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TISSUE FACTOR IN CARDIOVASCULAR DISEASES: AN OVERVIEW

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ABSTRACT

One of the major genetic factors that is associated with cardiovascular diseases (CVDs) is tissue factor (TF). Studies have investigated this association and identified possible correlation with CVDs and risk factors. Increased expression level of TF has been observed in individuals with high blood glucose level, which could be reduced by controlling glucose level. Furthermore, high cholesterol level has been associated with high TF levels. In addition, high level of TF is reported in obese individuals and those who lack physical activity, and improving these factors lowers TF levels. Therefore, TF has been used as a therapeutic target for reducing the risk of CVDs but with limited success so far. Thus, this study aims to explore the current advances regarding the association of TF with the risk of developing CVDs.

Keywords: Cardiovascular disease, genetics, gene, diabetes, hypercholesterolemia, tissue factor, coagulation cascade.

ABBREVIATIONS:
CVDs: cardiovascular diseases; F3: factor (coagulation) III; FVII: factor VII; FVIIa: factor VIIa; FX: factor X; Kb: kilobytes; kDa: kilodalton; LDL: low-density lipoprotein; LDLR: low-density lipoprotein (LDL) receptor; PI3-kinase: phosphoinositide 3-kinase; rTFPI: recombinant tissue factor pathway inhibitor; TF: tissue factor; TNF-α: tumour necrosis factor-α

INTRODUCTION

Cardiovascular diseases (CVDs) are a group of diseases that affect the heart and blood vessels. It includes a range of diseases from coronary artery disease such as myocardial infarction to heart failure, stroke, cardiomyopathy and many more. The number of deaths due to CVDs increases every year in the developing countries while they decrease in the developed countries due to the improved health care personally or nationally (Moran *et al.,* 2014).

Several risk factors have been associated with the development of CVDs including gender, age, physical inactivity, tobacco and alcohol use, obesity, raised blood pressure, raised blood sugar, raised blood cholesterol as well as family history and genetic factors. Although several risk factors are uncontrollable such as age, gender and (so far) genetic factors, other factors are controllable, even to an extent. Thus, it is believed that most CVDs are preventable (McGill *et al.,* 2008). Prevention can be simply achieved by healthy eating, exercising, and avoiding tobacco smoking and alcohol drinking. In addition to that, controlling risk factors such as blood pressure, sugar and lipids could significantly reduce the risk of developing CVDs (McGill *et al.,* 2008).

CVDs are multifactorial disorders and thus several genetic factors are expected to be associated with increased risk. Identification of genetic factors has been the focus of many researches in the past few decades in order to correlate phenotype with genotype (Kathiresan and Srivastava, 2012). Different genetic factors have been identified to be associated with different CVDs with low-density lipoprotein (LDL) receptor (LDLR) being the first genetic factor to be identified in 1985 (Lehrman *et al.,* 1985). Although this gene isn't directly correlated with CVDs, it is mainly associated with blood cholesterol level, which is one of the major risk factors for developing CVDs. Following that, several studies have identified a wide range of genetic variation associated with different CVDs and other diseases that are themselves associated with increased risk of CVDs (Kathiresan and Srivastava, 2012). Several genome wide association studies have been conducted on to identify genetic factors, all together reported significant association of over 5000 variants in several genes across the genome suggesting the importance of genetic factors on the risk of developing various CVDs (Altshuler *et al*., 2008; O'Donnell and Nabel, 2011).

TISSUE FACTOR GENE

The tissue factor gene (*CD142*), also referred to as coagulation factor III (*F3*) gene is located on chromosome 1 at the position p21-22 spanning 12.4k kb and encoding a 47-kDa protein that is expressed in vascular and nonvascular cells (Mackman *et al.,* 1989). The gene consists of 6 exons with one main transcript and one alternative splice variant have been reported so far. TF protein is known to have 3 domains, extracellular domain (consist of

219 amino acids), membrane spanning domain (consist of 23 amino acids) and cytoplasmic domain (consist of 21 amino acids) (Breitenstein *et al*., 2010). The extracellular domain has high affinity for factor VII or FVII binding which is important for the activation of FVII (Steffel *et al.,* 2006).

