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Tissue factor (TF) and tissue factor pathway inhibitor (TFPI) in the peritoneal fluid in patients with peritonitis – is the key towards intraperitoneal adhesions and complications?

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ABSTRACT

Introduction: The concentrations of tissue factor (TF) and tissue factor pathway inhibitor (TFPI) in the peritoneal fluid and blood plasma in patients with peritonitis were examined. The fibrinogenesis of the peritoneal cavity is not well-known although it is regarded as the main cause of intraperitoneal adhesions and the complications that arise from this.

Materials and methods: The study enrolled a group of 77 consecutive patients with peritonitis, 28 women and 49 men aged 18–79 years (with an average age of 45 ±18 years). The patients were divided into 2 subgroups: those with complications (n = 64) and those without (n = 13). Concentrations of TF and TFPI in the peritoneal fluid and blood plasma of patients were examined.

Results: In the peritoneal fluid, patients with complications had a higher concentration of TF ($p < 0.007$), but a lower concentration of TFPI ($p < 0.0006$). In blood plasma, TF was higher but TFPI was lower ($p < 0.00001$ in both). The area under curve (AUC) for TF and TFPI was 0.763 and 0.93 respectively, the cut-off point was 809.08 pg/mL and 21.6 pg/mL, respectively. The positive predictive value (PPV) and negative predictive value (NPV) for TF was 68% and 75% and for TFPI, 80% and 85%, respectively.

Conclusions: The data can be taken as an example of cross-linking between extravascular coagulation and intraperitoneal adhesions. On the basis of TF and TFPI, it is clearly illustrated that there is some connection between coagulation and peritoneal fibrinogenesis, which could be involved in the pathogenesis of many complications in abdominal surgery and also indicate therapeutic targets.

Keywords: peritoneal adhesions; fibrinogenesis; peritoneal fluid; peritonitis; complications.

INTRODUCTION

Peritonitis, as a typical inflammatory process, is regarded as the main cause of fibrin production in the peritoneal cavity [1, 2, 3].

The presence of some key components of the coagulation system in peritoneal fluid and the existence of extravascular activation of coagulation in the peritoneal cavity has been confirmed by many authors [1, 4, 5, 6, 7, 8]. Fibrin is key to recovering after surgery but may also be the cause of serious complications. Fibrin forms intraperitoneal adhesions which can facilitate the formation of intraperitoneal abscesses and sepsis [9, 10, 11, 12]. The risk of adhesive small-bowel obstruction after abdominal surgery is 11% within 1 year, increasing to 30% after 10 years. One in 5 patients undergoing a reoperation suffer from inadvertent enterotomy, resulting in significant postoperative morbidity and mortality. Roughly 3% of all surgical admissions are associated with intra-abdominal adhesions [13].

The inflammation process can trigger an increase in the concentration of tissue factor (TF) [1, 13, 14, 15, 16, 17, 18]. The mesothelial cells of the peritoneum are known as one of a rich source of factors of the coagulation cascade including TF [16, 17, 18, 19, 20, 21].

The importance of tissue factor pathway inhibitor (TFPI) for the intraperitoneal adhesions should also be determined. Tissue factor pathway inhibitor inhibits the TF in the complex with factor VIIa via an ordered sequence of reactions, then the active site of factor Xa binds to complex TFPI-TF-VIIa, blockades a coagulation cascade and ultimately the fibrin production [22]. The reactions occurring in patients' blood are well-known, but the current knowledge about the pathways of these processes in the peritoneal cavity is limited [23, 24, 25, 26, 27].

The main purpose of the study was to analyse the expression and concentration of the TF and its inhibitor, the TFPI in the peritoneal fluid collected from patients with peritonitis. The 2nd goal of this project was an analysis of the impact of TF and TFPI on the types of complications associated with the treatment of peritonitis.

MATERIALS AND METHODS

The study enrolled a group of 77 consecutive patients with peritonitis – 28 women and 49 men aged 18–79 years (average age: 45 ±18 years). The causes of peritonitis and methods of treatment are included in Table 1.

