

ORIGINAL PAPER

Semen and sex-steroid parameters among inflammatory bowel disease ulcerative colitis type according to rectal bleeding grade

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Summary

Introduction: Hypogonadism and inflammatory bowel disease (IBD) are often associated.

This association may influence sexual and reproductive function in IBD, including sperm profile and sex steroid hormones.

Patients and methods: This study included 59 IBD patients diagnosed with ulcerative colitis type IBD. Anamnesis was carried out regarding the history of the disease, along with a history of rectal bleeding. Evaluation proceeded with sperm and hormone examination if the patient agreed.

Results: Progressive motility sperm, immotile sperm, and normal sperm were found to be significantly different between the rectal bleeding groups. In grade 3 (more significant bleeding) progressive sperm (24.81 ± 5.85 , $p < 0.0001$) and normal sperm (6.33 ± 12.56 , $p = 0.0003$) rates tended to be lower, while immotile sperm tended to be higher (44.48 ± 11.21 , $p < 0.0001$).

Testosterone and free testosterone levels were also reported to be significantly different between groups, where grade 3 had lower levels 255.9 ± 30.08 , $p = 0.014$ and 4.645 ± 0.5 , $p = 0.002$ respectively.

Conclusions: Our study shows that the degree of rectal bleeding influences sperm motility and morphology, as well as testosterone and free testosterone levels. These results can concern managing IBD patients to fulfill reproductive health care.

KEY WORDS: Inflammatory bowel disease; Sperm analysis; Testosterone; Reproductive healthcare; Hypogonadism.

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INTRODUCTION

IBD is a non-specific chronic inflammatory disease that is brought on by a combination of factors as immune system, environment, intestinal flora, and genetics. IBD's aetiology and pathogenesis remain poorly understood. Ulcerative colitis (UC) and Crohn's disease (CD) are the IBD conditions that are most prevalent (1). About 2 million people in North America have IBD, while about 2.3 million people in Europe do. All over the world, IBD is a common disease, and developing nations with westernized lifestyles continue to see higher incidence rates. More than half of people with IBD are diagnosed when they are younger than 35 years old (2, 4).

Hypogonadism, which can lead to sexual dysfunction, affects about 40% of men with IBD (3, 5). Hypogonadism in IBD patients is linked to taking certain medications and chronic inflammation. Testosterone levels have been linked to the medication of opiates and steroids (3, 4, 6). Compared to the general male population, male patients with IBD have a higher incidence of sexual dysfunction, which ranges from 15 to 25% (7). About 64% of men with IBD actively experience sexual dysfunction (8).

Depression, medication, and hypogonadism are all factors that can affect erectile dysfunction in IBD patients (9). It appears that sexual dysfunction is largely caused by proinflammatory cytokines and reactive oxygen species (4).

When compared to men with UC and to general population, men with CD have an increased risk of infertility that ranges from 18 to 50%. A decrease in the number, motility, and morphology of spermatozoa is accompanied by an increase in the amount of TNF- α , which causes spermatozoa to undergo apoptosis and further proliferation and differentiation of B-cells, T-cells, and natural killer cells. The inflammatory process is mediated by interleukin-1 α and interleukin 1 β causing an increase in reactive oxygen species in sperm and direct damage to spermatozoa. In men with IBD, many other factors play a significant role in the development of infertility, including medication and surgical treatment, disease activity, malnutrition, and psychological factors (2, 4).

According to Wdowiak A *et al.*, men with IBD had significantly lower levels of the total number, concentration, percentage of normal spermatozoa morphology, viability, and progressive motility than the control group. There was no significant difference with the control group's sperm volume or levels of total testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) (2). The purpose of this study is to determine whether the severity (rectal bleeding) of IBD (especially in ulcerative colitis type) impacted on semen parameters (volume, concentration, progressive motility, non-progressive motility, count of immotile, leukocytes, and immature spermatozoa cells, and morphology) and sex hormone binding globulin (SHBG), estradiol, and free testosterone levels.

MATERIALS AND METHODS

We conducted a study on patients who came to the *Gastroenterology Polyclinic at Haji Adam Malik General Hospital, Medan, Indonesia*, diagnosed with inflammatory bowel disease. This study was designed as cross-sectional. This study was approved by the ethical commission of the *Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik General Hospital* with number 428/KEPK/USU/2022.

