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TafiIn Fibrinolysis - A Review

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Abstract: Thrombin activated fibrinolysis inhibitor, shortly known as TAFI, is a carboxypeptidase found in plasma. It is activated majorly by thrombomodulin associated-thrombin. It stabilizes clots and inhibits their lysis by decreasing their plasminogen binding sites. Besides, it activates protein C which is necessary to halt thrombin generation. Thus, it is more regulatory than inhibitory in function. Existing as three forms TAFI, TAFIa and TAFIi, assay methods of the same are not well standardized. However, TAFI is associated with conditions like hemophilia, venous thrombosis, myocardial infarction, angina pectoris, chronic liver disease and even disseminated intravascular coagulation (DIC). This review will throw light on the role, mechanisms and involvement of TAFI in associated pathological conditions.

Keywords :Clotlysis, coagulation, fibrinolysis, thrombin, TAFI

1. INTRODUCTION

At the site of an injured blood vessel, an activated coagulation pathway generates thrombin and facilitates the conversion of fibrinogen to fibrin, forming fibrin clots, preventing the loss of blood. To check the inadequate deposition of fibrin, the fibrinolytic system is on continuous surveillance, dissolving fibrin mesh, both in normal hemostatic conditions as well as in thrombosis. Thrombomodulin-associated-thrombin activated TAFI is a carboxypeptidase-U, that removes the C-terminal lysine and arginine residues present on fibrin, which are active binding sites of plasminogen, thereby allowing clot stabilization (Leung, Nishimura, and Myles 2008). Hendriks et al, in 1988, was the first to report the presence of an unstable basic carboxypeptidase generated from a precursor in blood. This enzyme was thus given the name ‘carboxypeptidase-U’ (unstable). After its function was elucidated, it gained the name ‘Thrombin activated fibrinolysis inhibitor’ or TAFI. Various other studies (Lin et al. 2013) also describe it to be a procarboxypeptidase B or R. This review will thus assess the major regulatory roles of TAFI in the fibrinolytic system and how its understanding can be effectuated in other diagnostic applications.

Previous studies have positively correlated the regulation of TAFI to thrombotic disorders. Eichinger et al (Eichinger et al. 2004) demonstrated that high levels of TAFI indicated a two-fold greater risk of the recurrence of thromboembolism. In another study, it was observed that the influence of TAFI on the vascular system lies in the levels of the risk of occurrence of thrombosis and the loss of balance in the delicate maintenance of the coagulation system. This may also be developed post operatively (Zhao et al. 2016) in specific conditions or cases, like splenectomy and hysterectomy (Kalaiselvi and Brundha 2016). However, an area that can be considered as a lacunae in the understanding of the roles of TAFI includes the poor testing standardization (Ravichandran and Brundha 2016) where, poor specificity of the currently existing assays for evaluating the three different forms of TAFI poses to be a drawback (Monasterio et al. 2003). Besides, the differences in age, gender and factors alike, in a population, make TAFI vary widely, when compared with the values of the other blood elements (Shreya and Brundha 2017). Therefore, the review aims to assess the extent of feasibility in implementing existing notions on the roles and functions of TAFI, in possible areas, including diverse treatment modes. It also aims to provide feed for inputs required in molecular biotechnology, associated with the development of synthetic TAFI.

2. MATERIALS AND METHODS

The review highlights the roles and involvement in the regulatory mechanisms of TAFI. This review has been assimilated using inputs from various other studies obtained using search engines including PubMed, NCBI, Google Scholar, Semantic Scholar, etc. The studies retrieved were validated and categorized using the quality assessment tool - Health evidence - for reviews, and were referred to, according to their relevance, strategy cover and level of evidence.

