

Soluble Fibrinogen-like protein 2 plays a role in varicocele induced male infertility

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Abstract

Varicocele is the most common cause of male infertility. Several theories have been proposed to explain how varicocele induces infertility. The role of epididymis in male infertility is not fully well established. Fibrinogen-like protein 2 is one of serine proteases and is a potent coagulant in membranous form and immune-modulator in soluble form (sFGL-2) and expressed in the epididymis. There are no previous reports about its possible role in varicocele. This case-controlled study aimed to evaluate the seminal level of sFGL-2 in infertile men with varicocele and in men with idiopathic infertility. This study included 85 participants divided into three groups; 25 normal fertile men, 30 infertile men with varicocele and 30 infertile men of idiopathic cause. Clinical examination, Doppler ultrasound, semen analysis and measurement of seminal level of sFGL-2 were done to all participants. Seminal level of sFGL-2 was significantly elevated in infertile than normal fertile men. Seminal level of sFGL-2 showed negative correlations with sperm concentration, motility and normal morphology. Seminal level of sFGL-2 had a positive correlation with seminal liquefaction time. This study concluded that seminal level of sFGL-2 is increased in infertile men with idiopathic cause and with varicocele induced infertility and affects seminal liquefaction.

KEYWORDS

male infertility, soluble fibrinogen-like protein 2, varicocele

1 | INTRODUCTION

Infertility can affect 12% of families worldwide and male factor contribution is up to 50% in this problem (Agarwal, Mulgund, Hamada, & Chyatte, 2015). Infertility in men is complex and multifactorial with different causes ranging from genetic backgrounds to environmental factors (Tournaye, Krausz, & Oates, 2017). The most common causes of male infertility are varicocele and idiopathic infertility (Vander Borgh & Wyns, 2018). The exact pathophysiological process of varicocele induce infertility is a matter of debate (Jensen et al., 2017).

Fibrinogen-like protein 2 (FGL-2) is a serine protease and belongs to fibrinogen family of proteins (Tang et al., 2017). FGL-2 is expressed on the surface of several immune cells as a membrane bound FGL2 (mFGL-2) and can also be secreted as a soluble form (sFGL-2) and can regulate both innate and adaptive immunity (Yang & Hooper, 2013). Previous studies showed the role of FGL-2 in autoimmune diseases (Melnyk et al., 2011), viral infection (Van Tong et al., 2018) and cancer progression (Latha et al., 2019). Some of these factors "as immunity and apoptosis" are suggested to have a role in varicocele induced infertility (Sedaghatpour & Berookhim, 2017); however, there are no previous studies about role of FGL-2 in varicocele induced infertility.

1.1 | Aim of the work

The present study aimed to evaluate the seminal level of sFGL-2 in infertile men with varicocele and in men with idiopathic infertility.

2 | SUBJECTS AND METHODS

2.1 | Ethical approval

This study was carried out after approval of IRP of Faculty of Medicine, Benha University, Egypt. A written informed consent was taken from each participant. The patients' personal data were secured.

2.2 | Study type

A case-controlled study.

2.3 | Participants

This study included 85 men, divided into three groups; 25 normal fertile; 30 infertile with varicocele and 30 men with idiopathic infertility. The infertile men included in this study were sexually active during at least 1 year of marriage and their wives had no cause of infertility. These infertile men were recruited from the Andrology Outpatient Clinic in Benha University Hospitals, Benha University, Egypt, in the period from period May 2019 to October 2019. The fertile controls had offspring in the previous 2 years and satisfying WHO guidelines criteria for normal semen analysis (WHO, 2010). Men with chronic

alcohol intake, drug consumption, hepatic, renal, malignancy or received chemotherapy, urogenital infections and hypogonadism were excluded from this study. All participants were subjected to complete history taking, clinical examination, semen analysis and estimation of seminal sFGL-2. All participants were examined in a warm room by one physician to prevent inter-observer bias in standing and supine positions. Varicocele was classified into grade I, grade II and grade III (Dubin & Amelar, 1970). A scrotal colour Doppler ultrasound with high-frequency linear array transducers >7.5 MHz was done to all participants.

2.4 | Laboratory procedures

The semen sample was obtained after sexual abstinence for 3–5 days by masturbation. Semen was left to clot and after liquefaction, the sample was divided into two parts; the first part was used for routine semen analysis according to the WHO guidelines (WHO, 2010). The second part was subjected to centrifugation at 1,200 g for 20 min for isolation of seminal plasma that was stored at -85°C till estimation of sFGL-2.

