REVIEW ARTICLE

A Review on the Relationship between Matrix Metalloproteinases (MMPS) and their Natural Inhibitors (Tissue Inhibitors of Matrix Metalloproteinases [Timps]) and the Success of an Autologous Arteriovenous Fistula (AVF)

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ABSTRACT

Since its introduction by Brescia and Cimino in 1966, arteriovenous fistula has been regarded as the best vascular access for haemodialysis purposes. However, it's not without any drawbacks which have cost over USD1 billion in the United States alone to rectify. Intimal hyperplasia has been shown to be a major contributory factor to this development. Intimal hyperplasia is a complex molecular process resulting in the unwarranted accumulation of contractile smooth muscle cells, myofibroblasts, fibroblasts, and macrophages. There is an increasing amount of evidence suggesting that matrix metalloproteinases (MMPs) and their natural inhibitors [(tissue inhibitors of matrix metalloproteinases (TIMPs)] play a pivotal role in the development of intimal hyperplasia. Our purpose in writing this review article is to examine these shreds of evidence and to suggest what future research questions need to be answered to further strengthen and clarify this relationship.

Keywords
Matrix metalloproteinases, tissue inhibitors of matrix metalloproteinases, autologous arteriovenous fistula, success

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INTRODUCTION

There were 40 000 Malaysian registered to be on dialysis according to the 24th Report of the Malaysian Dialysis and Transplant Registry 2016 with the majority (47%) involves elderly above the age of 55 years old by the end of 2016. This represents an expanding growth to 1155 pmp in 2014 from 504 per million population (pmp) in 2005.[1] Diabetes is the commonest aetiology (65%) among Malaysians. A multinational study, including Malaysia analysing 2914 renal failure patients showed a higher prevalence of renal failure among the underprivileged.[2] The same conclusion was found in a population-based study conducted in the United State involving 23,314 adults.[3]

End-stage renal failure (ESRF) only represents 0.02 – 0.03% of the total population in developing countries but the cost of its treatment represents 2-3% of total healthcare expenses.[4] In Malaysia, this is estimated at RM1.1 billion in 2015 and will increase to RM 2.4 billion in 2030.[5] According to the 24th Report of the Malaysian Dialysis and Transplant Registry 2016, the government is funding 67% of the total cost of dialysis.

The popular method of dialysis recorded in 2014 was haemodialysis (1046 pmp) in comparison to peritoneal dialysis (109 pmp).[1] Although, kidney transplant is the

best for end-stage renal failure, its rate is only at 3 pmp due to organ donor shortage.[1]

What is an arteriovenous fistula (AVF)

In 1966, Brescia and Cimino described a revolutionary breakthrough in providing vascular access for haemodialysis through the formation of an autologous arteriovenous fistula (AVF). This has been recognised as a default approach for repeated vascular in haemodialysis due to its' superior longevity, patient morbidity, and reduction in health care cost.[6] Other options of the long-term catheter and external shunt were common prior to this landmark invention, but the high incidence of thrombosis and infection associated with these approaches renders it to become less desirable.

The initiation of the Dialysis Outcomes and Quality Initiative (DOQI) in 1995, which is now being referred to as Kidney Disease Outcomes and Quality Initiative (KDOQI) by The National Kidney Foundation (NFK) aimed to improve the healthcare outcome among ESRF patients. It has the responsibility of setting up clinical guidelines driven by large evidence-based data. This has led to the introduction of the National Vascular Access Improvement Initiative (NAVII) and Fistula First. An increased number of AVF has been created in the United State since the establishment of KDOQI. There is an increment from 33% in 2003 to 41% in 2005 in AVF prevalence with an increase in incidence from 26.3% in 1999 to 36.3% in 2003.[7]