3. SYNTHESIS OF TAFI

TAFI is present in platelets, which are released upon the stimulation mediated by thrombin, adenosine diphosphate (ADP) and collagen. About 0.1% of total TAFI levels are platelet derived (Bouma and Mosnier 2003). Otherwise they are primarily synthesised in the liver, with a small fraction derived from megakaryocytic cell lines (Semeraro et al. 2009). Consequently, plasma and platelet derived TAFI do not vary functionally, they substantiate the same roles; modulating fibrinolysis. Therefore, an injury mediated localization of platelets at the given site of injury, which may even be estimated (Kaviya and Brundha 2017), is accounted for the action of TAFI in clot stabilisation. Besides, being synthesised from a proenzyme, its multiple forms include TAFI, TAFIa and TAFIi(Frère et al. 2005) with TAFIa being the catalytically more active form. This particular form is activated by thrombomodulin, which facilitates thrombin activated cleavage of the Arg93 site of TAFI, establishing a down-regulation of the same. The production of inflammatory mediators is also curtailed by its activity (Booth 2001). However, Bouma et al (Bouma and Mosnier 2006), in her study strongly emphasizes on the role of TAFI in inflammation and wound healing (Ferdioz and Brundha 2016). Its relation to exfoliative disorders of the mucosa are also not ascertained (Brundha 2015, Hannah et al. 2019).

4. REGULATION OF TAFI

A requisite for the regulation of TAFI is bound thrombomodulin. Plasminogen activators are also involved in the roles of TAFI which act as clot stabilizers (Zirlik 2004). However, two factors that determine and quantify the extent of TAFI's action at the site of injury include,

the strength of the stimuli/injurious agent nature and the location of the thrombus (D'Aprile et al. 2001). Studies indicate, based on an in-vitro observation, no relevant activity of TAFI in photochemically or radiation induced thrombotic injury (Brundha, Padma Shri, and Sundari 2019) even though certain instances show its levels in case of radiotherapy to be on the higher side (Saibeni et al. 2003). At the same time, other studies indicate the same levels of activity irrespective of the nature of the thrombotic injury; however, this is only based on the threshold of inflammation as a crucial factor (Mousa et al. 2004). Since the enzyme is unstable, TAFI has an extremely short half life of 10 minutes in the standard body temperature of 37℃. Yet, studies progressing towards developing genetic polymorphism in TAFI can synthesize more stable forms of the same. Moreover, it has also been recorded that subjects may become susceptible to thrombosis due to persistent attenuation of fibrinolysis by TAFI's synthetic variants. Attributed to its recent finding as hemostatic blood elements and its observed difficulty in estimation, clotting disorders which may involve the activity of TAFI, is often deemed idiopathic, while the importance of its investigation is not well imbibed.

5. ACTIONS OF TAFI

TAFI is known to exert an antifibrinolytic effect majorly. This is mediated by various mechanisms. As a carboxypeptidase, it is capable of cleaving basic amino acids including arginine and lysine from carboxyl terminals of proteins (Miljic et al. 2010). The tissue plasminogen activator (tPA) which is released on fibrin formation catalyses the activation of plasminogen to plasmin, potentiating the latter by 500 times (Schroeder, Kucher, and Kohler 2003). It is through the lysine and arginine residues that plasmin advances its fibrinolytic activity, in the process of which, it exposes new carboxy-terminal lysine residues thus providing additional binding sites for plasminogen. Thus, a positive feedback mechanism is involved in the activation of plasmin that ends within fibrin clot lysis(Kokame 1998).

TAFIa, however, interferes (Abshire 2012) with the positive feedback mechanism of plasmin activation by removing the lysine and arginine residues, completely eliminating the mechanism of plasminogen activation and slowing down fibrinolysis, thus stabilizing the fibrin clot so formed. Thus, antiplasmin TAFI (Bajzar, Manuel, and Nesheim 1995) exerts the antifibrinolytic effect. It can also be said that the functions of tPA itself, as a cofactor in plasminogen activation are revoked by the elimination of the lysine and arginine residues.

Another significant factor includes the regulatory clot dissolution aspect of TAFI, which is mediated by a threshold dependent mechanism (Ieko et al. 2010). From the time that TAFIa levels begin to decline below its threshold level, plasminogen binding sites on the peptides become available and the final C-terminal lysines and arginines are upregulated by the enhanced plasmin mediated feedback. On the other hand (Chatteriee et al. 2002), an increased TAFI level immediately halts the entire plasminogen associated fibrinolytic cascade. Moreover, this threshold dependent regulatory function of TAFI is well associated with the thrombin generation rate, in cases where thrombomodulin is not involved.

