Study stromal cell-derived factor-1 (*SDF1-α*) in patients infected Urinary tract infections and bacterial vaginosis

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Abstract:

Background: Study stromal cell-derived factor-1 is produced soon after an infection, an interesting immunological response is triggered, allowing for quick and effective bacterial clearance. Urinary tract infections and bacterial vaginosis are two major hazards that have an impact on millions of women worldwide that are of reproductive age. The purpose of this study is to analyze the connection between the *SDF1* gene in patients both urinary tract infections with bacterial vaginosis and healthy individuals as a control group.

Methods: In order to study the distribution of the SDF1 gene the Gynecology Consultant at the Imam Al-Sadiq General Educational Hospital in Iraq-Babylon split the topics to four collections after collecting medical data from (240) entrants. the patients and the control group (UTI, BV, UTI with BV groups), while the population study in this area included age and education, During the period from September to December 2022, *SDF1-α* detection by Conventional amplified technique (PCR) - We reveal alleles with a single primer and distinguished the alleles by molecular weight.

Results: The results revealed that patients and a control group who have G allele, and G/G genotyping in the *SDF1-α* gene, had no significance, therefore considered a protective factor to the development of disease, for urinary tract infection, particularly among women of childbearing age in college education. Also, women with bacterial vaginosis especially among women sexually active in Intermediate education, also women with both UTIs with BV especially among women sexually active studying in the institute.

Conclusion: According to our research, *SDF1-α/CXCL-12* gene polymorphism is not linked to BV-associated UTIs. To further explain these findings, a larger-scale and well planned case-control research should be carried out.

Keywords: *SDF1-α*, Chemokines(*CXCL12*), Bacterial vaginosis, Urinary tract infection .

1. Introduction

Urinary tract infections (UTIs), which are symptomatic inflammation of the lower or upper urinary tract caused by internalization of uropathogenic microorganisms, are the most common infections that can evolve at diverse stages of lifetime (Watson, 2023). Because of nature of the women lower urinary tract and its proximity to the reproductive system, female of all ages who arrive in primary care settings or outpatient departments are twice as likely to get a UTI as males (Alawkally et al., 2022). As a result of the female urethra's relative shortness, less space is available for germs to enter. Pathogens from the gastrointestinal tract are what cause UTIs, which are usually linked to vaginal infections (the urinary system is significantly influenced by the gut microbiota) (Abou Heidar et al., 2019; Czajkowski et al., 2021; Qin et al., 2020).

Whereas the vaginal microbial community is made up of a variety of bacteria that are frequently distinguished by abundant Lactobacilli and changes throughout a woman's life based on her age, hormonal estrogen levels, sexual habits, and environment (Tidbury et al., 2021). The most prevalent cause of discharge from the vagina in women of reproductive age is BV, which is responsible for around 30% of all reasons. It is caused by a disruption in the vaginal ecosystem, specifically the abrupt substitution of Lactobacilli with anaerobic bacteria (Abou Chacra et al., 2022). Although the cause of this dysbiosis is unknown, it has serious health consequences, including obstetrical complications, an increased risk of STIs and urogenital infections, inflammatory disease in pelvic and enhance the risk of having an abnormality in pregnancy (Ravel et al., 2021).

Chemokines are small proteins (7-14 kDa) that act as pro-inflammatory mediators as well as chemoattractants. Its primary function is to attract leukocytes to inflammatory sites (Valdivia-Silva et al., 2015). A chemokine known as stromal cell-derived factor (SDF) 1-alpha, also known as CXCL12, has been linked to immune cell differentiation and migration (Yang et al., 2018). On chromosome 10q11, the chemokine (C-X-C motif) ligand 12 (CXCL12) is preferentially clear up by B cell and T cell. CXCL12 conveys signals involved in critical cellular processes such differentiation, death, and leucocyte chemotaxis via binding to the chemokine (CX-C motif) receptor 4 (CXCR4) (Barinov et al., 2017; Khalid et al., 2017; Teicher et al., 2010).

Where G801A is an exon 4 of the CXCL12 gene transcripts single nucleotide polymorphism (SNP). In order to promote the reaction with CXCR4, the allelic and genotypic variation of SNP rs1801157 of the CXCL12 gene is being investigated. The 3′-untranslated region of the CXCL12 gene has an SNP, which entails a guanine to adenine (G - A) substitution at 801bp. an SNP has been connected to variations in CXCL12 synthesis in vitro and in vivo development in various research. This established connection has been shown to increase illness risk and susceptibility in a number of conditions (Chiraunyanann et al., 2019; Karakus et al., 2017).