Both autologous or prosthetic grafts can be used in AVF construction but two large meta-analyses described a much superior patency rate associated with autologous AVF.[8, 9] An estimated cost of more than USD 1 billion being spent every year to treat AVF-related morbidity and hospitalization.[10] Thrombosis, infection, and bleeding form the majority of this morbidity. Failure to mature among these AVF also contributed in a smaller proportion towards this morbidity.[11] Furthermore, among matured AVFs, the patency rate drops proportionately to its age. A recently published systematic review and meta-analysis of 46 articles concerning 12,383 AVF showed a 1 and 2 years primary patency rate of 60% and 51% respectively.[12] Among the Asian population, the latest publication examined autologous radio-cephalic fistula (RCF) reported a primary patency rate at 12-months, 24 months, 36 months, 48 months, 60 months, and 72 months of 72%, 69%, 58%, 57%, 56%, and 54% respectively.[13] An 8-year prospective study examined 505 AVF showed a 1-year primary patency rate of 78.8% which dropped to 14.8% at the end of 5 years.[14]

The primary reason for AVF failure has consistently been shown due to intimal hyperplasia (IH) in the venous outflow tract.[15-17] The combination of increase in wall shear stress, low and oscillating flow pattern increases the expression of pro-coagulant and pro-inflammatory mediators within the endothelial cells that promote the formation of IH.[18] IH will lead to a luminal narrowing or stenotic segment of vessels. In the case of AVF, this most commonly occurs at the juxta-anastomotic site. The resultant reduction of blood flow and turbulence beyond the stenosis will eventually cause a blood clot formation, thrombosis, which will render the AVF to become non-functional. The histological examination of IH revealed an excessive presence of contractile smooth muscle cells, myofibroblasts, fibroblasts, and macrophages. Extensive studies have been performed to examine possible factors affecting the formation of this undesirable effect, henceforth, improved AVF patency. Inflammation, uraemia, hypoxia, shear-stress, and thrombosis has been implicated to contribute towards IH formation, however, the exact pathophysiology is largely unknown.[15, 19-21]

Evidence suggested AVF creation related to both local and systemic inflammation. Trauma and local hypoxia related to fistula creation lead to local inflammation and uraemia potentially could set off systemic inflammation. The presence of macrophages represents a local inflammatory response accountable for the releasing of macrophage migration inhibitory factors.[22, 23] This pluripotent protein has been identified in clinical and experimental models to augment neointimal thickening and promote the proliferation of medial and intimal cells in vascular access.[24]

What are matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs)

Matrix metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are classified as the subfamily of the zinc metalloprotease family that performed many important roles in vascular physiology and pathological processes due to their capability of degrading every component of the extracellular matrix (ECM).[25] Initially thought to be exclusively extracellular, now evidence emerges to suggest MMP 1, MMP 2, and MMP 11 can be found intracellularly and may act on intracellular proteins.[26-28] MMPs can be broadly subdivided into five classes: collagenases, gelatinases, elastase, stromelysins, and membrane-type MMPs (MT-MMPs).

Their activities can be controlled at four levels: induction of MMP genes, vesicle trafficking and secretion, activation of latent proforms, and complexing with specific tissue inhibitors of metalloproteinases (TIMPs).

These enzymes require activation into their active forms in order to perform their functions since they are secreted in a latent, proenzyme structure. Most secreted proMMPs are activated by tissue or plasma proteinases, including other MMPs or non-proteinase agents such as reactive oxygen species (ROS), plasmin, and nitric oxide.[29] The principal activation of proMMP 2, however, takes place on the cell surface-mediated by the membrane-type-like MMPs (MT-MMPs) with the presence of TIMP 2.[30] Presently, three MT-MMPs, i.e. MT1-MMP, MT2-MMP, and MT3-MMP has the ability to activate proMMP 2.[31-33]

Tissue inhibitor of metalloproteinases (TIMPs)

The first endogenous matrixins, labelled as tissue inhibitor of metalloproteinases (TIMPs), was found by Bauer *et al.* in 1975.[34] They can readily be found in normal, transformed and inflammatory cells. Their expressions have been shown to influence by phorbol esters, corticosteroids, TGF-P, fibroblast growth factor (FGF), retinoids IL-1 and chemokines.[35, 36]

They are capable of inhibiting active MMPs and proMMP activation, cell growth promotion, matrix binding, inhibition of angiogenesis, and the induction of apoptosis among others.[37] They are subdivided into N-terminal, efficient inhibitors of all MMPs, and a C-terminal subdomain. Virtually all MMPs form tight 1:1 complexes with the TIMPs.[38] Two distinct subgroups of TIMPs have been identified and extensively studied, TIMP1 and TIMP2.