Therefore, theoretically (Kucher 2003) it can be established that a constantly high TAFIa level is a facilitatory factor in the chronic activation of the coagulation system and hypercoagulability. When this is not established, conditions pertaining to excessive bleeding including genetic bleeding disorders like haemophilia, are resulted (Wyseure et al. 2018). Thus, low TAFI concentrations and insufficient thrombin production is observed to cause

enhanced fibrinolysis, early lysis of fibrin clots and haemorrhage associated bleeding diathesis.

6. INVESTIGATING THE ROLES OF TAFI

As is previously described, reduced TAFI levels are common findings in haemophilic patients. On the contrary, hereditary thrombophilia, characterised by a chronic increase in thrombin levels (Sowbaraniya, Preejitha, and Brundha 2020) indicates the extent of the clot protection effect mediated by TAFI. A previous study (van Tilburg, Rosendaal, and Bertina 2000) on a group of Caucasians indicates high TAFI and low factor V (Leiden factor) levels, in cases of hereditary thrombophilia. This not only is caused due to increased fibrin deposition but also due to the overactive TAFI/TAFIa system. Other studies (De Bruijne et al. 2009) also indicate high TAFI levels in arterial thrombosis. Drugs that inhibit fibrinolysis i.e. antifibrinolyticdrugs, prevent the action of plasminogen to plasmin conversion. This has been found to occur by the activation of TAFI only. This finding is thus useful for preventing the degradation of fibrin clots in areas of high fibrinolytic activity which encompass the oral, nasal cavities and female genital tracts. E-aminocaproic acid and tranexamic acids are some common antifibrinolytic drugs.

There are other studies where the relation between TAFI concentration and thrombotic tendency have been inconclusive (Antovic et al. 2001). As reported by a retrospective study, inferred from TAFIa assays, TAFI plasma levels are increased in individuals with myocardial infarction and stable angina pectoris (Božič-Mijovski 2015). Further investigations are also required to confirm the magnitude of recent attacks of myocardial infarction, when it has occured just a short time ago. The relation between TAFI and arterial thrombosis thus requires more clarity.

7. DISCUSSION

TAFI, is thus described to downregulate fibrinolysis and inhibit direct clot lysis by a positive feedback associated plasminogen proteolysis activity. Epidemiological studies including one by Foley J. H. et al (Foley et al. 2013) indicate elevated levels of TAFI with evidence for establishing various thrombosis-causing intrinsic factors. Another study demonstrated a two-fold increase in half life by assessing just naturally occurring polymorphisms (Brouwers et al. 2001). Mutagenesis studies aimed at recreating these polymorphs synthetically may open horizons towards developing more stable forms of TAFI (Boffa et al. 1998).

Findings by Anand et al (Anand et al. 2008), and Marx et al (Marx et al. 2009), considered as breakthroughs in the understanding of TAFI include, respectively, elaborate and elucidate the crystal structures of human TAFI and bovine TAFI, and also describe the separation of TAFIa from the activation peptide, which was observed to cause no consequent effect on TAFI's activity or stability. Another study which identified a mutant, lacking the activation peptide, supports former studies on the persistent stability of the molecule without the need of the activation peptide. Ceresa et al (Ceresa et al. 2006) , developed ELISAs which allowed measuring the extent of TAFI activity, as mentioned in their study. An attestation that TAFI can be used as a biomarker for pulmonary thrombosis and hypertension, is described by Satoh et al (Satoh et al. 2017). Studying its role as a biomarker, in disorders like anemia and hormonal disorders are also in process, however, with a low level of existing awareness and much room for development (Chandrasekhar and Brundha 2016), where its relation to the

given medical conditions need further retrospection. A study (Wyseure et al. 2015) conducted on rodents with the administration of a specific inhibitor against TAFI observed a substantial profibrinolytic effect without affecting bleeding rates. TAFI is also stipulated as a regulatory promoter of stem cell regeneration (Edupuganti et al. 2017) which might enable further conclusions towards regenerative medicine (Timothy, Samyuktha, and Brundha 2019). TAFI has no probable relation with conditions like nocturia, vesicaltenesmus(Kumar and Brundha 2016) and psychological disorders (Harsha and Brundha 2017). Diabetes mellitus is a condition in which a marked decrease in TAFIa activity is observed(Małyszko et al. 2004), where again, the awareness regarding this and its associated hematologic complications are not often correlated (Preethikaa and Brundha 2018).