Seminal sFGL-2 was estimated using LEGEND MAX™ Human FGL2 Kit (Biolegend), which is a Sandwich Enzyme-Linked Immunosorbent Assay specifically designed for the accurate quantitation of analytes from cell culture supernatant, serum, plasma and other biological fluids. The concentration of sFGL-2 was determined according to manufacturing company instructions.

2.5 | Statistical analysis

The statistical package for social studies program version 22 (SPSS® Inc. for Windows 10®) was used for statistical analysis. The

	Infertile men with varicocele	Infertile men without varicocele	Fertile men
<i>n</i>	30	30	25
Age (year)	33.9 ± 8.3	32.3 ± 7.7	31.9 ± 7.4
Liquefaction time (minutes)	31 ± 5 ^a	33 ± 4 ^a	22 ± 3
Sperm concentration ($10^6/\text{ml}$)	27.35 ± 20.87 ^{a,b}	32.16 ± 19.15 ^a	72.05 ± 40.37
Sperm motility A + B (%)	26.26 ± 20.69 ^{a,b}	36.68 ± 14.68 ^a	61.2 ± 11.29
Sperm normal morphology (%)	2.11 ± 0.8 ^{a,b}	2.78 ± 1.3 ^a	6.73 ± 2.1
sFGL-2 (ng/ml)	2.37 ± 0.8 ^{a,b}	1.94 ± 0.54 ^a	1.18 ± 0.35
Left testicular volume (ml)	18.38 ± 4.22 ^{a,b}	20.12 ± 3.46 ^a	24.18 ± 2.29
Right testicular volume (ml)	19.16 ± 4.08 ^{a,b}	21.03 ± 3.35 ^a	24.58 ± 2.39

TABLE 1 Comparison between sperm parameters, seminal level of sFGL-2 and testicular volume between the studied participants

Note: Data are presented by mean ± SD. *p* value ≤ 0.05 is significant.

Abbreviation: sFGL-2, soluble fibrinogen-like protein 2.

^aStatistical difference compared with fertile men.

^bStatistical difference compared with infertile men without varicocele.

TABLE 2 Comparison between sperm parameters, seminal level of sFGL-2 between infertile varicocele patients according to varicocele laterality

	Unilateral varicocele	Bilateral varicocele
N	16	14
Sperm concentration (10^6 /ml)	33.4 ± 19.4	27.29 ± 23.1
Sperm motility A + B (%)	17.14 ± 6.08	11.64 ± 7.95 ^a
Sperm normal morphology (%)	2.34 ± 1.31	1.4 ± 0.91 ^a
sFGL-2 (ng/ml)	2.21 ± 1.1	2.95 ± 0.7 ^a
Liquefaction time (minutes)	29 ± 7	32 ± 8

Note: Data presented by mean ± SD. *p* value ≤.05 is significant.

Abbreviation: sFGL-2: soluble fibrinogen-like protein 2.

^aSignificant difference compared with unilateral varicocele cases.

quantitative data were expressed as mean ± SD, while qualitative data were in the form of frequency and percentage. Correlations between different variables were tested by Pearson test. *p* ≤ .05 was set as a statistically significant.

3 | RESULTS

The data of the included participants are summarised in Table 1. Results of this study showed a significant prolongation of liquefaction time in infertile men than normal fertile men. In addition, seminal level of sFGL-2 was increased in infertile men than normal fertile men. Results of this study showed a significant decrease of testicular volumes in infertile men with varicocele than other groups (Table 1).

The sperm morphology and motility were significantly decreased in infertile men with bilateral varicocele than patients with unilateral varicocele. Furthermore, infertile men with bilateral varicocele had a higher seminal level of sFGL-2 than patients with unilateral varicocele (Table 2).

Regarding varicocele grading, patients with grade I, III had a significant decrease in sperm morphology than patients with grade II

varicocele. However, seminal levels of sFGL-2 were significantly increased in patients with grade II, III than patients with grade I varicocele (Table 3).

Results of this study showed negative correlations between seminal level of sFGL-2 and sperm normal morphology ($r = -.33$, $p = .002$) and sperm concentration ($r = -.434$, $p = .001$), sperm motility ($r = -.434$, $p < .001$). However, there was a positive significant correlation between seminal level of sFGL-2 and liquefaction time ($r = .382$, $p < .001$) (Figure 1).