As a result, early after infection, SDF-1 is produced, provoking an interesting immunological response that is responsible for quick and efficient bacterial clearance (Abraham et al., 2015). The chemokine stromal cell-derived factor 1, which causes NK cells, T cells, and neutrophils to migrate and accumulate at the site of infection (Isaacson et al., 2017; Tecchio et al., 2016). In the existing survey, we look to identify *SDF1-α*

association SNP in patients with both urinary tract infections and bacterial vaginosis, as well as in healthy individuals serving like control category.

2. Material and methods

2.1. Study Design

In a group comparison research that began in September 2022, 240 participants were split into three categories: 60 femle have UTI, 60 female have BV, and 60 female who had both UTI and BV, as well as 60 women who were healthy, those participants from the Imam Al-Sadiq General Education Hospital/ Gynecology Consultant/Babylon /Iraq, the four categories demographic explore norm from age(15-50) years and education.

This treaties had the moral endorsement from Al-Furat Al-Awsat Technical University / College of Health and Medical Techniques / Kufa / Department of Medical Laboratory Techniques, Babylon Health Department / Training and Development Center, the moral status were put up with and the entrant was aware of the value of the survy, the confidentiality of the information, and its use for research purposes only, before taking samples.

2.2. Control and Patients

A gynaecologist was able to distinguish between patients with UTIs, BV, UTIs with BV, and control patients based on the signs and symptoms of the patient's and the results of the laboratory analyses. All of female in the control categories it has been checked for signs , symptoms and laboratory test results, and the total of control categories entrants were within the normal range and appeared healthy. The control group of women who entrants in the survey was correspond with diseased in terms of old and education. Gynaecology Consultant/Imam Al-Sadiq General Education Hospital, Babylon, Iraq is where the medical data that needed.

2.3. Samples Collection

The samples of blood that taken from patients by disinfected disposable syringe and scattered in sterile EDTA-tubes that used for processing of human DNA purified and genetic, the samples was stored at -20ºC with genomic DNA extraction specimen to be utilized.

Genomic DNA Extraction from Frozen Blood Sample: specimen that stored at -20ºC and taken from them should be dissolve in water bath at 37ºC for 15 minutes before it be utilized. DNA was extracted as per (Sim Bio Lab-Iran) protocol according to the manufacturer’s instructions. dsDNA's optical density mensuration at 260 nm in order to spectrophotometrically calculate concentricity of it. The OD260/OD280 ratio, whose (1.8 0.2) for pure DNA, shows the DNA solution's purity. Final preparations that were more than 1.8 were kept at -20°C and utilised as PCR templates.

Conventional Polymerase Chain reaction (PCR) - We detected alleles with a single primer and distinguished the alleles by molecular weight, method was used to genotype the G801A polymorphism in the *SDF-1α* gene. The primer sequences that used to amplify the *SDF-1a* G801A genotype were (Forward) 5-CAGTCAACCTGGGCAAAGCC-3 and (Reverse) 5-AGCTTTGGTCCTGAGAGTCC-3-(Gerli et al., 2005), PCR was performed in a 6.5µLvolume DNA template, (2 µl) from each (Macrogen, Korea) forward and reverse primer then (12.5 µl) from (Promega, USA) master mix were added to each micro centrifuge tube, The reaction mixture regulate to (25 µl) using (Bioneer, Korea) nucleases free deionized distilled water and then put in shaker and spinner for 10 cycles for better mix. After mix-up, the master mix tubes were put into a thermocycler that had been pre-programmed with the aforementioned protocol for the gene that needed to be amplified. The PCR conditions were 5 minutes at 94°C, followed by 35 cycles of 45 seconds at 94°C, 30 seconds at 60°C, and 30 seconds at 72°C, with a final step at 72°C for 5 minutes to allow a full extension of all PCR fragments. The bands were then seen and captured using a digital camera after DNA amplification was electrophoresed on a 2% agarose gel include ethidium bromide. A compare with a 100 bp ladder (Promega, USA) was used to identify the amplified products. SDF-1 wild-type alleles produced products with G=99 and 203 base pairs, while SDF-1 A alleles produced a 302-bp product.