Patients selection

Patients were assessed by a physician with more than three years of experience in diagnosing this disease. Male patients diagnosed with IBD, aged 20-45 years, married, and willing to undergo sperm and hormone analysis, were observed at the *Gastroenterology Polyclinic at Haji Adam Malik General Hospital* from June to September. Inflammatory bowel disease was diagnosed using colonoscopy findings, clinical symptoms (evaluation) or expertise opinion and histopathology. All these assessments were used to determine the type of IBD and to calculate the Mayo Score of IBD.

Patient were interviewed regarding IBD complaints and then a physical examination was carried out. Patient were advised to have sperm and sex steroids checked. If the patient agreed to be examined, he was explained the sperm analysis procedure.

Procedure and laboratory test

After being examined by an internist (enterologist) and diagnosed with IBD, the patient was directed to participate in the study. Patients will get an explanation of the purpose of the study. Then the patient who agreed signed an informed consent. Researchers interviewed marital history, alcohol consumption, smoking, duration of illness, and medication history. For clinical symptoms of IBD, we only stratified patients based on rectal bleeding by Mayo Score (10) The division based on these symptoms is simple, easy, and objective. This symptom is also what patients often complain about when they come to the clinic.

Patient were advised to come another day after fasting for at least 8 hours and abstinence from intercourse for 2-7 days.

Blood was taken at 07.00-09.00 am. It was processed with an enzyme-linked immunosorbent assay (ELISA) kit (*Roche Diagnostics Ltd., Shanghai, China*) for sex steroid examination.

Then, the patient was directed to masturbate to get a semen sample to be examined according to the 2010 edition of the WHO sperm analysis method.

Data analysis

Data were analysed using Graphpad Prism 9. Univariate analysis was performed for each numerical data, such as mean, median, and mode. The normality test was performed to assess parametric data. Normally distributed data are presented as mean \pm SD, whereas non-parametric data are shown as median (IQR). To see differences in semen and hormone analysis parameters between rectal bleeding groups, a one-way ANOVA test was performed. Kruskal Wallis was an alternative if the data was non-parametric.

Table 1.

Patients and laboratory profile of 59 IBD.

Parameters	Results (n=59)
Age	32.90 \pm 4.7 years
BMI (Body Mass Index)	22.68 \pm 3.6 kg/m ²
Semen Volume	5.0 (3.6-5.2) ml
Sperm Concentration	43.8 (14.5-54.5) million/ml
Sperm Motility	
PR (Progressive)	36.19 \pm 12.78%
NPR (Non-Progressive)	31.0 (26.0-34)%
IM (Immotile)	35.26 \pm 14.45%
Sperm Morphology	32 (21.0-43.0)%
Leukocyte	0.4 (0-0.6) million/ml
Immature Germ Cells	0.2 (0-0.4) million/ml
Total Testosterone	275 (248-330) ng/dl
Free Testosterone	5 (4.5-5.8) ng/dl
Oestradiol	4 (3.5-4.3) ug/ml
SHBG	16.81 (15.58-18.04) nmol/L
Overall Mayo Score	7.78 \pm 2.85
IBD Bleeding Grade	
Zero	9 (15.25%)
First	16 (27.11%)
Second	13 (22.03%)
Third	21 (35.59%)
On-Treatment	
Yes	7 (11.86%)
No	52 (88.14%)
Duration of treatment	2.57 months
Drug of choice Mesalazin and Methylprednisolone	7 (100%)
Smoking	13 (22.03%)
Alcohol	5 (10.16%)
Married and have child	55 (93.22%)

RESULTS

Patients profile

Fifty-nine patients agreed to undergo sperm and sex steroid hormone tests from June to September 2022. Based on whole assessment, all patients included in this series were IBD of the ulcerative colitis type. The mean age of the patients was 32.90 \pm 4.7 years. Some reported smoking (22.03%) and consuming alcohol (10.16%). Out of them 55 were married and had children. Bleeding degree 3 was mostly reported (35.59%). The majority (88.14%) of them never had treatment for IBD. The results of the overall frequency distribution of sperm analysis and sex steroid hormones are presented in Table 1.

Semen analysis and sex steroid

The results of semen and sex steroid analysis by rectal bleeding groups are presented in Figures 1, 2. On semen analysis, progressive motility, immotile, and morphology were significantly different. In group 3 (more significant bleeding) rate of progressive motility and normal sperm morphology was lower (24.81 \pm 5.85 and 6.33 \pm 12.56), while rate of immotile sperm was higher than the other groups (44.48 \pm 11.21). In other parameters, no significant difference was found.

