The Biology of Hemodialysis Vascular Access Failure

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Abstract

Arteriovenous fistulas (AVFs) are essential for patients and clinicians faced with end-stage renal disease (ESRD). While this method of vascular access for hemodialysis is preferred to others due to its reduced rate of infection and complications, they are plagued by intimal hyperplasia. The pathogenesis of intimal hyperplasia and subsequent thrombosis is brought on by uremia, hypoxia, and shear stress. These forces upregulate inflammatory and proliferative cytokines acting on leukocytes, fibroblasts, smooth muscle cells, and platelets. This activation begins initially with the progression of uremia, which induces platelet dysfunction and primes the body for an inflammatory response. The vasculature subsequently undergoes changes in oxygenation and shear stress during AVF creation. This propagates a strong inflammatory response in the vessel leading to cellular proliferation. This combined response is then further subjected to the stressors of cannulation and dialysis, eventually leading to stenosis and thrombosis. This review aims to help interventional radiologists understand the biological changes and pathogenesis of access failure.

Keywords
- interventional radiology
- hemodialysis
- intimal hyperplasia
- arteriovenous fistula failure
- end stage renal disease

Objectives: Upon completion of this article, the reader will be able to describe the biological forces that drive intimal hyperplasia leading to arteriovenous fistula failure.

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For the over 600,000 patients with end-stage renal disease (ESRD) in the United States alone, hemodialysis has been an indispensable lifeline. While there are several modes of vascular access including grafts and catheters, native fistulas are the most preferred, as they have lower rates of infection and complication compared with other alternatives.[1–4] These outcomes and the Fistula First Initiative have helped to increase the numbers of arteriovenous fistulas (AVFs) used throughout the world and in diverse patient populations.[4–7] However, AVFs can be affected by several problems that compromise venous access. Stenosis, thrombosis, infection, and aneurysm formation are the most common complications, and stenosis and thrombosis are the most relevant to AVF access failure.

Stenosis in the setting of hemodialysis (HD) usually occurs on the venous side, and is defined by the proliferation of several cell types leading to intimal hyperplasia (IH). These include inflammatory cells (mainly macrophages) along with vascular smooth muscle cells (SMCs), myofibroblasts, and fibroblasts. This rapid proliferation occurs due to uremic changes in ESRD patients along with stressors secondary to surgical trauma. To better understand the complications associated with AVFs and

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arteriovenous grafts (AVGs), it is helpful to study the chronology of these pathological changes. AVF failure can be thought of as occurring in three overly simplified steps: inflammation, proliferation, and thrombosis.

Initially, patients with ESRD have high baseline levels of inflammatory and platelet cell dysfunction secondary to uremic toxins and reactive species. During the creation of the AVF, there are changes in the vessel wall secondary to hypoxia and shear stress. These factors work together in a positive feedback loop propagating inflammation and cellular proliferation, which progresses to the point of stenosis and thrombosis.[8–13] By exploring the nature of these biological mechanisms, HD access failure can be better understood, which can help guide future research aimed to ameliorate it.

Uremia

As stated earlier, even before fistula or graft creation several important systemic and vascular changes take place.[14–17] The inherent uremia of ESRD increases inflammation and oxidative stress.[18,19] These changes are evidenced by increases in many inflammatory cytokines, namely, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and proliferate cytokines, such as transformative growth factor - β (TGF-β).

There are many other effects of uremia that involve the vascular system. Several studies have shown increased vessel thickness and calcification in patients with ESRD. This increased wall thickness is likely secondary to the proliferation of vascular smooth muscle cells in response to inflammation secondary to advanced glycation products and reactive oxygen species (ROS), both of which are increased in ESRD patients.[20–22] The increased thickness of the vessel wall has implications in cardiovascular risk and also in access failure as it, along with inflammation, predisposes the vessel to stenosis.[23–26] Increased vessel fibrosis, calcium phosphate deposition, and cellular calcium extrusion have been noted in ESRD patients. These changes are likely secondary to oxidative stress, dysfunctional cell signaling, and changes in mineral metabolism.[27,28] These effects are compounded by platelet and endothelial wall dysfunction leading to rapid atherosclerotic progression. These combined changes predispose the vessel wall to negative, stenotic, inward remodeling after access placement.