TIMP 1 is a 28.5 kDa glycoprotein and is the more abundant of the TIMPs. TIMP-1 secretion is constitutive in vascular smooth muscle cell (VSMC) and endothelial cell (EC) and can be augmented by the platelets-derived growth factor (PDGF), fibrogenic cytokines, and transforming growth factor (TGF).[39, 40]

TIMP 2 is a 21kDa glycoprotein that shares approximately 40% sequence identity with TIMP 1. Its secretion is exclusively constitutive within VSMC and EC.[39] *In vitro* studies demonstrate a preferential inhibition of MMP 1 by TIMP 1 and MMP 2 and MMP 9 by TIMP 2.[41]

How do MMPs and TIMPs affect AVF

The human vein has three distinct layers, namely intima, media, and adventitia. Normal intima has an endothelial layer sitting on the basement membrane separating it from the VSMC-enriched media layer. MMPs are capable of catalysing the denudation of basement membrane, which normally comprises polymerised type IV collagen, laminin, and heparan sulfate proteoglycans (HSPGs). Exposed VSMC change from quiescent, contractile VSMC into cells capable of migrating and proliferating to facilitate tissue repair. As a result, permissive matrix components such as monomeric collagen will be produced together with sequestration of growth factors capable of an autocrine effect. Resultant new tissue generation will eventually result in IH formation. This is a common feature in vein-artery

anastomosis and acts as a major contributor to the failure of maturation in the arteriovenous fistula.[42-44]

Animal model evidence

There are ample animal evidence suggestive of MMPs upregulation with intimal hyperplasia. The two commonest studied MMPs, namely MMP 2 and MMP 9 were found to be elevated in rat, pig, baboon, rabbit, and mouse.[45-49] Changes to TIMPs, however, are not as homogenous as MMPs. TIMP 1 showed to temporarily increase in the first 24 hours following arterial injury but become undetectable after 7 days.[50] TIMP 2 and 4 however, showed to be augmented following arterial injury even after 7 days after injury.[51, 52]

Ex vivo evidence

Harvested human saphenous vein was showed to have an increased level of MMP 2 and MMP 9, both belong to gelatinases group, as soon as surgical preparation is completed, with the absence of any extra stimulus apart from injury associated with surgical preparation. MMP 9 expression was found to be at its greatest in the highly proliferative neointimal smooth muscle cell after 12-days of culture.[53] Increase in intraluminal pressure, which is a natural adaptive response to any native vein after AVF procedure, would provoke a rigorous inflammatory response.[54] Following this response, there is an influx of neutrophil infiltration followed by more sustained macrophage deposition.[54] This inflammatory response could act as the initiator to MMPs recruitment and upregulation. Interestingly, MMP 1 (collagenase) and MMP 3 (stromelysin) were both not significantly elevated in human saphenous vein.[55]

The neointimal formation was prevented in cultured human saphenous vein transferred with TIMP 1 and 2 genes through inhibition of migration but not proliferation[56, 57]. The same net effect was seen with TIMP 3 but as well as inhibiting migration, it also stimulate apoptosis.[58] However, some researchers found although secretion of TIMP 1 and TIMP 2 greatly increased, this would not stop the neointimal formation in human saphenous vein.[59]