4 | DISCUSSION

Fibrinogen-like protein 2 is pleotropic protein and has two forms; the first form is mFGL-2 a potent procoagulant factor which is a cellularly expressed and soluble form sFGL-2 that has a distinctive function (Xu, Hu, Wu, Fan, & Song, 2019). Previous studies showed in situ expression of fibrinogen-like protein 2 in hamster epididymis tissue (Nagdasm, Winfrey, & Olson, 2016; Olson, Winfrey, NagDas, & Melner, 2004). sFGL-2 has 50 kDa weight and is an immune modulator protein secreted by cytotoxic and regulatory T lymphocytes and can be measured in biological fluids (El-Mesery, El-Mowafy, Elgaml, Youssef, & Abed, 2017). The function of sFGL-2 is through its ability to bind to FcγRII and FcγRIII (Luft et al., 2018), and these receptors are expressed on human spermatozoon (Klungland et al., 1997). Upon these receptor activations; sFGL-2 initiate activation of mitogen-activated protein kinase and nuclear NF-κβ in high concentration and in addition it acts as transforming growth factor beta factor in low concentration (Wang et al., 2014). These pathways are important in spermatozoa apoptosis (Karabulut, Demiroğlu-Zergeroğlu, Yılmaz, Sağır, & Delikara, 2014; Wang & Su, 2018) and capacitation (Luna et al., 2017) and immune-tolerance (Pierucci-Alves, Midura-Kiela, Fleming, Schultz, & Kiela, 2018).

Results of this study showed elevation of sFGL-2 in infertile men with varicocele than with idiopathic infertility patients. This elevation indicates the involving of the epididymis in varicocele induced infertility. Several hypotheses had been proposed to clarify how the epididymis modulates sperm maturation (Gervasi &

TABLE 3 Comparison between sperm parameters, seminal level of sFGL-2 between infertile varicocele patients according to varicocele grades

	Grade I varicocele	Grade II varicocele	Grade III varicocele
<i>n</i>	11	10	9
Sperm concentration (10^6 /ml)	31.22 ± 29.64	27.54 ± 25.41	28.04 ± 26.67
Sperm motility A + B (%)	15.81 ± 7.1	14.83 ± 5.86	16.87 ± 7.87
Sperm normal morphology (%)	2.6 ± 1.34 ^a	1.8 ± 0.87	2.53 ± 0.49 ^a
sFGL-2 (ng/ml)	1.1 ± 0.82	2.5 ± 1.8 ^b	2.8 ± 1.4 ^b
Liquefaction time (minutes)	30 ± 4	28 ± 7	31 ± 8

Note: Data presented by mean ± SD. *p* value ≤.05 is significant.

Abbreviation: sFGL-2, soluble fibrinogen-like protein 2.

^aStatistical difference compared with grade II varicocele.

^bStatistical difference compared with grade I varicocele.