One aspect that is commonly noticed among several related studies is the confirmation of the tests on TAFI, limited by conditions of confinement to in-vitro conditions. Biotesting on human subjects has not yet been made possible. Besides, inconsistent results pertaining to TAFI levels and thromboembolic complications make it all the more harder to proceed with biotesting extensively. Infact, in cases of radiotherapy where patients are in a procoagulant state (Pathmashri, Brundha, and Ganapathy 2019, Balaji, Brundha, and Path 2016), TAFIa levels are observed to be on the higher side. Therefore, it is necessary that future studies progress towards developing safer and effective Recombinant DNA TAFI for therapeutic uses and implement the same while controlling it for conditions like DIC and thrombosis. However, with the evolving understanding of TAFI and its implications, efforts to incorporate it into the study curriculum leaving room for developments are undertaken (Brundha and Nallaswamy 2019, Prashanthi and Brundha 2018).

8. CONCLUSION

The study has thus reviewed the role, mechanism and regulation of TAFI in fibrinolysis and has compared the current various efforts involved in developing the existing understanding of the roles of TAFI as well as the implementation of knowledge pertaining to it, in pathological conditions marked by a malfunctioning coagulation cascade.

AUTHOR CONTRIBUTIONS

SaishreeAnchanaRajeswaran contributed to data acquisition and drafting of the manuscript. Dr. MP Brundha contributed to the design, editing and critical review of the manuscript. Dr. SmilineGirija AS contributed to the supervision and proofreading of the manuscript.

CONFLICT OF INTEREST

The authors declare none.

9. REFERENCES

[1] Abshire, T. (2012) ‘TAFI Made Stickier’. in Blood [online] vol. 119 (15). 3380–3381. available from <http://dx.doi.org/10.1182/blood-2012-02-406652>

[2] Anand, K., Pallares, I., Valnickova, Z., Christensen, T., Vendrell, J., Wendt, K.U., Schreuder, H.A., Enghild, J.J., and Avilés, F.X. (2008) ‘The Crystal Structure of Thrombin-Activable Fibrinolysis Inhibitor (TAFI) Provides the Structural Basis for Its Intrinsic Activity and the Short Half-Life of TAFIa’. The Journal of Biological Chemistry 283 (43), 29416–29423

[3] Antovic, J., Schulman, S., Eelde, A., and Blomback, M. (2001) ‘Total Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) Antigen and pro-TAFI in Patients with

Haemophilia A'. in Haemophilia [online] vol. 7 (6). 557–560. available from <http://dx.doi.org/10.1046/j.1365-2516.2001.00571.x>

[4] Bajzar, L., Manuel, R., and Nesheim, M.E. (1995) 'Purification and Characterization of TAFI, a Thrombin-Activable Fibrinolysis Inhibitor'. The Journal of Biological Chemistry 270 (24), 14477–14484

[5] Balaji, S., Brundha, M.P., and Path, D.N.B. (2016) 'Awareness of About Breast Cancer among Dental Surgeons'. Research Journal of Pharmaceutical, Biological and Chemical Sciences 8 (8), 797

[6] Boffa, M.B., Wang, W., Bajzar, L., and Nesheim, M.E. (1998) 'Plasma and Recombinant Thrombin-Activable Fibrinolysis Inhibitor (TAFI) and Activated TAFI Compared with Respect to Glycosylation, Thrombin/thrombomodulin …'. The Journal of Biological Chemistry [online] available from <http://www.jbc.org/content/273/4/2127.short>

[7] Booth, N. (2001) 'TAFI Meets the Sticky Ends'. in Thrombosis and Haemostasis [online] vol. 85 (01). 1–2. available from <http://dx.doi.org/10.1055/s-0037-1612653>