Hypoxia

It is in this background of widespread cellular dysfunction that patients usually undergo placement of an AVG or AVF creation. The trauma induced by surgery induces hypoxia secondary to ischemia, both from cross-clamping and disruption of the vasa vasorum. This hypoxic injury is thought to also occur due to repeat needle sticks during cannulation for dialysis. This insult induces a series of cytokine cascades that promote inflammation, angiogenesis, and proliferation, which ultimately results in IH.

Ischemia and the release of ROS activate early response elements such as hypoxia-inducible factor 1-alpha (HIF-1α) and immediate-early responsive gene (IEX-1).[29–31] These in turn activate endothelial cells (ECs), inflammatory cells, and vascular SMCs. HIF-1α, ROS, and hypoxia have been shown to upregulate vascular endothelial growth factors (VEGFs), which increase inflammation and promote EC proliferation. In addition, VEGF-A subsequently activates metalloproteinase (MMPs), namely, MMP-2, MMP-9, and ADAMTS-1, which allows for remodeling of the extracellular matrix (ECM) allowing for increased cellular proliferation.[25,30,32–36] Hypoxia also activates platelet-derived growth factor, which has been shown to increase myofibroblasts.[13,31,35,37]

These are the main proliferative changes that occur. However, cytokines such as VEGF-A, IEX-1, HIF-1α have also been shown to propagate inflammation, which can subsequently induce proliferation resulting in a dangerous positive feedback loop. VEGF-a can serve as a leukocyte attractant. HIF-1α can induce activation of inflammatory cells.[38] These and other early cytokines have been linked to activation of IL-8 and MCP-1. MCP-1 serves a leukocyte attractant and activator via CXCR motif receptors drawing monocytes, memory T lymphocytes, and natural killer cells toward the AVF.[39] IL-8 also recruits monocytes via the same receptors. Macrophage migration inhibitory factor also becomes elevated, and is thought to direct inflammatory cells toward the neointima, inducing negative remodeling through the proliferation of vascular SMCs and ECs.[40,41] Another set of molecules implicated in AVF failure are Heme oxygenase-1 (HO-1) and Heme oxygenase-2 (HO-2). HO-1 is a stress protein that acts in a vasoprotective capacity by reducing inflammation, proliferation, fibrosis, and oxidant stress. Based on knockout (KO) gene models, it is likely that it acts on plasminogen activator inhibitor-1 (PAI-1), MCP-1, MMP2, and MMP9.[42,43] HO-2 is thought to act in a similar manner.[44]

Along with these agents, TGF-β and TNF-α have also been implicated in IH. TGF-β1 has been shown to lead to changes in the ECM, cellular proliferation, and thrombus formation. TNF-α is an inflammatory cytokine that has been shown to be activated by local inflammation and to hypoxia.[45,46] TNF-α is released by leukocytes and also by SMCs and ECs.[4] TNF-α can act via the receptor for advanced glycation end products (RAGE). This receptor has been linked to upregulation of VCAM-1. TNF-α can also act through more specific receptors upregulating inflammatory cytokines such as IL-1β; it also promotes cellular proliferation in fibroblasts. The ability of TNF-α to be released from and act on cells enables it to serve as a strong mediator of cellular proliferation and inflammation in the setting of AVF failure.

