The concentration of serum zinc, iron, calcium, and 25-OH vitamin D in Group A was far less than in Group B, and the level of copper was greater (all $p < 0.001$). Lower levels of zinc and vitamin D have biological significance because these have been known to have an effect on the integrity of epithelial barriers and immune regulation. Decreased serum iron could be indicative of inflammatory-related sequestration, but increased copper would be indicative of an acute-phase response.

The level of abnormal micronutrients was much higher in infected women (Table 4). Disproportional representation of zinc deficiency, iron deficiency and vitamin D deficiency in Group A as in the forest plot (Figure 3) suggested a very strong relationship between infection status and micronutrient imbalance.

Multivariate patterns also support a combination pattern biological. Figure 4 shows that there are coordinated relationships between inflammatory mediators and micronutrients as shown in the correlation heatmap. According to the logistic regression curve (Figure 5), there is a declining probability of predicted infection as the vitamin D increases. Figure 6 (principal component analysis) indicates that there is a clear segregation in clustering among the groups indicating the existence of a clear inflammatory nutrition profile with P. aeruginosa vaginal infection.

1. Demographic Characteristics

Table 1: Baseline Characteristics of Study Population

Variable	Group A (n=100)	Group B (n=100)	P-value
Age (years), mean ± SD	42.1 ± 4.3	41.8 ± 4.5	0.64
Age range	35–50	35–50	—
Married (%)	100%	100%	—

No statistically significant difference in age distribution was observed between groups.

2. Local Vaginal Inflammatory and Immune Markers

Table 2: Vaginal Inflammatory Parameters

Parameter	Group A (n=100)	Group B (n=100)	P-value
Vaginal pH (mean ± SD)	5.5 ± 0.5	4.3 ± 0.4	<0.001
WBC/HPF (median [IQR])	24 [15–40]	4 [1–6]	<0.001
IL-1β (pg/mL), median [IQR]	82 [40–150]	13 [6–20]	<0.001
IL-6 (pg/mL), median [IQR]	25 [10–60]	4 [0–8]	<0.001
IL-8 (pg/mL), median [IQR]	901 [400–1800]	251 [120–450]	<0.001
TNF-α (pg/mL), median [IQR]	26 [10–45]	6 [0–12]	<0.001
Secretory IgA (µg/mL), mean ± SD	261 ± 91	151 ± 61	<0.001

Women in Group A demonstrated significantly elevated vaginal inflammatory markers, including increased leukocyte infiltration and higher pro-inflammatory cytokine concentrations compared to controls.

3. Serum Trace Elements and Vitamin D Levels

Table 3: Serum Micronutrient Levels

Parameter	Group A (n=100)	Group B (n=100)	P-value
Zinc (µg/dL), mean ± SD	67 ± 13	93 ± 15	<0.001
Copper (µg/dL), mean ± SD	126 ± 23	106 ± 19	<0.001
Serum Iron (µg/dL), mean ± SD	56 ± 21	91 ± 26	<0.001
Total Calcium (mg/dL), mean ± SD	9.2± 0.5	9.4 ± 0.5	<0.001
25-OH Vitamin D (ng/mL), mean ± SD	19 ± 8	29 ± 10	<0.001

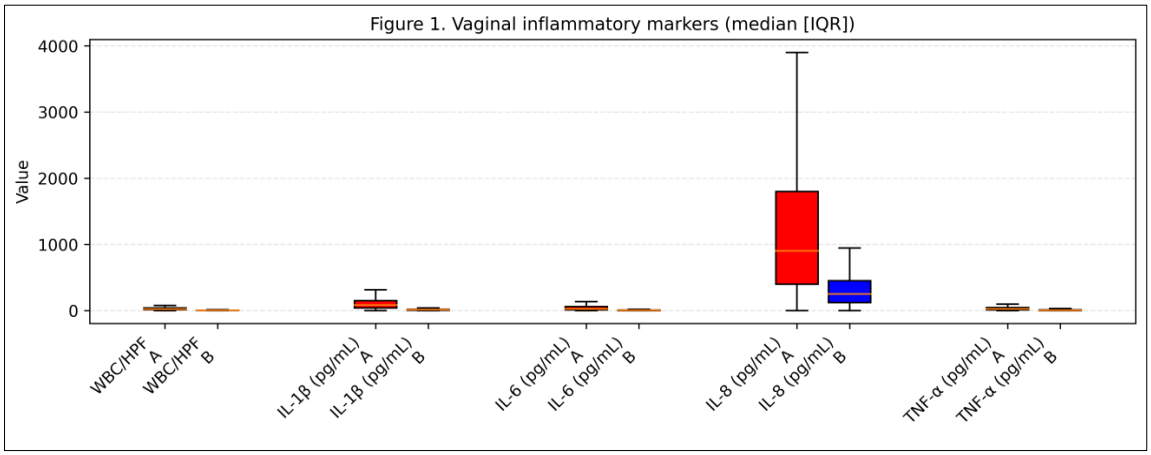
Group A showed significantly lower zinc, iron, calcium, and vitamin D levels, while copper levels were significantly higher compared to Group B.