2-4 Statistical Analysis:

The software package SPSS issuance 28 was used for all statistical analyses, and the data were reported as (mean + standard deviation) for descriptive statistics. For inferential statistics, T-test was used check difference among categories, one-way ANOVA was also used to check difference among categories for numerical data and Freidman for categorical data. These statistical screening suppose at the level of 0.05 and a confidence interval of 95%.

3- Results

During- September 2022 to, December -2022, the total- number of respondents was- 180- patients and 60 control, divided into three groups: (Urinary –Tract- Infection, Bacterial- Vaginosis, Urinary- Tract Infection -with -Bacterial -Vaginosis, and Control group).

There was no statistically important variation between groups for the age at level 0.05 (0.08). The results of this study are demonstrated in Table 1. patients' distribution (age) based on 10 years. The case study showed It has been detected that the popular UTI diseased were in the old categories (15-36) years. The current study also showed the majority of BV diseased were in the old categories (26-36) years and in the group UTI with BV, most of the respondents were in the age group (15-25) years. While the age (48-58) years showed the lowest rate, moreover, the group of control had the highest rate of (15-25) years.

Table (1): Distribution of age groups among women in study groups

Age Groups	Urinary Tract Infection	Bacterial Vaginosis	Urinary Tract Infection with Bacterial Vaginosis	Control Group	P-value
	No.%	No.%	No.%	No.%	
15-25 Y	21(35.0)	20(33.3)	22(36.7)	19(31.7)	
26-36 Y	21(35.0)	23(38.3)	21(35.0)	15(25.0)	0.08
37-47 Y	14(23.3)	16(26.7)	17(28.3)	16(26.7)	
48-58 Y	4(6.7)	1(1.7)	0(0)	10(16.7)	

One-way ANOVA significant at 0.05, Freidman significant at 0.005, (Figure: Age groups among study populations Appendix 9)

The result of this table (2) shows that D-dimer test, for the BV group and the group of UTI with BV the result based on the statistical analysis findings, the comparison of means. indicates that there is a substantial variance between them rising level of statistical considerable (p-value 0.001). In the current study, nonspecific blood markers were used for the diagnosis of the UTI group, BV group, and UTI with BV group, these appeared to the elevation of D-dimer in patients with BV compared with those in normal controls.

Table (2): D-dimer comparison among study groups

Groups	No.	Avg.	Std. Deviation	Std. Error	Lower Bounds	Upper Bounds	*P-value
UTI	60	416.9835	275.78210	35.60332	345.7414	488.2256	
BV	60	523.3337	299.44432	38.65810	445.9790	600.6883	
UTI and BV	60	517.5682	310.17058	40.04285	437.4426	597.6937	0.001
Control	60	278.7167	100.31815	12.95102	252.8017	304.6316	
Total	240	434.1505	277.53797	17.91500	398.8590	469.4420	

3.2 Genetic results of SDF1-α

A pair of primers of *Stromal cell-derived parameter 1-α* gene (*SDF1-α*) has been utilized for detecting the existence of *SDF1-α* gene (Therefore, alleles with a single primer and distinguished the alleles by molecular weight) in blood specimens for patients and healthy women with UTI set, BV set, UTI and BV set, *SDF1-α* had been successfully amplified from all participates (100%) of *SDF1-α* with length of molecular 302bp, the amplicon has been noticed in gel-electrophoresis and associated with allelic-ladder as demonstrated in Figure (1).

When analyzing genotypes and alleles of *SDF1-α* gene polymorphisms in healthy control and in patients with UTI, BV, and UTI with BV. found that there was no important variant (p-value 1.000) distribution of *SDF-1* genotypes between UTI, BV, UTI with BV groups and control group, the genotyping shown in Table (3) that all groups have the A allele only with 100%. Therefore, in this gene *SDF1-α* not associated with the risk of diseases progression in the study groups between patients and healthy women.

Table (3): The genotype frequencies of *SDF1-α* in patients with study and controls groups.