Shear Stress

In addition to hypoxia and inflammation, shear stress also plays a role in negative remodeling. After AVF creation, the venous ECs undergo increases in shear stress due to greater flow. Over the course of maturation, levels of shear stress decrease as the vessel dilates and laminar flow is reestablished. While there is normalization of shear stress distal to anastomoses, ECs near the anastomosis experience continued wall shear stress (WSS). ECs respond in three interrelated

mechanisms: by rearranging the cytoskeleton, expressing different signaling cytokines, and affecting vasodilation.[47–50]

Increased WSS increases inflammatory cytokines such as Il-1β, TNF-α, and interferon (IF-γ).[51–53] Additionally, WSS has been shown to increase VEGF-A, MMP2, MM9, intercellular adhesion molecule-1 (ICAM-1), and other cytokines implicated in the proliferative aspect of negative remodeling.[54] Many of these changes are likely tied to nuclear factors such as decreased Krüppel-like factor 2 (KLF-2) and increased AKT signaling. KLF-2 has been shown to maintain a resting cell state and suppress inflammatory cytokines such as MCP-1 and IL-8. AKT is linked to the ERK/MAPK pathways, which propagate cell survival and mitotic changes.

WSS can induce mechanical tension on vascular endothelial (VE)-cadherin and platelet endothelial cell adhesion molecule (PECAM)-1.[55,56] This mechanical stress serves to remodel the actin fibers and intracellular junctions. This allows the cell to change shape, and also induces cellular mobility.[57,58] Beyond structural changes within cells, WSS also affects the vessel structure by affecting heme oxygenase and nitric oxide (NO) synthesis. NO acts to dilate the vessel, but this response can become blunted in cases of persistent activation such as hypertension.[59]

Thrombosis

Thrombosis of HD access is a cumulative step and often signals the end of access viability. The same factors that drive IH lead to thrombosis. It is important to note that in the setting of ESRD, patients often experience increased bleeding time. The increased bleeding is secondary to dysfunctional platelets and also due to impaired platelet endothelial interactions. It is likely that much of the platelet dysfunction seen can be attributed to metabolic changes, and activation of coagulative and fibrinolytic cascades.[60] Platelets in uremia have accelerated apoptosis. Levels of ADP and serotonin are lower in ESRD patients. These reduced levels limit platelet aggregation and activation.[60] Thromboxane A2 is also systemically decreased in ESRD patients, which limits vasoconstriction and platelet aggregation. Additionally, uremia appears to have an impact on the cytoskeletal structure of platelets, which are found to have lower levels of actin, inhibiting contractile mechanisms and mobility.[61] These and other changes account for the bleeding aspect caused by uremia.

On a systemic level, these factors lead to increased bleeding, but at the site of access, venous stenosis, shear stress, and endothelial damage can precipitate clot formation.[62–69] The process of dialysis has also been shown to activate platelets, depending mainly on the membrane used in the dialysis machine. This can result in thrombocytopenia due to platelet destruction, and can also yield cell aggregates. Platelet–leukocyte aggregates can induce atherosclerosis and thrombosis.[70] Additionally, dialysis has been shown to increase circulating levels of p-selectin, CD40L, von Willebrand factor (WF), and D-dimer. This suggests that platelet activation in dialysis may lead to temporarily higher coagulability in the postdialysis period.[71–73]

Another major factor specific to the AVF is inflammation due not just to AVF creation but also to repeat needle stick injury. Platelets can adhere to the already inflamed endothelial tissue and potentiate the process by releasing MCP-1, VCAM-1, ICAM-1, IL-1 β, and TNF-α, among others. These cytokines further the activation cascade leading to increased inflammation, adhesion, and eventually plaque or thrombus formation. Additionally, platelets can also directly induce these cytokines by direct interaction via P-selectin and with the monocyte receptor Mac-1 ($\alpha_M\beta_2$) via $\alpha_{IIb}\beta_3$ or GPIbα.[74] Uremia along with shear stress and indoxyl sulfate have also been linked with increased endothelial micro particles. These by-products of EC activation or apoptosis can inhibit endothelial NO, further reducing the dilatory capacity of the vessel.[75,76]