In the analysis of sex steroid levels, testosterone and free testosterone levels were significantly different. Testosterone and free testosterone levels in group 3 were lower (255.9 \pm

Figure 1.
Analysis of semen parameters among rectal bleeding group

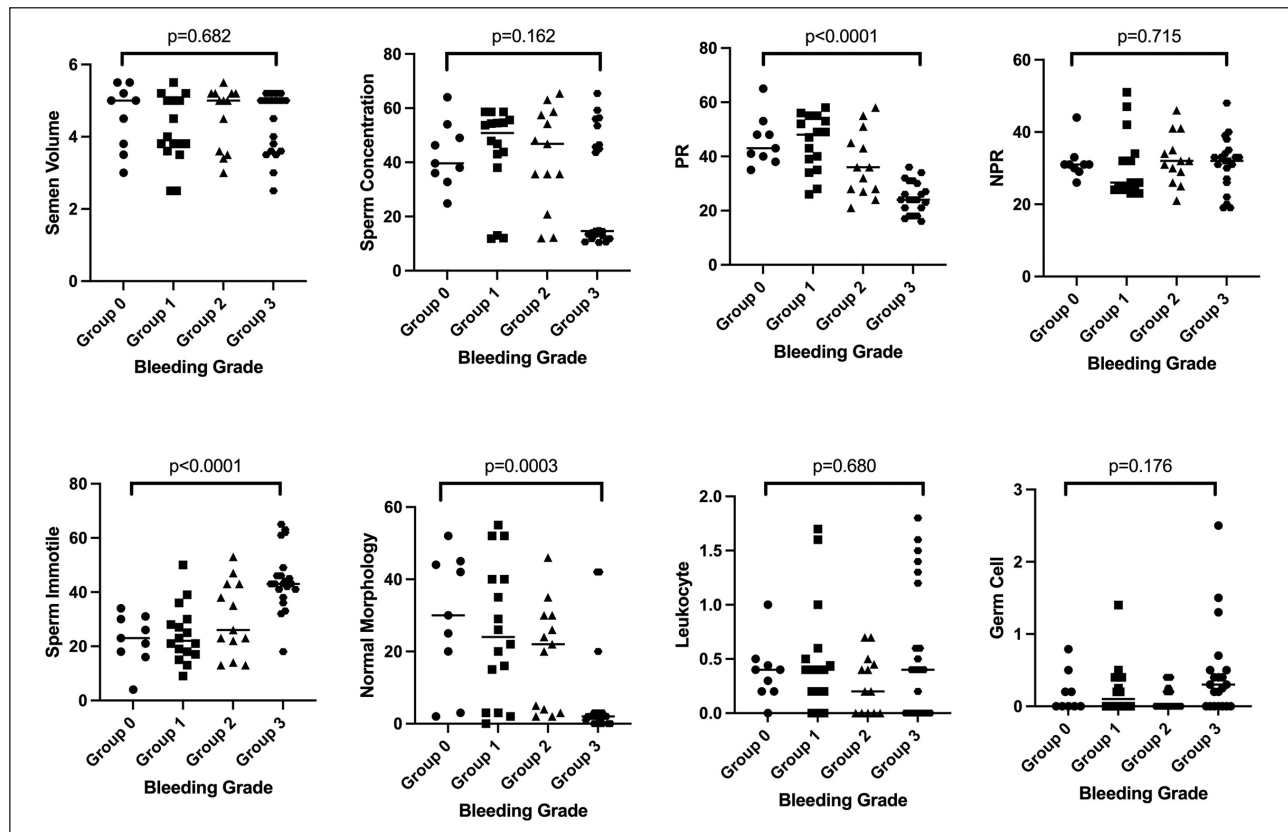
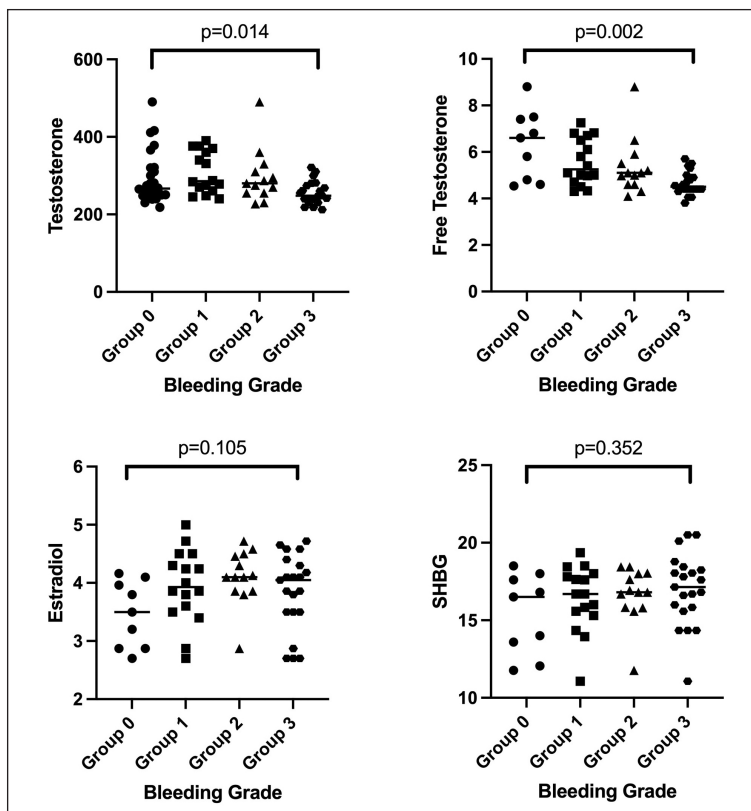