Genotype	Patients No. (%)			Controls No. (%)	*P-value*
	UTI	**BV**	**UTI with BV**		
G/G	60 (100)	60 (100)	60 (100)	60 (100)	1.000
A/G	٠	٠	٠	٠	
A/A	٠	٠	٠	٠	
Total	60 (100)	60 (100)	60 (100)	60 (100)	

Where a pair of primers of the gene (*SDF1-α*) has been utilized for detecting the existence of *SDF1-α* gene (We detected alleles with a single primer and distinguished the alleles by molecular weight) in blood specimens for patients and healthy women with UTI set, BV set, UTI with BV set, *SDF1-α* had been successfully amplified from all participates (100%) of *SDF1-α* with length of molecular 302bp, the amplicon has been noticed in gel-electrophoresis and associated with alleles-ladder as demonstrated in (Figure 1).

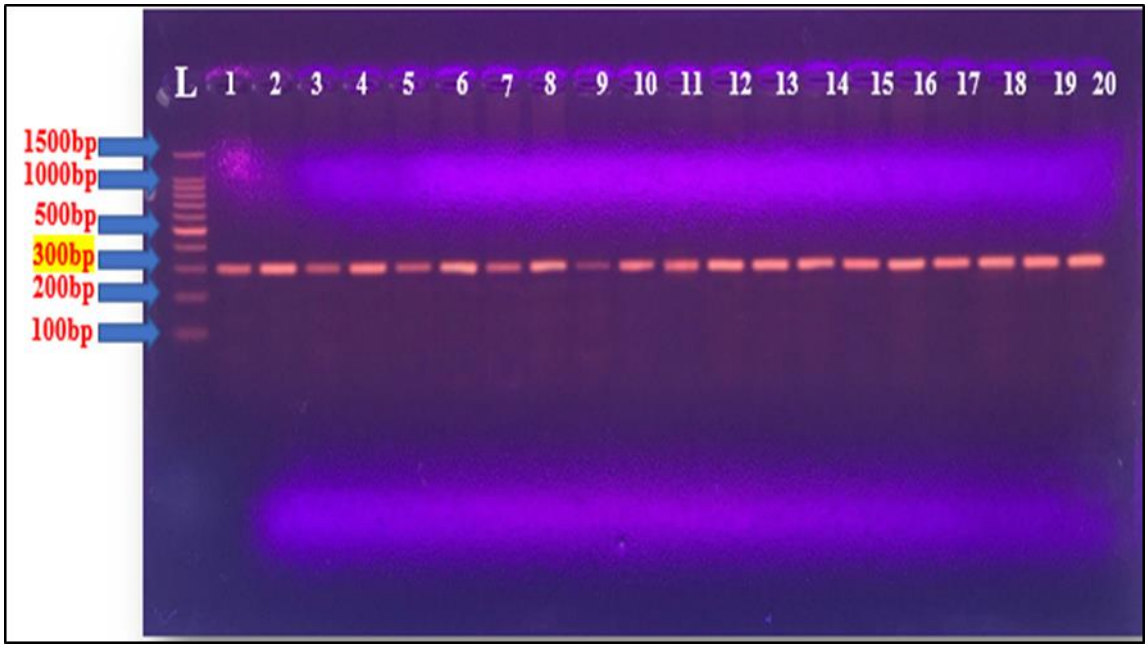

Figure (1): 2 %- Agarose Gel Electrophoresis at (75 volts for 90min) for SDF1-α 1 PCR Products. Visualized under UV light after staining with ethidium bromide. 1500 bp ladder; All lines were positive for *SDF1-α* Gene in blood samples among the patient's groups and control group. The size of the product is 302 bp. (Sample No. 1 to 20). Homozygous wild type (GG). heterozygous genotype (GA). homozygous mutant genotype (AA).

Patients groups and a control group who had G allele not present A allele and G\G genotyping (homozygous alleles were proposed to be related to upregulating the expression of SDF1 protein preparation, so it increased plasma levels of *SDF1* and delayed development to UTI, BV, UTI with BV as well as the risk of developing disorders or the precipitation of illness improvement. According to the study's findings, there were no appreciable differences in *SDF-1* genotype distributions between the patient groups and the control group.

4. Discussions

The present investigation found that the contrast between patient sets and a suspected set of controls based on their level of education had been comparable to that of an earlier investigation conducted by (David et al., 2019; Javaheri Tehrani et al., 2014; Lelie-van der Zande et al., 2021) for UTI ,UTI with BV. According to the means of the study groups . In the current study, nonspecific blood markers were used for the diagnosis of the UTI group, BV group, UTI with BV group, these appeared to elevation of D-dimer in patients with BV compared with those in normal controls.