Genetics

There is a growing body of evidence examining the genetics of fistula failure. Many of the driving forces implicated in the activation of genes leading to AVF failure can also lead to epigenetic changes. Epigenetic changes affect the expression of genes through changes in histone modifications without changes in the DNA sequence. For example, HIF-1α has been shown to alter a set of histone-modifying genes.[77] It is likely that chronic kidney disease (CKD) and the comorbidities seen in ESRD patients also result in epigenetic changes that affect fistula functionality.[78] In addition to these changes, several polymorphisms have been linked to AVF patency rates, specifically VEGF-A, HO-1, and TGF-β.[12,79–81]

There have been genetic studies focused on thrombosis. For example, polymorphisms in the TNF-α promoter region have been linked to AVF thrombosis.[82] There have also been studies assessing platelet function. Platelet antigens such as human platelet antigen-3aa (HPA-3aa) have been found to be linked to AVF failure. This gene codes for a part of glycoprotein IIb (GbIIb). Certain alleles of these genes have been correlated with higher rates of access thrombosis.[83] Studies examining genetic predispositions to AVF failure lend credence and support to the current understanding of the molecular changes leading to AVF failure. Future work aiming at gene-specific therapy may help alleviate IH.

Conclusion

Hypoxia, uremia, shear stress, and thrombosis are the major factors implicated in AVF failure. These forces act on fibroblasts, macrophages, ECs, and platelets. They induce many interrelated genes implicated in inflammation and proliferation. These cytokines, along with the stressors of surgical anastomosis, repeat needle stick injury, and dialysis itself leads to IH and thrombosis.