TABLE 1. The causes of peritonitis and methods of treatment

Cause of peritonitis	Surgical procedure	Number of patients
Acute appendicitis	appendectomy	25
Intraperitoneal abscess	laparotomy/drainage/ resection	9
Acute pancreatitis	laparotomy/drainage/ necrectomy	4
Cholecystitis	cholecystectomy	11
Perforation of digestive tract	laparotomy/resection	6
Sclerosing peritonitis in CAPD	laparotomy	2
Mechanical ileus	laparotomy/resection	20
Total		77

The exclusion criteria were any neoplastic diseases and haemostasis disorders of any form. Diagnosis of peritonitis was established in clinical examinations and routine laboratory tests. The results were also confirmed by imaging examinations involving an ultrasound examination and computer tomography (CT). Follow-up was conducted for 12 months after hospital dismissal.

During this period, many early complications were noted, which included minor ones like fever, wound infection or prolongated paralytic ileus to severe ones, like abdominal abscess, mechanical ileus or sepsis with multiorgan failure.

Patients were divided into 2 subgroups: patients with some complications and patients who had a smooth postoperative course. The purpose of this was to compare differences in the concentrations of TF and TFPI between the 2. A detailed analysis of the observed complications is presented in Table 2.

TABLE 2. The causes of peritonitis and methods of treatment

Type of complications	Number of patients
Intra-peritoneal	2
Sepsis with multi-organ failure (MOF)	2
Gastrointestinal bleeding	2
Mechanical ileus	1
Wound infection	6
Total number	**13 (16%)**

Preparation of blood plasma

All examined blood samples were obtained by direct intraluminal needle aspiration into pyrogen-free plastic disposable syringes and immediately collected into pyrogen-free plastic tubes with 3.8% sodium citrate in a 9:1 volume ratio. Platelet-poor plasma was obtained by centrifugation at 1,900 G for 10 min at room temperature. The tubes of samples were aliquoted and stored at – 70°C before being assayed.

Preparation of peritoneal fluid

Peritoneal fluid was obtained from patients during surgery. The peritoneal fluid was directly discharged from the peritoneal cavity to a plastic tube containing 3.8% sodium citrate in a proportion of 9:1. The liquid was then centrifuged, portioned and stored in a similar way to the plasma.

According to laboratory standards on objectively comparing 2 different fluids, each concentration of TF and TFPI was recounted per gram of protein in blood plasma and peritoneal fluid.

Tissue factor concentration was determined by IMUBIND ELISA using commercial kits (American Diagnostica Inc, Imubind™ Tissue Factor, USA), according to manufacturer's protocol.

The TFPI was assessed by IMUBIND ELISA using a commercially available enzyme-linked immunosorbent assay (ELISA; American Diagnostica Inc. Imubind® Total TFPI, USA) according to manufacturer's protocol.

All experiments were performed in triplicate.

The study was approved by the Institutional Review Board Ethics (blood and peritoneal fluid were taken from the patients with peritonitis after they signed an informed consent form). All methods were carried out in accordance with the approved guidelines.

Statistical analysis

Statistical methods and analyses were tested with the use of StatSoftPol version 13. The distribution of examined parameters including TF and TFPI were tested for normality with the Shapiro–Wilk test. Parameters which deviated from normal distribution were presented as a median (M) with an interquartile range (IQR and IIIQR). The parameters with normal distribution were presented as an average (X) and a standard deviation (SD). The Mann–Whitney U test was applied if the distribution of an examined parameter deviated from normal distribution and the Student's t-test was used for those with a normal distribution. Correlations were tested with the use of the Pearson ratio. Receiver operator characteristic (ROC) curves with area under curve (AUC) were employed to determine the corresponding cut-off points and to assess the diagnostic importance of TF and TFPI in the detection of the risks of complications in peritonitis. Positive predictive value (PPV) and negative predictive value (NPV) were calculated for each examined parameter. Statistical significance was set at $p < 0.05$.

RESULTS

Table 3 presents the concentration of TF in the peritoneal fluid and in the blood plasma. This shows that both the mean and median of TF in the peritoneal fluid were higher than in the blood plasma (statistically significant difference $p < 0.00001$).

Table 4 compares the concentration of TF in peritoneal fluid between both groups of patients, those with post-operative complications and those without. The concentration of TF in

patients with complications was much higher than in other patients (statistically significant difference $p < 0.007$).

Table 5 shows the concentration of TFPI in the peritoneal fluid and blood plasma. The mean and median of TFPI in the peritoneal fluid were significantly lower than those in blood plasma (statistically significant $p < 0.00001$).

Table 6 shows TFPI concentration in the peritoneal fluid between patients with complications and those without. In patients with complications, TFPI was lower when compared to those without (statistically significant difference $p < 0.0006$).