Tissue factor (TF), previously known as thromboplastin, is constitutively expressed in the vessel wall, and once the wall is damaged, TF rapidly initiates coagulation cascade (Steffel *et al.,* 2006).

It has been reported to be associated with the pathogenesis of CVDs and has been under investigation as a target for various therapeutic approaches. Yet, neither its exact mechanism nor its possible use as a therapeutic approach is clearly defined.

TISSUE FACTOR FUNCTION

Coagulation cascade is a complex system that aims to maintain blood fluidity and limit its loss in case of injury. There are two independent pathways that trigger the coagulation cascade which are the intrinsic and extrinsic (TF) pathways (Gailani and Renne, 2007). The extrinsic pathway is initiated once TF comes into contact with the circulating active form of FVII which leads to the formation of TF-FVIIa complex. In addition, it could bind to the inactive form of FVII leading directly to its activation. TF-FVIIa complex in turn binds to factor X (FX) and activates FX or it could directly bind to and activate FX (Gailani and Renne, 2007).

In addition to its key role in coagulation, TF has also been suggested to be involved in various cellular processes including vascular smooth muscle cells migration and proliferation. In addition to that, TF is a key factor in embryonic blood vessels development (Pedersen *et al.,* 2005). Furthermore, TF has also been reported to enhance tumour metastasis and neovascularization (Ngo *et al.,* 2007).

Additionally, there is a link between haemostasis and vascular alteration such as atherosclerosis. This in turn suggests an association between the coagulation cascade with the vascular pathophysiology. This association has been suggested to be due to the role of TF in mediating intercellular signalling (Bazan, 1990). It has been reported that binding of TF to activated form of FVII induces calcium transient intracellularly in addition to the activation of major mitogen activated protein kinase family members as well as Src-like kinases and phosphoinositide 3-kinase (PI3-kinase) which in turn results in cytoskeletal reorganization (Rottingen *et al.,* 1995; Camerer *et al.,* 1996; Versteeg *et al*., 2000). This in turn shows the involvement of TF in regulating the transcription of several genes involved in various cellular processes such as cellular growth, migration and apoptosis (Pendurthi *et al*., 1997; Camerer *et al.,* 1999).

In endothelial cells, TF expression level is very minimal during normal haemostatic conditions. Its expression is enhanced by some cytokines such as interleukin-1β and tumour necrosis factor-α (TNF-α) (Napoleone *et al.,* 1997; Holy *et al*., 2009). On the other hand, vascular smooth muscle cells highly express TF providing enough TF to initiate coagulation cascade as previously mentioned. TF has been reported to be expressed at low levels in the plasma and urine which is increased in response to inflammations such as in the case of atherosclerosis, diabetes or disseminated intravascular coagulation (Cermak *et al.,* 1993; Guha and Mackman, 2002; Luyendyk *et al.,* 2008). This is expected as monocytes are known to store large amounts of TF which can be released after exposure to inflammatory mediators (Cai *et al.,* 2007). In addition, other types of white blood cells have also been reported to express TF including eosinophils, granulocytes, and neutrophils. TF has also been suggested to be driven from platelets, however, the exact mechanism is not clearly understood (Muller *et al.,* 2003; Maugeri *et al.,* 2006; Moosbauer *et al.,* 2007).

It is clearly noticeable that there are various pools of TF present in the human body, each of which has its own uses, of which several are still not clearly understood. Storage of TF in vascular smooth muscle cells is important to reduce blood loss in case of vascular injury. Additionally, vascular injury leads to the release of inflammatory mediators which in turn leads to further release of TF from monocytes to further enhance the initiation of coagulation cascade. It is suggested that a constantly active TF is required to maintain the coagulation process, thus, fibrin clot is formed to prevent further activation of inactive coagulation factors once the blood loss is controlled (Hathcock and Nemerson, 2004).