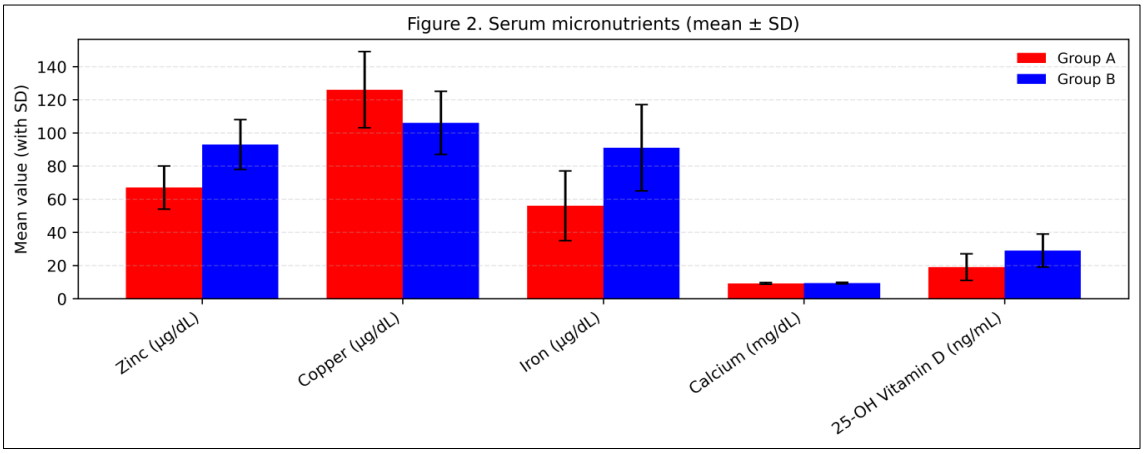
4. Prevalence of Abnormal Micronutrient Levels

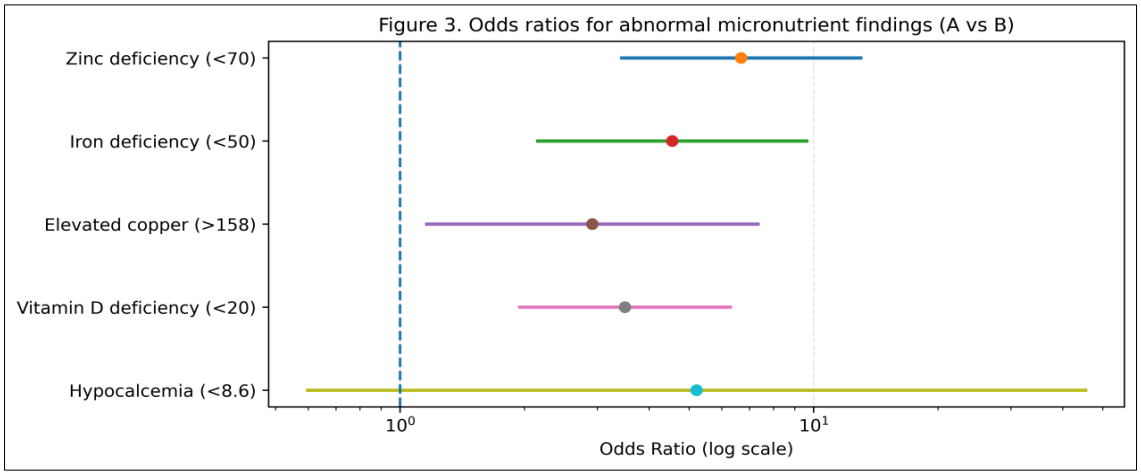
Table 4: Frequency of Abnormal Laboratory Findings

Abnormality (Cut-off)	Group A (n=100)	Group B (n=100)	P-value
Zinc deficiency (<70 µg/dL)	56%	16%	<0.001
Iron deficiency (<50 µg/dL)	36%	11%	<0.001
Elevated copper (>158 µg/dL)	18%	7%	0.01
Vitamin D deficiency (<20 ng/mL)	60%	30%	<0.001
Hypocalcemia (<8.6 mg/dL)	5%	1%	0.09

Vitamin D deficiency and zinc deficiency were notably more prevalent in Group A compared to controls.