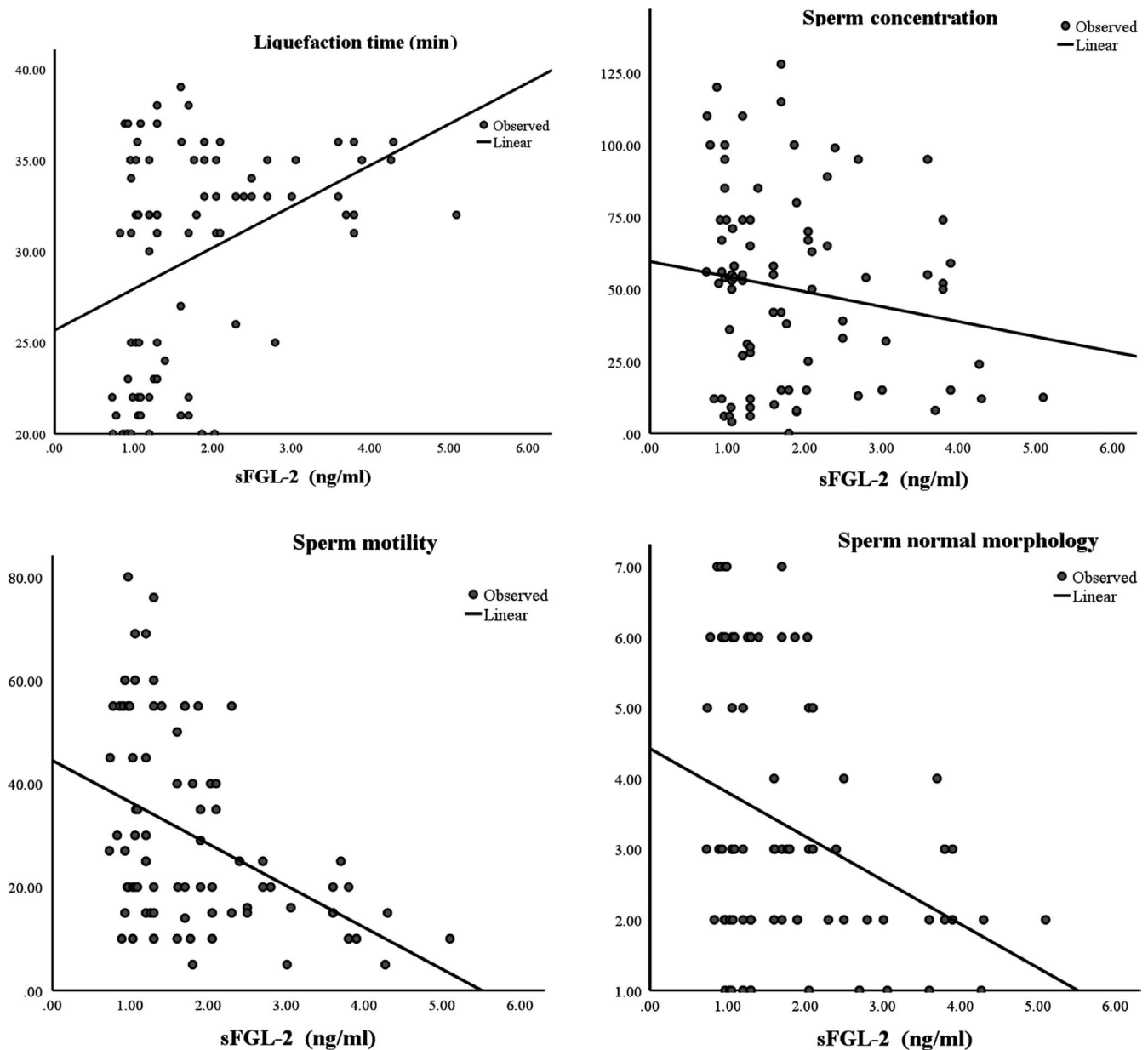


FIGURE 1 Correlations between liquefaction time, sperm concentration, sperm motility, sperm normal morphology and semen and seminal level of sFGL-2

Visconti, 2017). Important epididymal secretions are decreased in varicocele (Ozturk et al., 2008; Roaiah et al., 2007; Vivas-Acevedo, Lozano-Hernandez, & Camejo, 2011). Epididymal microenvironment is changed and increase of hypoxia-related markers in varicocele (Zhang et al., 2016).

Results of this study showed more affection of varicocele bilaterality on sperm parameters and seminal level of sFGL-2. This agrees with previous studies about the effect of bilaterality of varicocele on sperm parameters (Lehtihet, Arver, Kalin, Kvist, & Pousette, 2014; Mikhael et al., 2018).

The prolongation of liquefaction time in infertile men in this study may be due to mFGL-2 expressed on macrophage and other dendritic cells (Tang et al., 2018). These cells are increased in semen of infertile men and negatively impact epididymal function (Duan

et al., 2014). The prolongation of liquefaction time may increase the viscosity of the semen and interferes with sperm motility (Lwaleed, Greenfield, Birch, & Cooper, 2005). Although bacterial infection is the most common cause that increases semen viscosity (Du Plessis, Gokul, & Agarwal, 2013); varicocele “especially if associated with concomitant dilation of the periprostatic venous plexus” can increase semen viscosity (Condorelli et al., 2015).

5 | CONCLUSIONS

Seminal level of sFGL-2 is increased in infertile men with idiopathic cause and with varicocele induced infertility and affects seminal liquefaction.

5.1 | Limitations

Seminal level of sFGL-2 had not been measured before and after varicocelectomy in infertile men with varicocele.

AUTHOR CONTRIBUTIONS

Category 1: All authors involved in conception and design, analysis of data and interpretation of data. Category 2: All authors involved in drafting the article and revising it critically for important intellectual content. Category 3: All authors involved in final approval of the version to be published. All authors state that the material contained in this manuscript has not been published, has not been submitted, or is not being submitted elsewhere for publication. All authors in the manuscript were contributed for collecting the materials, revising the data, putting the draft and intellectual revision.

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How to cite this article: Elesawy FM, Abdel Hafeez NA, Abdelsalam OH, Akl EM. Soluble Fibrinogen-like protein 2 plays a role in varicocele induced male infertility. *Andrologia*. 2020;52:e13626. <https://doi.org/10.1111/and.13626>