Except if your body is making and thawing sizable blood coagulate, D-dimer is typically undetectable or only detectable at a very low level. excessive D-dimer levels without a blood clotting disorder. Pregnancy is just one example of a condition or circumstance that might result in higher-than-normal D-dimer levels.Heart conditions, infections, and inflammation. A study conducted by the researcher (Asakura et al., 2021) (Asakura et al., 2021) explained fibrin is formed and then broken down. TNF and IL- β act as plasminogen activators, especially the urokinase-type plasminogen activator, which results in plasminogen to plasmin and this leads to the destruction of the blot. Inflammation-induced coagulation, in which some pro-inflammatory cytokines, such as interleukin-1, interleukin-6, and the tumor-necrosis factor-alpha, determine an increased inducible tissue factor

According to a study done by the researcher (Lee et al., 2018) (Lee et al., 2018), D-dimer is markedly elevated after severe bacterial infections that affect the reproductive and urinary systems. In the physiological host response to pathogens, coagulation is crucial. Immunothrombosis, which is mediated by immune cells and particular thrombosis-related molecules, helps recognise, contain, and kill pathogens while determining its spreading out of the circulatory system, safeguarding the integrity of the host and determining major injured organ (Korn et al., 2019; Meini et al., 2021).

Women have Both UTI with BV were all more common in people who were homozygous for the A/A genotype than in other people (Lin et al., 2022). As a result, it has been established that SDF-1 is one of the chemokines that attracts and accumulates T-lymphocytes (Nerviani et al., 2018) as well as that activates, binds to, and drives the migration of neutrophil leukocytes to inflammatory areas (David et al., 2019). It has been demonstrated that several viral and inflammatory disorders are linked to increased SDF-1 production (Chalin et al., 2018). In another study, a new combination was present between genetic differences of *CXCL12* and the development of pelvic inflammatory disease (AL-Kafajy et al., n.d.). Additionally, a meta-analysis research

indicated that *SDF-1/CXCL-12* A-base nucleotide gene polymorphism was related to CAD susceptibility (Prabawa et al., 2020). To further support the assertion that this gene is linked to a number of disorders, a larger-scale and well planned case-control research should be proceed. In accordance with a different British research, SDF-1 can promote the invasion and migration of breast cancer cells. Its levels are related to nodal involvement and long-term survival in patients with breast cancer. Consequently, SDF-1 may have potential utility in assessing the clinical outcomes of breast cancer patients (Kang et al., 2005).

There was no different distribution of *SDF-1* genotypes between UTI, BV, and UTI with BV groups and control group, all groups have the G allele only with 100%. The findings of other studies (Hughes et al., 2018), do not provide evidence to suggest that the (*SDF1-G801A*) gene variant confers an increased risk for the development cancer of the breast in a cohort of individuals from Poland (Lin et al., 2022).

Do not preclude the possibility that the (*SDF1- G801A*) variation could be a contributing factor to heightened SDF1-alpha protein synthesis, the finding of another investigation suggests that the (*SDF1 G801A*) does not pose a risk for the development of the disease. Patients groups and the control group who had, an allele not present A allele and GG genotyping (homozygous alleles were proposed to be related to up-regulating the expression of SDF1 protein preparation, so it increased levels of SDF1 and delayed development to UTI, BV, UTI with BV as well as the risk of developing disorders or the acceleration of disease progression. According to this study's findings, there were no appreciable differences in *SDF-1* genotype distributions between the patient groups and the control group (Ajalloueian et al., 2018; Folliero et al., 2020). Moreover, the other SDF‑1 receptor, CXCR7, needed more seeking. The roles of the SDF-1/CXCL-12 signaling pathways and their crosstalk in UTIs with BV should also be search in aftertime survey.

5-Conclusion

Urinary tract infection was a major health issue in third-world countries. Therefore, our study suggests that gene polymorphism of *SDF-1/CXCL-12* was not related to UTIs with BV. However, a bigger-scale and well-designed case-control survey should be conducted to explain these conclusions. Since the patients and the control group had the G allele, was in the SDF1-α gene, so it is considered a protective factor for the development of the disease.

Ethical Approval: The study was carried out after obtaining the approvals of the patient and the Iraqi Ministry of Health. In addition to this survey had the moral agreement taken fromAl-Furat Al-Awsat Technical University / College of Health and Medical Techniques / Kufa / Department of Medical Laboratory Techniques.

Study Conflict: There are no studies conflictly.

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