Figure 2.
Analysis of sex steroid among rectal bleeding group.



30.08 and 4.645 ± 0.5), while they were not significantly different for oestradiol and SHBG.

DISCUSSION

Inflammatory bowel diseases (IBD) have emerged as global diseases.(2) Recent evidence indicates that a systemic state of inflammation may exert a negative effect on male fertility (2, 11). Then it should be pointed out that male infertility is considered to be more prevalent in IBD patients than in the general population (12). Therefore, both sexual health and fertility are serious concerns among many patients with IBD, and adequate knowledge of causative factors is of great importance (2).

This study analysis showed significantly different of progressive motility, rate of immotile sperm cells, and morphology on semen analysis among rectal bleeding groups.

The more severe the bleeding, the more likely is the decrease of motility and of normal sperm shape decreases and the increase of immotile sperm. Previous study explained that inflammatory conditions are considered to lead to infertility such as decreased sperm motility, low sperm count, damage to sperm DNA, and/or poor semen quality due to a number of factors like high levels of *reactive oxygen species* (ROS) and oxidative stress. Oxidative stress has been

known to affect spermatogenesis in the testis, epididymis and at a seminal level (13). Then inflammation is accompanied by high levels of reactive oxygen species and oxidative stress, which may exert a negative effect on semen parameters (12). Furthermore, the presence of the pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-alpha), interleukin-1alpha (IL-1alpha) and interleukin-1beta (IL-1beta) in the male uro-genital tract may also increase cytokine-mediated anti-fertility effects (13). Immunological factors associated with humoral immunity against sperm also may lead to infertility. The underlying mechanism is the induction of *antisperm antibodies* (ASA) due to the cross-reactivity between antigens of spermatozoa and exogenous antigens, such as bacteria (12).

Our research study also showed significantly different testosterone and free testosterone levels among our study group. Our study analysis also showed that patients with higher degree of bleeding, had significantly lower testosterone and free testosterone compared to other group. This result support previous studies reporting consistently reduced serum androgens and an important role in decreasing androgen receptor protein of TNF (12) which plays a central role in the pathogenesis of inflammatory bowel disease.

This study has several limitations, mainly concerning the low number of inflammatory bowel disease cases we can include in this study. Therefore, additional studies with larger populations might be helpful to a better understanding of the importance and role of the severity of rectal bleeding in the context of male fertility. We also did not consider other opportunistic infections that might have affected our data study.

CONCLUSIONS

Our study showed that semen parameters (motility and sperm morphology) are associated with the severity of rectal bleeding among IBD patients. The more severe the bleeding, the more likely the decrease of motility and normal sperm shape and the increase of immotile sperm. This suggests that the severity of rectal bleeding contribute to reduce semen quality. Testosterone and free testosterone in patients with a more significant degree of bleeding are significantly lower compared to other patients with less severe bleeding. This suggests that the severity of rectal bleeding also play an important role to control this androgen hormone. The result of this study has shown that low motility level, sperm shape, testosterone and free testosterone are related to the severity of rectal bleeding caused by unregulated inflammation led by TNF.

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Conflict of interest: The authors declare no potential conflict of interest.