[8] Bouma, B.N. and Mosnier, L.O. (2006) 'Thrombin Activatable Fibrinolysis Inhibitor (TAFI)—How Does Thrombin Regulate Fibrinolysis?' in Annals of Medicine [online] vol. 38 (6). 378–388. available from <http://dx.doi.org/10.1080/07853890600852898>

[9] Bouma, B.N. and Mosnier, L.O. (2003) 'Thrombin Activatable Fibrinolysis Inhibitor (TAFI) at the Interface between Coagulation and Fibrinolysis'. in Pathophysiology of Haemostasis and Thrombosis [online] vol. 33 (5-6). 375–381. available from <http://dx.doi.org/10.1159/000083832>

[10] Božič-Mijovski, M. (2015) Thrombosis, Atherosclerosis and Atherothrombosis: New Insights and Experimental Protocols. BoD – Books on Demand

[11] Brouwers, G.-J., Vos, H.L., Leebeek, F.W.G., Bulk, S., Schneider, M., Boffa, M., Koschinsky, M., van Tilburg, N.H., Nesheim, M.E., Bertina, R.M., and Gómez García, E.B. (2001) 'A Novel, Possibly Functional, Single Nucleotide Polymorphism in the Coding Region of the Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) Gene Is Also Associated with TAFI Levels'. in Blood [online] vol. 98 (6). 1992–1993. available from <http://dx.doi.org/10.1182/blood.v98.6.1992>

[12] Brundha, M.P. (2015) 'A Comparative Study-The Role of Skin and Nerve Biopsy in Hansen's Disease'. Research Journal of Pharmaceutical, Biological and Chemical Sciences 7 (10), 837

[13] Brundha, M.P. and Nallaswamy, D. (2019) 'Hide and Seek in Pathology- A Research on Game-Based Histopathology Learning'. International Journal of Research in Pharmaceutical Sciences 10 (2), 1410–1414

[14] Brundha, M.P., Pathmashri, V.P., and Sundari, S. (2019) 'Quantitative Changes of Red Blood Cells in Cancer Patients under Palliative Radiotherapy-A Retrospective Study'. Research Journal of Pharmacy and Technology 12 (2), 687–692

[15] Ceresa, E., Brouwers, E., Peeters, M., Jern, C., Declerck, P.J., and Gils, A. (2006) 'Development of ELISAs Measuring the Extent of TAFI Activation'. Arteriosclerosis, Thrombosis, and Vascular Biology 26 (2), 423–428

[16] Chandrasekhar, H. and Brundha, M.P. (2016) 'Awareness of Polycystic Ovarian Disease among Females of Age Group 30-50 Years'. Research Journal of Pharmaceutical, Biological and Chemical Sciences 8 (8), 817

[17] Chatteriee, T., Schroeder, V., Fleisch, M., Windecker, S., Seiler, C., Ebarli, F.R., Meier, B., and Kohler, H.P. (2002) 'Thrombin Activatable Fibrinolysis Inhibitor (TAFI) Levels in Patients with Coronary Artery Disease Investigated by Anglography'. in Journal of the American College of Cardiology [online] vol. 39. 204. available from <http://dx.doi.org/10.1016/s0735-1097(02)80902-0>

[18] D'Aprile, A., Italia, A., Gresele, P., Morser, J., Semeraro, N., and Colucci, M. (2001)

'Thrombin Activatable Fibrinolysis Inhibitor (TAFI) Does Not Inhibit In Vitro Thrombolysis by Pharmacological Concentrations of T-PA'. in Thrombosis and Haemostasis [online] vol. 85 (04). 661–666. available from <http://dx.doi.org/10.1055/s-0037-1615650>

[19] De Bruijne, E.L.E., Gils, A., Guimaraes, A.H.C., Dippel, D.W.J., Deckers, J.W., Van Den Meiracker, A.H., Poldermans, D., Rijken, D.C., Declerck, P.J., De Maat, M.P.M., and Others (2009) 'The Role of Thrombin Activatable Fibrinolysis Inhibitor in Arterial Thrombosis at a Young Age: The ATTAC Study 1'. Journal of Thrombosis and Haemostasis: JTH 7 (6), 919–927