To standardize the laboratory comparison of blood plasma with the peritoneal fluid, both were evaluated for protein concentration, and then TF and TFPI concentrations in the plasma and peritoneal fluid were recounted per gram of protein.

Table 7 shows the concentrations of TF and TFPI in the peritoneal fluid and blood plasma per gram of protein. After recounting, the level of TF in the peritoneal fluid was still higher than in the blood plasma, however the statistical significance was slightly lower ($p < 0.001$). Similar tendencies were seen in TFPI which also had a slightly lower statistical significance ($p < 0.01$).

TABLE 3. Tissue factor (TF) and tissue factor pathway inhibitor (TFPI) concentrations in peritoneal fluid and blood plasma in patients with peritonitis

Statistic parameter	TF (pg/mL)			TFPI (pg/mL)		
	blood plasma	peritoneal fluid	p	blood plasma	peritoneal fluid	p
n	77	77		77	77	
X ±SD	401.3 ±165.3	684.9 ±312.4	<0.00001 na	108.3 ±44.6	27 ±14	<0.00001 na
Median	398.7	765.4	<0.00001	116.4	21.8	<0.00001
IQR	298.7	428.7	na	81.4	13.7	na
IIIQR	498.7	900.9	na	133.9	39.8	na
Minimum	109.7	107.9	na	13.7	10.8	na
Maximum	879.6	1456.8	na	221.6	55.9	na

n – number of patients; X ± – average ±; SD – standard daviation; IQR – 1st quartile; IIIQR – 3rd quartile; p – statistical significance according to Mann–Whitney test; na – non applicable

TABLE 4. Comparison of tissue factor (TF) and tissue factor pathway inhibitor (TFPI) in peritoneal fluid in patients with complications (complicat) and patients without (uncomplicat)

Statistic parameter	TF (pg/mL)			TFPI (pg/mL)		
	complicat	uncomplicat	p	complicat	uncomplicat	p
n	13	64		13	64	
X ±SD	955 ±191.1	642 ±313.9	<0.007 na	15.3 ±4.7	29.3 ±18.9	<0.0006 na
Median	987.7	690.7	<0.007	13.3	29.7	<0.0006
IQR	885.9	389.6	na	11.2	13.1	na
IIIQR	994.9	879.6	na	20.3	41.9	na
Minimum	809	109.7	na	10.8	8.1	na
Maximum	1130.4	1456.8	na	21.8	112.0	na

n – number of patients; X ± – average ±; SD – standard deviation; IQR – 1st quartile; IIIQR – 3rd quartile; p – statistical significance according to Mann–Whitney test; na – non applicable

TABLE 5. The concentration of tissue factor (TF) and its inhibitor (TFPI) in the peritoneal fluid and blood plasma recounted per gram of protein

Examined parameter	n	Peritoneal fluid	Blood plasma	Statistical level
		X ±SD	X ±SD	
TF (pg/mL/g%)	77	18.6 ±13.7	7.6 ±2.5	p < 0.001
TFPI (pg/mL/g%)	77	0.8 ±0.2	3.7 ±0.7	p < 0.01

p – statistical significance according to Mann–Whitney test; X – average; SD – standard deviation

TABLE 6. Comparison of tissue factor pathway inhibitor (TFPI) in the peritoneal fluid in patients with complications and patients without

The examined group of patients	TFPI (pg/mL)						
	n	X ±SD	median	IQ	IIIQ	minimum	maximum
Complicated	11	15.3 ±4.7; p < 0.0006	13.3	11.2	20.3	10.8	21.8
Uncomplicated	64	29.3 ±18.9	29.7	13.1	41.9	8.1	112.0

n – number of patients; X ±SD – average ± standard deviation; IQR – 1st quartile; IIIQR – 3rd quartile; p – statistical significance according to Mann–Whitney test

TABLE 7. The concentration of tissue factor (TF) and its inhibitor (TFPI) in the peritoneal fluid and blood plasma recounted per gram of protein

Examined parameter	n	Peritoneal fluid	Blood plasma	Statistical level
		X ±SD	X ±SD	
TF (pg/mL/g%)	77	18.6 ±13.7	7.6 ± 2.5	p < 0.001
TFPI (pg/mL/g%)	77	0.8 ±0.2	3.7 ± 0.7	p < 0.01

n – number of patients; X ±SD – average ± standard deviation; p – statistical significance according to Mann–Whitney test

As displayed in Figure 1, the concentration of TF in the peritoneal fluid did not strongly correlate with that in plasma (r = 0.321, p < 0.056). Similar tendencies with TFPI can be observed in Figure 2, its concentrations in the peritoneal fluid also did not statistically correlate with its levels in plasma (r = 0.2106, p < 0.066). This may indicate that in addition to the vascular source of TF and TFPI, there is another source in the peritoneal cavity.