TISSUE FACTOR PATHOLOGY

It is known that thrombosis is not always formed as a result of vascular damage, which in turn can lead to serious cardiovascular complications. TF is thought to play an essential role in this pathology. Previous studies have shown that in an uninjured vessel, inhibition of TF expression reduced thrombus growth (Himber *et al.,* 2003). However, another study did not shown association between TF expression level and thrombus formation in mice (Day *et al*., 2005). This in turn suggests that further study is required to investigate further the association between TF expression and thrombus formation.

On the other hand, inflammation and atherosclerosis are suggested to be closely linked (Hansson, 2005). It is reported that some cytokines such as TNF- α are observed in early stages of atherosclerosis lesion. The same cytokines are known to release TF (Wilcox *et al.,* 1989). It has also been reported that TF level is elevated in atherosclerosis plaques, suggesting that there might be association between them (Annex *et al.,* 1995).

The possible association between TF and the risk of developing CVDs do not stop there, various studies have shown association between increased levels of TF with various diseases and risk factors part of or associated with CVDs. A previous study showed elevated levels of TF in coronary artery specimens which is in line with another study that showed elevated level of TF in plasma in cases with acute coronary syndromes which also has been associated with poor prognosis (Ardissino *et al*., 1997; Misumi *et al.,* 1998). Additionally, individuals with myocardial infarction have also shown increased TF levels (Ardissino *et al.,* 1997).

Several studies have observed increased TF levels and activity in patients with diabetes mellitus, which is one of the major risk factors for CVDs (Lim *et al.,* 2004; El-Ghoroury *et al.,* 2008). This is in line with these observations, regulating blood glucose levels resulted in reduction in TF levels in patients with diabetes mellitus (Golledge *et al.,* 2007). Additionally, increased blood glucose levels in normal individuals have been linked with increased TF levels in monocytes and endothelial cells (Stegenga *et al.,* 2006; Vaidyula *et al.,* 2006).

In addition to that, patients with hyperlipidaemia have shown higher risk for thrombosis (Durrington, 2003). High level of low-density lipoprotein is observed in patients with hyperlipidaemia. Previous studies have observed an increase of TF with increased level of low-density lipoprotein (LDL) as oxidizes LDL is suggested to TF synthesis by monocytes suggesting that hyperlipidemia, which is another major risk factor for CVDs, could be directly associated with increased TF levels (Wada *et al*., 1994; Penn *et al.,* 1999; Sambola *et al.,* 2003). Furthermore, Patients with hypertension have also demonstrated increased TF levels which are lowered by managing blood pressure using antihypertensive medication (Koh *et al.,* 2004).

CONCLUSION

Given all of these reports and all possible associations between TF and the risk of developing CVDs, it was then an area of interest to explore the therapeutic implication of controlling TF expression and activity levels. Various methods have been investigated ranging from the use of anti-TF antibodies, Recombinant tissue factor pathway inhibitor (rTFPI) in addition to other various methods. However, none have shown a high level of success (Stephens and Rivers, 1997; Erlich *et al.,* 2000; Cavusoglu *et al.,* 2002; Pedersen *et al.,* 2005).

Even though TF has been studied extensively, weak understanding of various mechanisms involved in the interaction between TF and other factors associated with the risk of developing CVDs. In addition, to our current knowledge, no similar study has been conducted on TF on the Saudi population. Therefore, there is still much to be explored in this area.

REFERENCES

Altshuler, D., M.J. Daly and E.S. Lander (2008). Genetic mapping in human disease. *Science,* 322(5903): 881–888.

Annex, B. H., S.M. Denning, K.M. Channon, M. H. JR. Sketch, R.S. Stack, J.H. Morrissey and K.G. Peters. (1995). Differential expression of tissue factor protein in directional atherectomy specimens from patients with stable and unstable coronary syndromes. *Circulation,* 91(3): 619–622.

Ardissino, D., P.A. Merlini, R. Ariens, R. Coppola, E. Bramucci and P.M. Mannucci (1997). Tissue-factor antigen and activity in human coronary atherosclerotic plaques. *Lancet,* 349 (9054):769–771.