[20] Edupuganti, R.R., Harikumar, A., Aaronson, Y., Biran, A., Sailaja, B.S., Nissim-Rafinia, M., Azad, G.K., Cohen, M.A., Park, J.E., Shivalila, C.S., Markoulaki, S., Sze, S.K., Jaenisch, R., and Meshorer, E. (2017) 'Alternative SET/TAFI Promoters Regulate Embryonic Stem Cell Differentiation'. Stem Cell Reports 9 (4), 1291–1303

[21] Eichinger, S., Schönauer, V., Weltermann, A., Minar, E., Bialonczyk, C., Hirschl, M., Schneider, B., Quehenberger, P., and Kyrle, P.A. (2004) 'Thrombin-Activatable Fibrinolysis Inhibitor and the Risk for Recurrent Venous Thromboembolism'. Blood 103 (10), 3773–3776

[22] Ferdioz, J. and Brundha, M.P. (2016) 'Awareness of Stye'. International Journal of Pharmaceutical Sciences Review and Research 40 (1), 30–32

[23] Foley, J.H., Kim, P.Y., Mutch, N.J., and Gils, A. (2013) 'Insights into Thrombin Activatable Fibrinolysis Inhibitor Function and Regulation'. Journal of Thrombosis and Haemostasis: JTH 11 Suppl 1, 306–315

[24] Frère, C., Morange, P.E., Saut, N., Tregouet, D.A., Grosley, M., Beltran, J., Juhan-Vague, I., and Alessi, M.-C. (2005) 'Quantification of Thrombin Activatable Fibrinolysis Inhibitor (TAFI) Gene Polymorphism Effects on Plasma Levels of TAFI Measured with Assays Insensitive to Isoform-Dependent Artefact'. in Thrombosis and Haemostasis [online] available from <http://dx.doi.org/10.1160/th04-08-0497>

[25] Hannah, R., Ramani, P., Brundha, M.P., Sherlin, H.J., Ranjith, G., Ramasubramanian, A., Jayaraj, G., Don, K.R., and Archana, S. (2019) 'Liquid Paraffin as a Rehydrant for Air Dried Buccal Smear'. Research Journal of Pharmacy and Technology 12 (3), 1197–1200

[26] Harsha, L. and Brundha, M.P. (2017) 'Prevalence of Dental Developmental Anomalies among Men and Women and Its Psychological Effect in a given Population'. Research Journal of Pharmaceutical, Biological and Chemical Sciences 9 (6), 869

[27] Ieko, M., Yoshida, M., Naito, S., Nakabayashi, T., Kanazawa, K., Mizukami, K., Mukai, M., Atsumi, T., and Koike, T. (2010) 'Increase in Plasma Thrombin-Activatable Fibrinolysis Inhibitor May Not Contribute to Thrombotic Tendency in Antiphospholipid Syndrome because of Inhibitory Potential of Antiphospholipid Antibodies toward TAFI Activation'. International Journal of Hematology 91 (5), 776–783

[28] Kalaiselvi, R. and Brundha, M.P. (2016) 'Prevalence of Hysterectomy in South Indian Population'. Research Journal of Pharmacy and Technology 9 (11), 1941–1944

[29] Kaviya, S.A. and Brundha, M.P. (2017) 'Analysis of Platelet Count in Patients with Bleeding Gums'. Journal of Clinical & Experimental Pathology 7 (325), 2161–0681

[30] Kokame, K. (1998) 'TAFI Activation and Thrombomodulin Structure'. in Japanese Journal of Thrombosis and Hemostasis [online] vol. 9 (6). 445–450. available from <http://dx.doi.org/10.2491/jjsth.9.445>

[31] Kucher, N. (2003) 'Novel Management Strategy for Patients with Suspected Pulmonary Embolism'. in European Heart Journal [online] vol. 24 (4). 366–376. available from <http://dx.doi.org/10.1016/s0195-668x(02)00476-1>

[32] Kumar, M.D. and Brundha, M.P. (2016) 'Awareness about Nocturia-A Questionnaire Survey'. Research Journal of Pharmacy and Technology 9 (10), 1707–1709