Clinical evidence

The first evaluation of MMPs and TIMPs content in a human vein tissue prior to AVF construction recruited a total of fourteen patients who underwent either a radiocephalic fistula (RCF) or brachiocephalic fistula (BCF) had their excess vein harvested for MMP 2, MMP 9, TIMP 2, TIMP 4 and MT1-MMP (MMP 2 activator) evaluation using zymography and Western blotting technique. MT1-MMP, MMP 2 latent, total MMP 2, and TIMP 2 were significantly higher in successfully matured AVF in comparison to AVF that failed to mature. In this study, the excess vein segment was harvested intraoperatively prior to the anastomosis. However, the vascular remodelling that leads to the formation of IH occurs after the anastomosis creation.[60] The same group of researchers examined the serum taken from an artery in twenty chronic kidney disease (CKD) and ESRF patients undergoing AVF, they found a significantly higher MMP 2/TIMP 2 in comparison to those that failed.[61] However due to the heterogeneity of the study population, especially different stages of chronic renal failure, in addition to the small sample size, a substantial-conclusion is difficult to draw. In addition, in both of these studies, there was no consideration was made to include other factors, such as BMI, vessels diameter, presence of peripheral occlusive arterial disease, and location of the AVF, that also contributes towards the maturation and patency of an AVF in their analysis.

Serum from the blood taken from AVF access during dialysis of seventy-nine patients was analysed for MMP 2 level and was found to be significantly higher in those who experienced a vascular access loss in a prospective observational study between August 2014 and July 2016, which was later published in 2017 stated that the cut off value for significantly better primary AVF survival was found to be at 50ng/ml.[62] However, in this study, MMP 2 analysis was only limited to one reading at the beginning of the study. A serial value may be more valuable since vessels remodelling is a dynamic process. There was no attempt at evaluating MMP 2 inhibitors that may also play a vital role and may provide significant insight into how do these MMPs and their inhibitors contribute towards the long-term patency of an AVF.

Future research area

An animal study utilising RO113-2908, a broad-spectrum MMP inhibitor, showed a significant systemic MMP inhibitory activity and angiogenesis but failed to prevent significant intimal hyperplasia after angioplasty and stenting in atherosclerotic animal models.[63] Another animal model using CGS 27023A, another broad-spectrum MMP inhibitor also failed to show the promising result in preventing restenosis.[64] Other animal studies also found the same conclusion with regard to the effect of broad-spectrum MMP inhibitors.[65, 66]

Doxycycline, a second-generation tetracycline, is a broad -spectrum antibiotic that has been shown to have an inhibitory effect on MMPs.[67] Therapeutic dose of doxycycline was investigated with cultured human long saphenous vein and was found to significantly reduce intimal hyperplasia and reduction in the production of MMP 9.[68] Similar result was shown when the cultured artery was utilised instead of the vein.[69] However, in an *in-vivo* rodent model of vascular injury, systemic doxycycline administration before or at the time of vascular injury does not significantly reduce the progress of intimal hyperplasia.[70]

HMG-CoA reductase inhibitors, widely known as statins, have also been consistently shown to possess a matrix-stabilising effect, through MMPs and TIMPs modulation.[71] This is partially related to the ability of statins to inhibit the isoprenylation of signalling proteins, resulting in modification of proinflammatory and proatherogenic genes.[72] A recently published comprehensive meta-analysis among 587 human subjects showed that statin therapy was associated with reduces plasma concentrations of TIMP 1 but failed to significantly alter plasma level of MMP 9 and MMP 2.[73]

CONCLUSION

In conclusion, there is an increasing number of evidence suggesting a pivotal role of MMPs and TIMPs towards the prognosis of an AVF. Pharmacotherapy and alteration of individual MMPs and TIMPs among animal, cultured human tissue, and clinical studies as well has shown some positive results towards the maturity and patency of an AVF. However, there is still a lack of a breakthrough clinical study to support the use of these pharmacological therapies in combating the formation of intimal hyperplasia. The way forward may need to involve altering both the MMPs and also its tissue inhibitors.

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