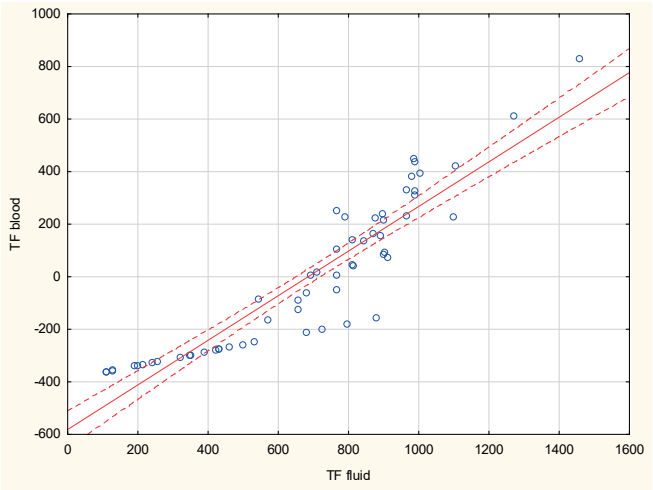

FIGURE 1. Diagram showing the correlation of the tissue factor (TF) between fluid and blood plasma of patients with peritonitis (r = 0.321; p < 0.056)

The analysis of ROC for TF and the risk of complications in peritonitis revealed AUC was 0.763 (p < 0.0001). The cut-off point for TF was 809.08 pg/mL. The PPV of TF was 68% and the NPV was even higher at 75%. The analysis of ROC for TFPI and the risk of complications in peritonitis revealed the AUC was 0.93 (p < 0.000001). The cut-off point for TFPI was 21.6 pg/mL. The PPV and NPV of TFPI for the risk of complications in peritonitis were 80% and 85%, respectively. In light of this, TFPI seems to be a stronger marker of possible complications of peritonitis.

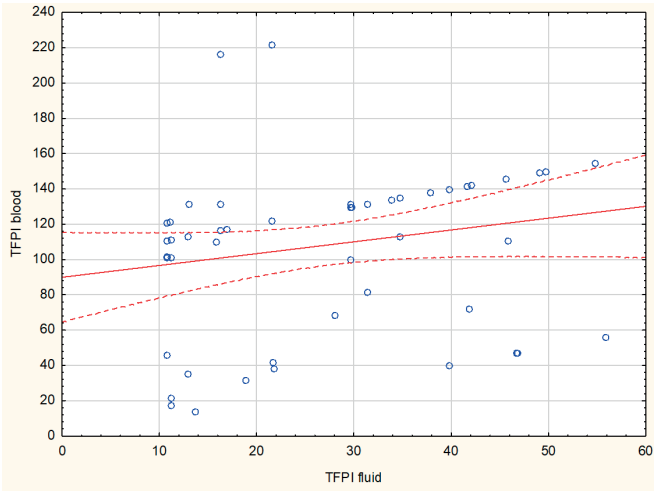

FIGURE 2. Diagram showing the correlation of the tissue factor pathway inhibitor (TFPI) between fluid and blood plasma of patients with peritonitis (r = 0.2106; p < 0.066)

DISCUSSION

The main purpose of this study was to re-evaluate the hypothesis that the presence of TF in peritoneal fluid plays a significant role in adhesions and complications after treatment. Theoretically, in peritoneal fluid, TF could promote the development of an unfavorable course of peritonitis by activating the fibrillogenesis, which would facilitate the formation of intra-abdominal abscesses.

There are few clinical and experimental studies on this issue and the evaluation of the impact of peritoneal adhesions on the pathophysiology of peritonitis remains to be controversial [28]. Abdominal adhesions are a significant medical problem worldwide, and unfortunately little progress has been made in understanding their pathophysiology in the last decade. However, the outcomes of this study are promising and should contribute to an increasing interest among clinicians

and pathophysiologists to understand the etiology of adhesion formation and the negative impact they have on patients' health [13].