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References

1 Sands JJ. Increasing AV fistulas: revisiting a time-tested solution. Semin Dial 2000;13(6):351–353
2 Rayner HC, Pisoni RL. The increasing use of hemodialysis catheters: evidence from the DOPPS on its significance and ways to reverse it. Semin Dial 2010;23(1):6–10
3 Lopez-Vargas PA, Craig JC, Gallagher MP, et al. Barriers to timely arteriovenous fistula creation: a study of providers and patients. Am J Kidney Dis 2011;57(6):873–882
4 Vassalotti JA, Jennings WC, Beathard GA, et al; Fistula First Breakthrough Initiative Community Education Committee. Fistula first breakthrough initiative: targeting catheter last in fistula first. Semin Dial 2012;25(3):303–310
5 Schinstock CA, Albright RC, Williams AW, et al. Outcomes of arteriovenous fistula creation after the Fistula First Initiative. Clin J Am Soc Nephrol 2011;6(8):1996–2002
6 Rayner HC, Besarab A, Brown WW, Disney A, Saito A, Pisoni RL. Vascular access results from the Dialysis Outcomes and Practice Patterns Study (DOPPS): performance against Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines. Am J Kidney Dis 2004;44(5, Suppl 2):22–26
7 Manook M, Calder F. Practical aspects of arteriovenous fistula formation in the pediatric population. Pediatr Nephrol 2013; 28(6):885–893
8 Wasse H, Huang R, Naqvi N, Smith E, Wang D, Husain A. Inflammation, oxidation and venous neointimal hyperplasia precede vascular injury from AVF creation in CKD patients. J Vasc Access 2012;13(2):168–174
9 Roy-Chaudhury P, Wang Y, Krishnamoorthy M, et al. Cellular phenotypes in human stenotic lesions from haemodialysis vascular access. Nephrol Dial Transplant 2009;24(9):2786–2791
10 Roy-Chaudhury P, Lee TC. Vascular stenosis: biology and interventions. Curr Opin Nephrol Hypertens 2007;16(6):516–522
11 Roy-Chaudhury P, Arend L, Zhang J, et al. Neointimal hyperplasia in early arteriovenous fistula failure. Am J Kidney Dis 2007;50(5): 782–790
12 Stracke S, Konner K, Köstlin I, et al. Increased expression of TGF-beta1 and IGF-I in inflammatory stenotic lesions of hemodialysis fistulas. Kidney Int 2002;61(3):1011–1019
13 Simone S, Loverre A, Cariello M, et al. Arteriovenous fistula stenosis in hemodialysis patients is characterized by an increased adventitial fibrosis. J Nephrol 2014;27(5):555–562
14 Kokubo T, Ishikawa N, Uchida H, et al. CKD accelerates development of neointimal hyperplasia in arteriovenous fistulas. J Am Soc Nephrol 2009;20(6):1236–1245
15 Yang B, Vohra PK, Janardhanan R, Misra KD, Misra S. Expression of profibrotic genes in a murine remnant kidney model. J Vasc Interv Radiol 2011;22(12):1765–72.e1
16 Lee T, Chauhan V, Krishnamoorthy M, et al. Severe venous neointimal hyperplasia prior to dialysis access surgery. Nephrol Dial Transplant 2011;26(7):2264–2270
17 Liang A, Wang Y, Han G, Truong L, Cheng J. Chronic kidney disease accelerates endothelial barrier dysfunction in a mouse model of an arteriovenous fistula. Am J Physiol Renal Physiol 2013;304(12): F1413–F1420
18 Granata S, Zaza G, Simone S, et al. Mitochondrial dysregulation and oxidative stress in patients with chronic kidney disease. BMC Genomics 2009;10:388
19 Font R, Prats M, Gutiérrez C, et al. [Is there a relationship between cystatin C and inflammatory status, oxidative stress and other cardiovascular risk factors in non-diabetic patients with chronic kidney disease?] Nefrologia 2009;29(3):228–235
20 Koyama H, Nishizawa Y. AGEs/RAGE in CKD: irreversible metabolic memory road toward CVD? Eur J Clin Invest 2010;40(7):623–635
21 Gawdzik J, Mathew L, Kim G, Puri TS, Hofmann Bowman MA. Vascular remodeling and arterial calcification are directly mediated by S100A12 (EN-RAGE) in chronic kidney disease. Am J Nephrol 2011;33(3):250–259