[33] Leung, L.L.K., Nishimura, T., and Myles, T. (2008) 'Regulation of Tissue Inflammation by Thrombin-Activatable Carboxypeptidase B (or TAFI)'. in Advances in Experimental Medicine and Biology [online] 59–67. available from <http://dx.doi.org/10.1007/978-0-387-78952-1_5>
[34] Lin, J.H.H., Novakovic, D., Rizzo, C.M., Zagorac, B., Garand, M., Filipieva, A., Koschinsky, M.L., and Boffa, M.B. (2013) 'The mRNA Encoding TAFI Is Alternatively Spliced in Different Cell Types and Produces Intracellular Forms of the Protein Lacking TAFIa Activity'. in Thrombosis and Haemostasis [online] vol. 109 (06). 1033–1044. available from <http://dx.doi.org/10.1160/th12-09-0668>
[35] Małyszko, J., Małyszko, J.S., Hryszko, T., and Myśliwiec, M. (2004) 'Thrombin Activatable Fibrinolysis Inhibitor (TAFI) and Markers of Endothelial Cell Injury in Dialyzed Patients with Diabetic Nephropathy'. Thrombosis and Haemostasis 91 (3), 480–486
[36] Marx, P.F., Verkleij, C.J.N., VallsSeron, M., and Meijers, J.C.M. (2009) 'Recent Developments in Thrombin-Activatable Fibrinolysis Inhibitor Research'. Mini Reviews in Medicinal Chemistry 9 (10), 1165–1173
[37] Miljic, P., Heylen, E., Willemse, J., Djordjevic, V., Radojkovic, D., Colovic, M., Elezovic, I., and Hendriks, D. (2010) 'Thrombin Activatable Fibrinolysis Inhibitor (TAFI): A Molecular Link between Coagulation and Fibrinolysis'. in Srpski Arhiv Za Celokupno Lekarstvo [online] vol. 138 (suppl. 1). 74–78. available from <http://dx.doi.org/10.2298/sarh10s1074m>
[38] Monasterio, J., Bermüdez, P., Quiroga, D., Francisco, E., Meneses, B., and Montaner, J. (2003) 'Plasma Thrombin-Activatable Fibrinolytic Inhibitor (TAFI) among Healthy Subjects and Patients with Vascular Diseases: A Validation Study'. in Pathophysiology of Haemostasis and Thrombosis [online] vol. 33 (5-6). 382–386. available from <http://dx.doi.org/10.1159/000083833>
[39] Mousa, H., Downey, C., Alfirevic, Z., and Toh, C.-H. (2004) 'Thrombin Activatable Fibrinolysis Inhibitor and Its Fibrinolytic Effect in Normal Pregnancy'. in Thrombosis and Haemostasis [online] vol. 92 (11). 1025–1031. available from <http://dx.doi.org/10.1160/th04-06-0387>
[40] Pathmashri, V.P., Brundha, M.P., and Ganapathy, D. (2019) 'Red Blood Cell Count Changes in Cancer Patients under Radiation Therapy--A Prospective Study'. Drug Invention Today [online] 11 (9). available from <http://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=09757619&AN=139165856&h=xGTj7cS78%2F85kbzEDqIdYdfY1CK40p9oyUQX%2FZ0%2FMbij9A6zY7RetCkKiNbuZC31yzz6aRrg4WTn3ECqphpzYQ%3D%3D&crl=c>
[41] Prashaanthi, N. and Brundha, M.P. (2018) 'A Comparative Study between Popplet Notes and Conventional Notes for Learning Pathology'. Research Journal of Pharmacy and Technology 11 (1), 175–178
[42] Preethikaa, S. and Brundha, M.P. (2018) 'Awareness of Diabetes Mellitus among General Population'. Research Journal of Pharmacy and Technology 11 (5), 1825–1829
[43] Ravichandran, H. and Brundha, M.P. (2016) 'Awareness about Personal Protective Equipments in Hospital Workers (sweepers and Cleaners)'. International Journal of Pharmaceutical Sciences Review and Research 40 (1), 28–29
[44] Saibeni, S., Vecchi, M., Bottasso, B., Spina, L., Bajetta, M., and De Franchis, R. (2003) 'Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) Plasma Levels Are Increased in Inflammatory Bowel Diseases and Correlate with Acute Phase Reactants'. in Gastroenterology [online] vol. 124 (4). A211. available from <http://dx.doi.org/10.1016/s0016-5085(03)81060-0>
[45] Satoh, T., Satoh, K., Yaoita, N., Kikuchi, N., Omura, J., Kurosawa, R., Numano, K., Al-