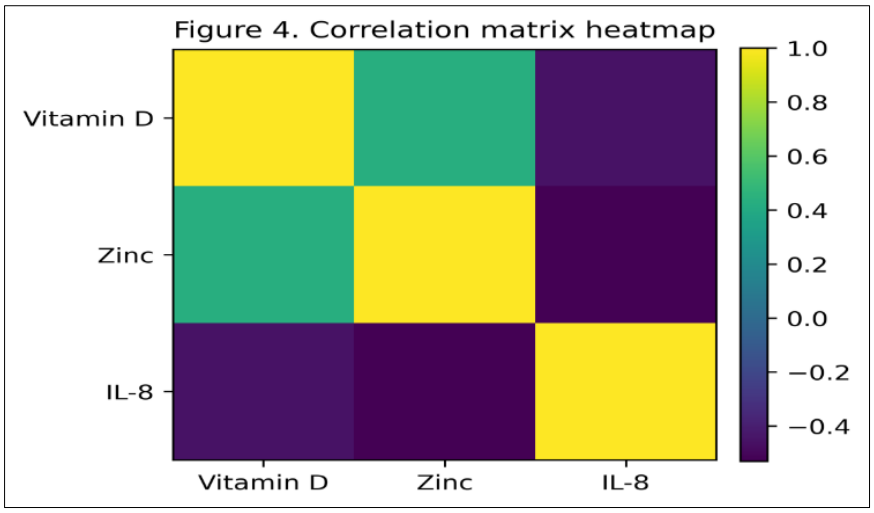


Figure 4. Correlation matrix heatmap
Vitamin D
Zinc
IL-8
Vitamin D
Zinc
IL-8
1.0
0.8
0.6
0.4
0.2
0.0
−0.2
−0.4

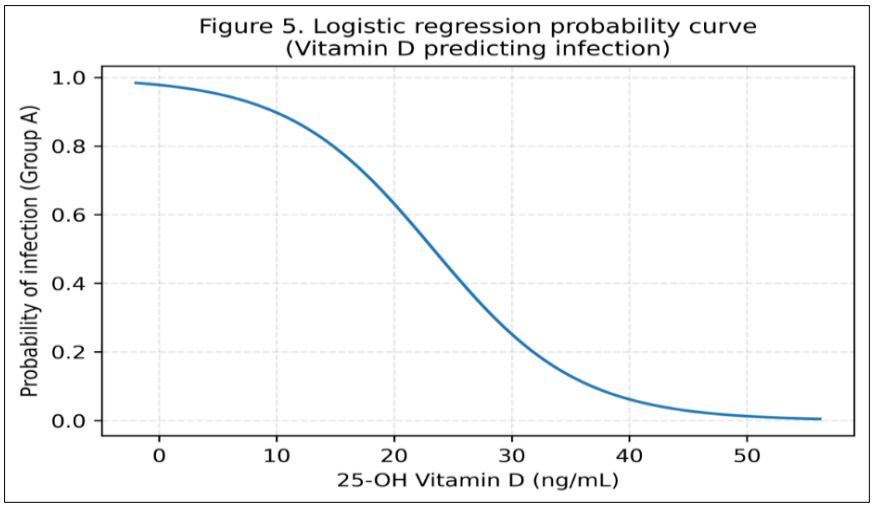


Figure 5. Logistic regression probability curve
(Vitamin D predicting infection)
Probability of infection (Group A)
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
25-OH Vitamin D (ng/mL)