22 Nasrallah MM, El-Shehaby AR, Osman NA, Salem MM, Nassef A, El Din UA. Endogenous soluble receptor of advanced glycation end-products (esRAGE) is negatively associated with vascular calcification in non-diabetic hemodialysis patients. Int Urol Nephrol 2012;44(4):1193–1199
23 Dursun B, Dursun E, Suleymanlar G, et al. Carotid artery intima-media thickness correlates with oxidative stress in chronic haemodialysis patients with accelerated atherosclerosis. Nephrol Dial Transplant 2008;23(5):1697–1703
24 Garcia-Bello JA, Gómez-Díaz RA, Contreras-Rodríguez A, et al. Carotid intima media thickness, oxidative stress, and inflammation in children with chronic kidney disease. Pediatr Nephrol 2014;29(2):273–281
25 Janda K, Krzanowski M, Gajda M, et al. Cardiovascular risk in chronic kidney disease patients: intima-media thickness predicts the incidence and severity of histologically assessed medial calcification in radial arteries. BMC Nephrol 2015;16:78
26 Kotur-Stevuljević J, Peco-Antić A, Spasić S, et al. Hyperlipidemia, oxidative stress, and intima media thickness in children with chronic kidney disease. Pediatr Nephrol 2013;28(2):295–303
27 Fujisaki K, Tsuruya K, Yamato M, et al. Cerebral oxidative stress induces spatial working memory dysfunction in uremic mice: neuroprotective effect of Tempol. Nephrol Dial Transplant 2014; 29(3):529–538
28 Hruska KA, Mathew S, Memon I, Saab G. The pathogenesis of vascular calcification in the chronic kidney disease mineral bone disorder (CKD-MBD): the links between bone and the vasculature. Semin Nephrol 2009;29(2):156–165
29 Brahmbhatt A, NievesTorres E, Yang B, et al. The role of Iex-1 in the pathogenesis of venous neointimal hyperplasia associated with hemodialysis arteriovenous fistula. PLoS ONE 2014;9(7):e102542
30 Misra S, Shergill U, Yang B, Janardhanan R, Misra KD. Increased expression of HIF-1alpha, VEGF-A and its receptors, MMP-2, TIMP-1, and ADAMTS-1 at the venous stenosis of arteriovenous fistula in a mouse model with renal insufficiency. J Vasc Interv Radiol 2010; 21(8):1255–1261
31 Wan J, Lata C, Santilli A, Green D, Roy S, Santilli S. Supplemental oxygen reverses hypoxia-induced smooth muscle cell proliferation by modulating HIF-alpha and VEGF levels in a rabbit arteriovenous fistula model. Ann Vasc Surg 2014;28(3):725–736
32 Ohtani K, Egashira K, Hiasa K, et al. Blockade of vascular endothelial growth factor suppresses experimental restenosis after intraluminal injury by inhibiting recruitment of monocyte lineage cells. Circulation 2004;110(16):2444–2452
33 Shibuya M. Differential roles of vascular endothelial growth factor receptor-1 and receptor-2 in angiogenesis. J Biochem Mol Biol 2006;39(5):469–478
34 Huusko J, Merentie M, Dijkstra MH, et al. The effects of VEGF-R1 and VEGF-R2 ligands on angiogenic responses and left ventricular function in mice. Cardiovasc Res 2010;86(1):122–130
35 Semenza GL. Targeting HIF-1 for cancer therapy. Nat Rev Cancer 2003;3(10):721–732
36 Fragoso A, Silva AP, Gundlach K, Büchel J, Neves PL. Magnesium and FGF-23 are independent predictors of pulse pressure in predialysis diabetic chronic kidney disease patients. Clin Kidney J 2014;7(2):161–166
37 Yang B, Janardhanan R, Vohra P, et al. Adventitial transduction of lentivirus-shRNA-VEGF-A in arteriovenous fistula reduces venous stenosis formation. Kidney Int 2014;85(2):289–306
38 Veillat V, Carli C, Metz CN, Al-Abed Y, Naccache PH, Akoum A. Macrophage migration inhibitory factor elicits an angiogenic phenotype in human ectopic endometrial cells and triggers the production of major angiogenic factors via CD44, CD74, and MAPK signaling pathways. J Clin Endocrinol Metab 2010;95(12):E403–E412