Bazan, J. F. (1990). Structural design and molecular evolution of a cytokine receptor superfamily. *Proc Natl Acad Sci U S A,* 87 (18): 6934–6938.

Breitenstein, A., F.C. Tanner, and T.F. Luscher (2010). Tissue factor and cardiovascular disease: quo Vadis? *Circ J,* 74(1): 3–12.

Cai, H., C. Song, I. Endoh, J. Goyette, W. Jessup, S.B. Freedman, H.P. Mcneil, and C. L. Geczy (2007). Serum amyloid A induces monocyte tissue factor. *J Immunol,* 178 (3): 1852–1860.

Camerer, E., J.A. Rottingen, E. Gjernes, K. Larsen, A.H. Skartlien, J.D. Iversen, and H. Prydz (1999). Coagulation factors VIIa and Xa induce cell signaling leading to up-regulation of the egr-1 gene. *J Biol Chem,* 274 (45): 32225–32233.

Camerer, E., J.A. Rottingen, J.G. Iversen, and H. Prydz (1996). Coagulation factors VII and X induce Ca2+ oscillations in Madin-Darby canine kidney cells only when proteolytically active. *J Biol Chem,* 271(46): 29034–29042.

Cavusoglu, E., I. Chen, J. Rappaport and J.D. Marmur (2002). Inhibition of tissue factor gene induction and activity using a hairpin ribozyme. *Circulation*, 105(19): 2282–2287.

Cermak, J., N.S. Key, R.R. Bach, J. Balla, H.S. Jacob and G.M. Vercellotti (1993). C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood,* 82(2): 513–520.

Day, S. M., J.L. Reeve, B. Pedersen, D.M. Farris, D.D. Myers, M. Im, T.W. Wakefield, N. Mackman and W.P. Fay (2005). Macrovascular thrombosis is driven by tissue factor derived primarily from the blood vessel wall. *Blood*, 105(1): 192–198.

Durrington, P. (2003). Dyslipidaemia. *Lancet,* 362(9385): 717–731.

El-Ghoroury, E. A., H.G. El-din, M. Abdel-Kader and S. Ragab (2008). Study of factor VII, tissue factor pathway inhibitor and monocyte tissue factor in noninsulin-dependent diabetes mellitus. *Blood Coagul. Fibrinolysis*, 19(1): 7–13.

Erlich, J. H., E.M. Boyle, J. Labriola, J.C. Kovacich, R. A. Santucci, C. Fearns, E.N. Morgan, W. Yun, T. Luther, O. Kojikawa, T.R. Martin, T.H. Pohlman, E.D. Verrier and N. Mackman (2000). Inhibition of the tissue factor-thrombin pathway limits infarct size after myocardial ischemia-reperfusion injury by reducing inflammation. *Am J Pathol*, 157(6): 1849–1862.

Gailani, D. and T. Renne (2007). Intrinsic pathway of coagulation and arterial thrombosis.
Arterioscler Thromb Vasc Biol, 27(12): 2507–2513.

Golledge, J., S. Mangan and P. Clancy (2007). Effects of peroxisome proliferator-activated receptor ligands in modulating tissue factor and tissue factor pathway inhibitor in acutely symptomatic carotid atheromas. *Stroke*, 38(5): 1501–1508.

Guha, M. and N. Mackman (2002). The phosphatidylinositol 3-kinase-Akt pathway limits lipopolysaccharide activation of signaling pathways and expression of inflammatory mediators in human monocytic cells. *J Biol Chem,* 277(35): 32124–32132.

Hansson, G. K. (2005). Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med,* 352(16): 1685–1695.

Hathcock, J. J. and Y. Nemerson. (2004). Platelet deposition inhibits tissue factor activity: in vitro clots are impermeable to factor Xa. *Blood,* 104(1): 123–127.

Himber, J., C. Wohlgensinger, S. Roux, L.A. Damico, J.T. Fallon, D. Kirchhofer, Y. Nemerson and M.A. Riederer (2003). Inhibition of tissue factor limits the growth of venous thrombus in the rabbit. *J Thromb Haemost,* 1(5): 889–895.