In the peritoneal fluid in patients with peritonitis, we found a higher TF level and lower TFPI when compared to blood plasma. The observed differences in TF between the peritoneal fluid and blood plasma may indicate a different source of TF in the peritoneal cavity. In the case of complications that arise from peritonitis, the discrepancy in these parameters deepened further, showing an even greater increase in TF and a greater decrease in TFPI. This indicates that they could be used as markers of a risky course of peritonitis. This is also confirmed in the findings from the analysis of ROC, cut-off point and PPV and NPV of TF and TFPI. The discrepancy was especially apparent in TFPI, where the highest values were those for AUC and NPV. These observations could be evidence of an unfavorable phenomenon for patients with peritonitis, especially if they have a lower concentration of TFPI in peritoneal fluid.

According to many authors, peritonitis causes the influx of inflammatory cells into the peritoneal cavity which activates the mesothelial cells and leads to the production of many profibrinitic factors, which are then released into the peritoneal fluid [1, 16, 18, 21]. This would explain the presence of TF in peritoneal fluid. However, there are some problems with TFPI. Although the source of vascular TFPI is well-known, up until now, the place where TFPI is produced in the abdominal cavity is unknown. It could be provided by peritoneal mesothelial cells or macrophages [29]. Macrophages seem to be an interesting explanation for this as they are involved in defense mechanisms. Fewer macrophages in the peritoneal cavity during peritonitis could explain the lower level of TFPI and the increased risk of complications. However, this requires further study.

In peritonitis, the fluid can contain a temporary or long-lasting increase in fibrinogenetic factors, which ultimately could lead to fibrin adhesions [13].

It is well-documented that inflammatory fluids are rich in fibrinogen which, in a multistep process under the impact of TF, could be converted to fibrin [30, 31]. The presence of TF in the peritoneal fluid may suggest that there is also a conversion of fibrinogen to fibrin. An increase in TF can lead to the overproduction of fibrin which, with an insufficient dissolution mechanism lowering TFPI, may be one of the factors which unfavorably affect the results of the peritonitis treatment. In contrast to the poorly established mechanisms of fibrinogenesis in the peritoneal cavity, there is a similar well-known mechanism found in blood plasma, which is called blood coagulation [1, 19, 32].

Only a few authors have shown the presence of TF in the peritoneal fluid in peritonitis [33, 34, 35], including Fareed et al. However, in their study, they demonstrated lower concentrations of TF than in our patients [33].

Unlike in blood plasma, where there are many publications on TFPI, there are no data on TFPI in the peritoneal cavity. Our work is likely the 1st to investigate TFPI in the peritoneal fluid in peritonitis. At this stage of our study, it is extremely difficult to explain its origin, however, there is a chance that the key to explaining this are the peritoneal mesothelial cells. This certainly requires further research. Tissue factor pathway inhibitor levels have been shown to be slightly elevated in the blood plasma of patients with sepsis and in those with acute respiratory distress syndrome. Low plasma TFPI levels also have been detected in some patients who have had an unfavorable course of peritonitis [36, 37].

Opal et al., in their experimental model, showed some positive effects of TFPI in peritonitis and sepsis [38], however there are also some opinions which contradict this [2]. The possibility of the activation of fibrinogen into fibrin in peritoneal fluid has been pointed out by Hariharan et al. [34]. Many components of the intraperitoneal process conversion of fibrinogen into fibrin include the same factors as in the blood coagulation cascade [34]. In our opinion, to distinguish them and avoid confusion, the process in the peritoneal cavity should instead be called fibrinogenesis. The increase of TF activity in the peritoneal fluid in cirrhosis was shown by Thaler et al., but they did not observe any other factors of blood coagulation and fibrinolysis [35].

It seems that the key to improving the results of peritonitis treatment is understanding the mechanisms of intraperitoneal adhesions. It may also contribute to the implementation of more effective anti-adhesive therapies.

This has already been partially confirmed by experimental studies conducted on animal models which showed a positive effect on preventing intra-peritoneal conversion of the fibrinogen, contributing to the improvement of the outcomes in the treatment of peritonitis [19, 34, 39].

CONCLUSIONS

We hope that our data contribute to extending the knowledge of the impact of the TF/TFPI system on the conversion of fibrinogen and intraperitoneal adhesions in peritonitis. The mutual intraperitoneal interactions of TF and TFPI could explain some aspects of peritonitis and complications that occur thereafter. It seems that the balance of TF/TFPI could be involved in the pathogenesis of many complications not only in peritonitis, but also in abdominal surgery, and may also indicate possibilities for final therapeutic targets.

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