39 Deshmane SL, Kremlev S, Amini S, Sawaya BE. Monocyte chemoattractant protein-1 (MCP-1): an overview. J Interferon Cytokine Res 2009;29(6):313–326
40 Stangenberg S, Nguyen LT, Chen H, et al. Oxidative stress, mitochondrial perturbations and fetal programming of renal disease induced by maternal smoking. Int J Biochem Cell Biol 2015; 64:81–90
41 van der Weerd NC, Grooteman MP, Nubé MJ, ter Wee PM, Swinkels DW, Gaillard CA. Hepcidin in chronic kidney disease: not an anaemia management tool, but promising as a cardiovascular biomarker. Neth J Med 2015;73(3):108–118
42 Durante W, Lin C-C. HOming in on arteriovenous fistula survival. Kidney Int 2008;74(1):9–11
43 Juncos JP, Tracz MJ, Croatt AJ, et al. Genetic deficiency of heme oxygenase-1 impairs functionality and form of an arteriovenous fistula in the mouse. Kidney Int 2008;74(1):47–51
44 Kang L, Grande JP, Farrugia G, Croatt AJ, Katusic ZS, Nath KA. Functioning of an arteriovenous fistula requires heme oxygenase-2. Am J Physiol Renal Physiol 2013;305(4):F545–F552
45 Feldman HI, Joffe M, Rosas SE, Burns JE, Knauss J, Brayman K. Predictors of successful arteriovenous fistula maturation. Am J Kidney Dis 2003;42(5):1000–1012
46 Huijbregts HJT, Bots ML, Wittens CHA, Schrama YC, Moll FL, Blankestijn PJ; CIMINO Study Group. Hemodialysis arteriovenous fistula patency revisited: results of a prospective, multicenter initiative. Clin J Am Soc Nephrol 2008;3(3):714–719
47 Sho E, Nanjo H, Sho M, et al. Arterial enlargement, tortuosity, and intimal thickening in response to sequential exposure to high and low wall shear stress. J Vasc Surg 2004;39(3):601–612
48 Dardik A, Chen L, Frattini J, et al. Differential effects of orbital and laminar shear stress on endothelial cells. J Vasc Surg 2005;41(5): 869–880
49 Nanjo H, Sho E, Komatsu M, Sho M, Zarins CK, Masuda H. Intermittent short-duration exposure to low wall shear stress induces intimal thickening in arteries exposed to chronic high shear stress. Exp Mol Pathol 2006;80(1):38–45
50 Jia L, Wang L, Wei F, et al. Effects of wall shear stress in venous neointimal hyperplasia of arteriovenous fistulae. Nephrology (Carlton) 2015;20(5):335–342
51 Ma Y, Zhou L, Dong J, Zhang X, Yan S. Arterial stiffness and increased cardiovascular risk in chronic kidney disease. Int Urol Nephrol 2015;47(7):1157–1164
52 Jiang Z, Berceli SA, Pfahnl CL, et al. Wall shear modulation of cytokines in early vein grafts. J Vasc Surg 2004;40(2):345–350
53 Ali BH, Adham SA, Al Za'abi M, et al. Ameliorative effect of chrysin on adenine-induced chronic kidney disease in rats. PLoS ONE 2015;10(4):e0125285
54 Misra S, Fu AA, Puggioni A, et al. Increased shear stress with upregulation of VEGF-A and its receptors and MMP-2, MMP-9, and TIMP-1 in venous stenosis of hemodialysis grafts. Am J Physiol Heart Circ Physiol 2008;294(5):H2219–H2230
55 Conway DE, Schwartz MA. Mechanotransduction of shear stress occurs through changes in VE-cadherin and PECAM-1 tension: implications for cell migration. Cell Adhes Migr 2015;9(5): 335–339
56 Conway DE, Breckenridge MT, Hinde E, Gratton E, Chen CS, Schwartz MA. Fluid shear stress on endothelial cells modulates mechanical tension across VE-cadherin and PECAM-1. Curr Biol 2013;23(11):1024–1030
57 Galbraith CG, Skalak R, Chien S. Shear stress induces spatial reorganization of the endothelial cell cytoskeleton. Cell Motil Cytoskeleton 1998;40(4):317–330
58 Osborn EA, Rabodzey A, Dewey CF Jr, Hartwig JH. Endothelial actin cytoskeleton remodeling during mechanostimulation with fluid shear stress. Am J Physiol Cell Physiol 2006;290(2):C444–C452
59 Paniagua OA, Bryant MB, Panza JA. Role of endothelial nitric oxide in shear stress-induced vasodilation of human microvasculature: diminished activity in hypertensive and hypercholesterolemic patients. Circulation 2001;103(13):1752–1758