Holy, E. W., A. Akhmedov, T.F. Luscher and F.C. Tanner (2009). Berberine, a natural lipidlowering drug, exerts prothrombotic effects on vascular cells. *J Mol Cell Cardiol,* 46(2): 234– 240.

Kathiresan, S. and D. Srivastava (2012). Genetics of human cardiovascular disease. *Cell,* 148(6):1242–1257.

Koh, K. K., W.J. Chung, J.Y. Ahn, S.H. Han, W.C. Kang, Y.H. Seo, T.H. Ahn, I.S. Choi and E.K. Shin (2004). Angiotensin II type 1 receptor blockers reduce tissue factor activity and plasminogen activator inhibitor type-1 antigen in hypertensive patients: a randomized, double-blind, placebo-controlled study. *Atherosclerosis,* 177(1): 155–160.

Lehrman, M. A., W.J. Schneider, T.C. Sudhof, M.S. Brown, J.L. Goldstein and D.W. Russell (1985). Mutation in LDL receptor: Alu-Alu recombination deletes exons encoding transmembrane and cytoplasmic domains. *Science*, 227(4683): 140–146.

Lim, H. S., A.D. Blann and G.Y. Lip (2004). Soluble CD40 ligand, soluble P-selectin, interleukin-6, and tissue factor in diabetes mellitus: relationships to cardiovascular disease and risk factor intervention. *Circulation,* 109(21): 2524–2528.

Luyendyk, J. P., G.A. Schabbauer, M. Tencati, T. Holscher, R. Pawlinski and N. Mackman (2008). Genetic analysis of the role of the PI3K-Akt pathway in lipopolysaccharide-induced cytokine and tissue factor gene expression in monocytes/macrophages. *J Immunol,* 180(6): 4218–4226.

Mackman, N., J. H. Morrissey, B. Fowler and T.S. Edgington (1989). Complete sequence of the human tissue factor gene, a highly regulated cellular receptor that initiates the coagulation protease cascade. *Biochemistry,* 28(4): 1755–1762.

Maugeri, N., M. Brambilla, M. Camera, A. Carbone, E. Tremoli, M.B. Donati, G. de Gaetano G and C. CERLETTI (2006). Human polymorphonuclear leukocytes produce and express functional tissue factor upon stimulation. *J Thromb Haemost*, 4(6): 1323–1330.

Mcgill, H. C. JR., C.A. McMahan and S.S. Gidding (2008). Preventing heart disease in the 21st century: implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study. *Circulation,* 117(9): 1216–1227.

Misumi, K., H. Ogawa, H. Yasue, H. Soejima, H. Suefuji, K. Nishiyama, K. Takazoe, K. Kugiyama, I. Tsuji, K. Kumeda and S. Nakamura, S. (1998). Comparison of plasma tissue factor levels in unstable and stable angina pectoris. *Am J Cardiol,* 81(1): 22–26.

Moosbauer, C., E. Morgenstern, S.L. Cuvelier, D. Manukyan, K. Bidzhekov, S. Albrecht, P. Lohse, K.D. Patel and B. Engelmann, B (2007). Eosinophils are a major intravascular location for tissue factor storage and exposure. *Blood*, 109(3): 995–1002.

Moran, A. E., M.H. Forouzanfar, G.A. Roth, G.A. Mensah, M. Ezzati, C.J. Murray and M. Naghavi (2014). Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. *Circulation,* 129(14): 1483–1492.

Muller, I., A. Klocke, M. Alex, M. Kotzsch, T. Luther, E. Morgenstern, S. Zieseniss, S. Zahler, K. Preissner and B. Engelmann (2003). Intravascular tissue factor initiates coagulation via circulating microvesicles and platelets. *FASEB J,* 17(3): 476–478.

Napoleone, E., A. di Santo and R. Lorenzet (1997). Monocytes upregulate endothelial cell expression of tissue factor: a role for cell-cell contact and cross-talk. *Blood,* 89(2): 541–549.