Mamun, E., Siddique, M.A.H., Sunamura, S., Nogi, M., Suzuki, K., Miyata, S., Morser, J., and Shimokawa, H. (2017) 'Activated TAFI Promotes the Development of Chronic Thromboembolic Pulmonary Hypertension: A Possible Novel Therapeutic Target'. Circulation Research 120 (8), 1246–1262

[46] Schroeder, V., Kucher, N., and Kohler, H.P. (2003) 'Role of Thrombin Activatable Fibrinolysis Inhibitor (TAFI) in Patients with Acute Pulmonary Embolism'. in Journal of Thrombosis and Haemostasis [online] vol. 1 (3). 492–493. available from <http://dx.doi.org/10.1046/j.1538-7836.2003.00112.x>

[47] Semeraro, F., Ammollo, C.T., Semeraro, N., and Colucci, M. (2009) 'Tissue Factor-Expressing Monocytes Inhibit Fibrinolysis through a TAFI-Mediated Mechanism, and Make Clots Resistant to Heparins'. in Haematologica [online] vol. 94 (6). 819–826. available from <http://dx.doi.org/10.3324/haematol.2008.000042>

[48] Shreya, S. and Brundha, M.P. (2017) 'Alteration of Haemoglobin Value in Relation to Age, Sex and Dental Diseases-A Retrospective Correlation Study'. Research Journal of Pharmacy and Technology 10 (5), 1363–1366

[49] Sowbaraniya, S.M., Preejitha, V.B., and Brundha, M.P. (2020) 'Knowledge, Awareness, and Attitude on Dental Post-Operative Complications in Diabetes among General Population'. Drug Invention Today [online] 13 (2). available from <http://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=09757619&AN=142963132&h=hZhkxsbCkjijfyjX0l9%2FCMrT%2BBIENoXxBKcNeFlHXA5GZ2VICI41AOpDhyabS4WF0YGNWrxJ2Jxd2agjcHLYKw%3D%3D&crl=c>

[50] van Tilburg, N.H., Rosendaal, F.R., and Bertina, R.M. (2000) 'Thrombin Activatable Fibrinolysis Inhibitor and the Risk for Deep Vein Thrombosis'. Blood 95 (9), 2855–2859

[51] Timothy, C.N., Samyuktha, P.S., and Brundha, M.P. (2019) 'Dental Pulp Stem Cells in Regenerative Medicine – A Literature Review'. in Research Journal of Pharmacy and Technology [online] vol. 12 (8). 4052. available from <http://dx.doi.org/10.5958/0974-360x.2019.00698.x>

[52] Wyseure, T., Cooke, E.J., Declerck, P.J., Behrendt, N., Meijers, J.C.M., von Drygalski, A., and Mosnier, L.O. (2018) 'Defective TAFI Activation in Hemophilia A Mice Is a Major Contributor to Joint Bleeding'. Blood 132 (15), 1593–1603

[53] Wyseure, T., Rubio, M., Denorme, F., Martinez de Lizarrondo, S., Peeters, M., Gils, A., De Meyer, S.F., Vivien, D., and Declerck, P.J. (2015) 'Innovative Thrombolytic Strategy Using a Heterodimer Diabody against TAFI and PAI-1 in Mouse Models of Thrombosis and Stroke'. Blood 125 (8), 1325–1332

[54] Zhao, H., Xiao, W., Hu, C., Gao, X., Zhu, Y., and Yang, X. (2016) 'Impacts of Laparoscopic Hysterectomy on Functions of Coagulation and Fibrinolysis System'. Blood Coagulation & Fibrinolysis: An International Journal in Haemostasis and Thrombosis 27 (4), 365–369

[55] Zirlik, A. (2004) 'TAFI: A Promising Drug Target?' in Thrombosis and Haemostasis [online] vol. 91 (03). 420–422. available from <http://dx.doi.org/10.1055/s-0037-1614285>