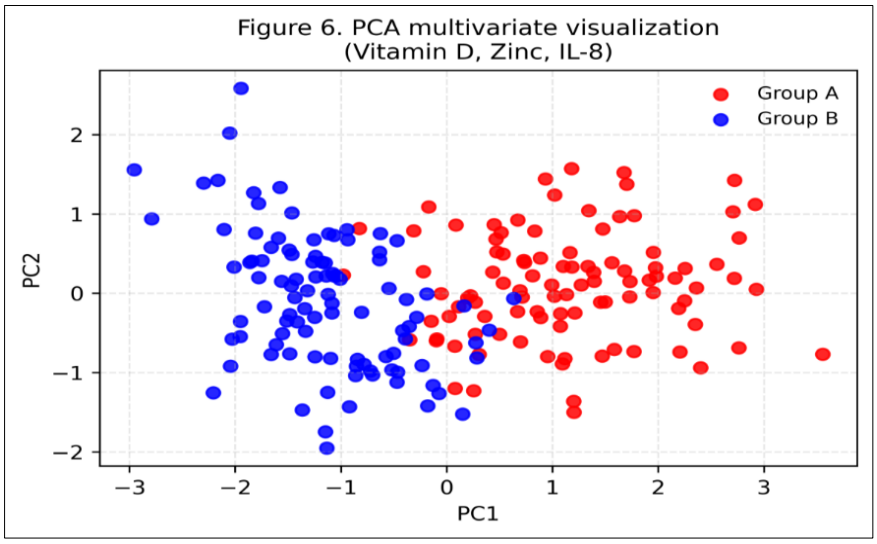
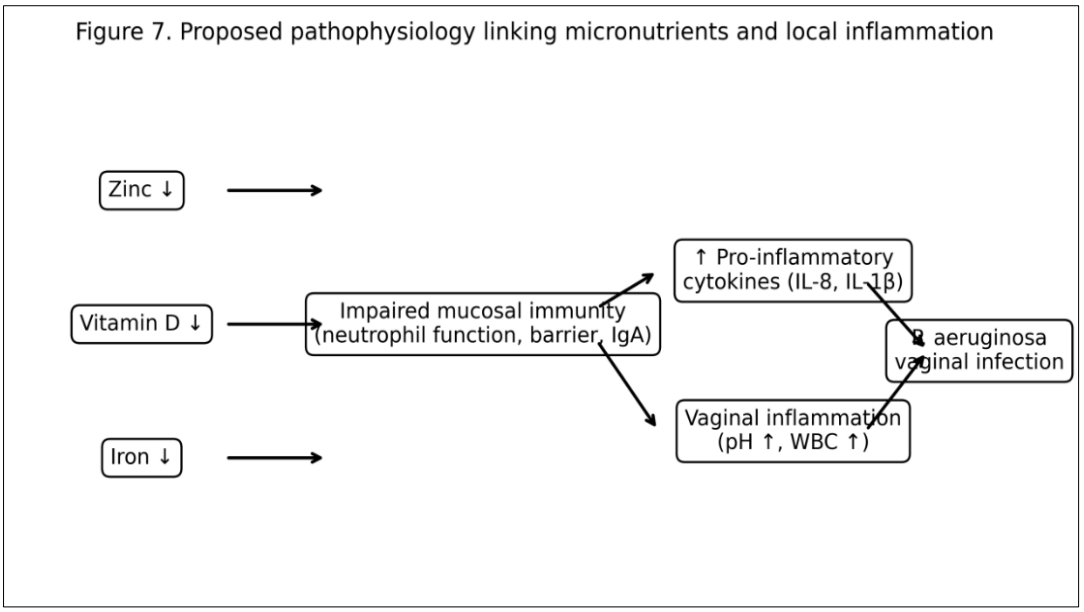


Figure 6. PCA multivariate visualization
(Vitamin D, Zinc, IL-8)
Group A
Group B
PC2
2
1
0
−1
−2
−3
−2
−1
0
1
2
3
PC1



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There were also evident systemic biochemical differences (Table 3; Figure 2). The concentration of serum zinc, iron, calcium, and 25-OH vitamin D in Group A was far less than in Group B, and thelevel of copper was greater (all $p < 0.001$). Lower levels of zinc and vitamin D have biological significance because these have been known to have an effect on the integrity of epithelial barriers and immune regulation. Decreased serum iron could be indicative of inflammatory-related sequestration, but increased copper would be indicative of an acute-phase response.

The level of abnormal micronutrients was much higher in infected women (Table 4). Disproportional representation of zinc deficiency, iron deficiency and vitamin D deficiency in Group A as in the forest plot (Figure 3) suggested a very strong relationship between infection status and micronutrient imbalance.

Multivariate patterns also support a combination pattern biological. Figure 4 shows that there are coordinated relationships between inflammatory mediators and micronutrients as shown in the correlation heatmap. According to the logistic regression curve (Figure 5), there is a declining probability of predicted infection as the vitamin D increases. Figure 6 (principal component analysis) indicates that there is a clear segregation in clustering among the groups indicating the existence of a clear inflammatory nutrition profile with P. aeruginosa vaginal infection. [35–37].