Ngo, C. V., K. Picha, F. Mccabe, H. Millar, R. Tawadros, S.H. Tam, M.T. Nakada and G.M. Anderson (2007). CNTO 859, a humanized anti-tissue factor monoclonal antibody, is a potent inhibitor of breast cancer metastasis and tumor growth in xenograft models. *Int J Cancer,* 120(6): 1261–1267.

O'donnell, C. J. and E.G. Nabel (2011). Genomics of cardiovascular disease. *N Engl J Med,*
365(22): 2098–2109.

Pedersen, B., T. Holscher, Y. Sato, R. Pawlinski, R. and N. Mackman (2005). A balance between tissue factor and tissue factor pathway inhibitor is required for embryonic development and hemostasis in adult mice. *Blood,* 105(7): 2777–2782.

Pendurthi, U. R., D. Alok and L.V. Rao (1997). Binding of factor VIIa to tissue factor induces alterations in gene expression in human fibroblast cells: up-regulation of poly(A) polymerase. *Proc Natl Acad Sci U S A,* 94 (23): 12598–12603.

Penn, M. S., C.V. Patel, M.Z. Cui, P.E. Dicorleto and G.M. Chisolm. (1999). LDL increases inactive tissue factor on vascular smooth muscle cell surfaces: hydrogen peroxide activates latent cell surface tissue factor. *Circulation,* 99(13): 1753–1759.

Rottingen, J. A., T. Enden, E. Camerer, J.G. Iversen and H. Prydz (1995). Binding of human factor VIIa to tissue factor induces cytosolic Ca2+ signals in J82 cells, transfected COS-1 cells, Madin-Darby canine kidney cells and in human endothelial cells induced to synthesize tissue factor. *J Biol Chem*, 270(9): 4650–4660.

Sambola, A., J. Osende, J. Hathcock, M. Degen, Y. Nemerson, V. Fuster, J. Crandall, and J.J. Badimon (2003). Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. *Circulation,* 107(7): 973–977.

Steffel, J., T.F. Luscher and F.C. Tanner (2006). Tissue factor in cardiovascular diseases: molecular mechanisms and clinical implications. *Circulation,* 113(5): 722–731.

Stegenga, M. E., S.N. van der Crabben, M. Levi, A.F. D. de Vos, M.W. Tanck, H. P. Sauerwein T. van der Poll (2006). Hyperglycemia stimulates coagulation, whereas hyperinsulinemia impairs fibrinolysis in healthy humans. *Diabetes,* 55(6): 1807–1812.

Stephens, A. C. and R.P. Rivers (1997). Suppression of human monocyte tissue factor synthesis by antisense oligodeoxynucleotide. *Thromb Res,* 85(5): 387–398.

Kent, W. J., C. W. Sugnet, T.S. Furey, K.M. Roskin, T.H. Pringle, A.M. Zahler and D. Haussler (2002). The human genome browser at UCSC. *Genome Res,* 12(6): 996–1006.

Vaidyula, V. R., A.K. Rao, M. Mozzoli, C. Homko, P. Cheung and G. Boden (2006). Effects of hyperglycemia and hyperinsulinemia on circulating tissue factor procoagulant activity and platelet CD40 ligand. *Diabetes,* 55(1): 202–208.

Versteeg, H. H., I. Hoedemaeker, S.H. Diks, J.C. Stam, M. Spaargaren, P.M. van Bergen En Henegouwen, S.J. van Deventer and M.P. Peppelenbosch (2000). Factor VIIa/tissue factorinduced signaling via activation of Src-like kinases, phosphatidylinositol 3-kinase, and Rac. *J Biol Chem*, 275(37): 28750–28756.

Wada, H., T. Kaneko, Y. Wakita, K. Minamikawa, S. Nagaya, S. Tamaki, K. Deguchi and S. Shirakawa (1994). Effect of lipoproteins on tissue factor activity and PAI-II antigen in human monocytes and macrophages. Int J Cardiol, 47(1 Suppl): S21-5.

Wilcox, J. N., K.M. Smith, S.M. Schwartz and D. Gordon (1989). Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. *Proc Natl Acad Sci U S A,* 86(8): 2839–2843.

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