Persistent innate activation at mucosal sites is usually reflected by increased IL-8 (neutrophil chemoattractant) and IL-1 b / TNF - (enhancement of inflammatory cascades), which is also in line with the cytokine response in Group A (Table 2). At the mechanistic level, the immune response of the female reproductive tract is epibiotic barrier-response-mediated and cross-talking with immune cells, which presents a paradigm of comprehending how dysbiosis can be retained post-treatment.[31–29] .

Table 3; Figure 2 showed a much lower serum zinc, iron, calcium and 25-OH vitamin D, and a higher level of copper in Group A. Mechanistically, this trend conforms to inflammatory redistribution and immune-metabolic adaptation. Zinc plays a crucial role in immune cell communication and activity and is commonly mentioned as a predictor of immune potential; zinc depletion can be a marker of nutritional health and /or immune system alterations in response to inflammation [38,39]. Reduced serum iron can be an indicator of inflammation-induced iron absorption via hepcidin pathways- known host response mechanisms of

limiting circulating iron during immune response . .[40,41]

An acute-phase pattern also appears to be compatible with higher copper due to the fact that ceruloplasmin is a large copper-carrier protein and has been characterized as an acute-phase reactant that is induced during inflammation. [42]. In the case of vitamin D, the biological plausibility of a relationship between reduced vitamin D levels and disturbed immune control has been supported by immunoregulatory activity of both innate and adaptive pathways (Table 3; Figure 5) although observational results cannot be used to determine causality.

The observed greater zinc deficiency, iron deficiency and vitamin D deficiency in Group A (Table 4) and the direction/magnitude of association showed in Figure 3 demonstrate that the abnormalities in micronutrients are not balanced between groups. Although these findings do not show that deficiencies enhance infection or persistence, they reveal quantifiable host variables that may reasonably impact mucosal immune restoration as well as resistance to dysbiosis [38, 41, 43].

Figure 4 (correlation heatmap) and Figure 5 (logistic model visualization) data support the fact that there is coordinated relationships between micronutrient status and inflammatory markers and the PCA separation (Figure 6) indicates that the combination of biomarker set produce a characteristic group pattern. These multivariate signatures are consistent with recent conceptualisations of the vaginal ecosystem as a combined hostmicrobeimmune ecosystem occurring due to colonisation resistance (through lactobacilli/pH), immune signalling, and ecological stability. [28,29]. The suggested mechanistic schematic (Figure 7) is an overall representation of the biologically coherent mechanism whereby micronutrient dysregulation could cause mucosal immune dysfunction and inflammatory activation; it needs to be referred to as a hypothesis-generating framework as opposed to a proven cause-effect pathway. [29–31,38,43]. The presence of a specific geographic catchment (Thi-Qar), a predetermined post-diagnosis period (5 months) and elimination of significant confounders (excluding chronic diseases) as well as the use of both local mucosal markers and systemic micronutrients are also considered as the key strengths. Nonetheless, interpretation must take into account that a post-infection timepoint cannot determine the nature of the existence of micronutrient differences as to whether they were pre-infection, inflammatory or as a consequence of unmeasured dietary/behavioral changes. Also, the presence of repeat culture at the sampling point is important in differentiating the post-infectious inflammation and persistent colonization hence reporting of contemporaneous culture results and history of antibiotic exposure reinforces causality. Lastly, longitudinal and microbiome profiling would be useful to measure resolution versus persistence as well as to relate biomarker dynamics to transitions in community states. [28,32-34].

5. CONCLUSIONS

In this study demonstrates that women who have been previously diagnosed with Pseudomonas aeruginosa vaginal infection are not free of inflammatory-nutritional signature five months following the administration of antimicrobials. High vaginal pH, leukocyte infiltration, and high IL-1B, IL-6, IL-8, and TNF-alpha show persistent mucosal immune response. Reduced systemic zinc, iron, calcium, and 25-hydroxyvitamin D and increased copper are indicative of inflammation related to the redistribution of micronutrients. Multivariate analysis showed that there was clear separation between previously infected and control groups which was a coordinated biological phenotype. In spite of the fact that causality cannot be determined, prior infection seems to be associated with lasting mucosal and systemic changes, and holistic host-centered consideration and subsequent mechanistic and interventional research should be performed.

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