60 Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. Semin Dial 2006;19(4):317–322
61 Li M, Wang Z, Ma T, et al. Enhanced platelet apoptosis in chronic uremic patients. Ren Fail 2014;36(6):847–853
62 Rios DR, Carvalho Md, Lwaleed BA, Simões e Silva AC, Borges KB, Dusse LM. Hemostatic changes in patients with end stage renal disease undergoing hemodialysis. Clin Chim Acta 2010;411(3–4): 135–139
63 Turitto VT, Hall CL. Mechanical factors affecting hemostasis and thrombosis. Thromb Res 1998;92(6, Suppl 2):S25–S31
64 Corti R, Hutter R, Badimon JJ, Fuster V. Evolving concepts in the triad of atherosclerosis, inflammation and thrombosis. J Thromb Thrombolysis 2004;17(1):35–44
65 Serrano A, García F, Serrano M, et al. IgA antibodies against β2 glycoprotein I in hemodialysis patients are an independent risk factor for mortality. Kidney Int 2012;81(12):1239–1244
66 Fischer MJ, Rauch J, Levine JS. The antiphospholipid syndrome. Semin Nephrol 2007;27(1):35–46
67 Costa E, Rocha S, Rocha-Pereira P, et al. Cross-talk between inflammation, coagulation/fibrinolysis and vascular access in hemodialysis patients. J Vasc Access 2008;9(4):248–253
68 Erdem Y, Haznedaroglu IC, Celik I, et al. Coagulation, fibrinolysis and fibrinolysis inhibitors in haemodialysis patients: contribution of arteriovenous fistula. Nephrol Dial Transplant 1996;11(7): 1299–1305
69 Milburn JA, Ford I, Cassar K, Fluck N, Brittenden J. Platelet activation, coagulation activation and C-reactive protein in simultaneous samples from the vascular access and peripheral veins of haemodialysis patients. Int J Lab Hematol 2012;34(1):52–58
70 Daugirdas JT, Bernardo AA. Hemodialysis effect on platelet count and function and hemodialysis-associated thrombocytopenia. Kidney Int 2012;82(2):147–157
71 Milburn JA, Cassar K, Ford I, Fluck N, Brittenden J. Prothrombotic changes in platelet, endothelial and coagulation function following hemodialysis. Int J Artif Organs 2011;34(3):280–287
72 Bartels PC, Schoorl M, Schoorl M, Wiering JG, Nubé MJ. Activation of coagulation during treatment with haemodialysis. Scand J Clin Lab Invest 2000;60(4):283–290
73 Milburn JA, Ford I, Mutch NJ, Fluck N, Brittenden J. Thrombin-antithrombin levels and patency of arterio-venous fistula in patients undergoing haemodialysis compared to healthy volunteers: a prospective analysis. PLoS ONE 2013;8(7):e67799
74 Gawaz M, Langer H, May AE. Platelets in inflammation and atherogenesis. J Clin Invest 2005;115(12):3378–3384
75 Amabile N, Guérin AP, Leroyer A, et al. Circulating endothelial microparticles are associated with vascular dysfunction in patients with end-stage renal failure. J Am Soc Nephrol 2005;16(11):3381–3388
76 Boulanger CM, Amabile N, Guérin AP, et al. In vivo shear stress determines circulating levels of endothelial microparticles in end-stage renal disease. Hypertension 2007;49(4):902–908
77 Mimura I, Nangaku M, Kanki Y, et al. Dynamic change of chromatin conformation in response to hypoxia enhances the expression of GLUT3 (SLC2A3) by cooperative interaction of hypoxia-inducible factor 1 and KDM3A. Mol Cell Biol 2012;32(15):3018–3032
78 Campos B, Lee T, Roy-Chaudhury P. Arteriovenous fistula failure: is there a role for epigenetic regulation? Semin Nephrol 2013;33(4): 400–406
79 Candan F, Yildiz G, Kayataş M. Role of the VEGF 936 gene polymorphism and VEGF-A levels in the late-term arteriovenous fistula thrombosis in patients undergoing hemodialysis. Int Urol Nephrol 2014;46(9):1815–1823
80 Heine GH, Ulrich C, Sester U, Sester M, Köhler H, Girndt M. Transforming growth factor beta1 genotype polymorphisms determine AV fistula patency in hemodialysis patients. Kidney Int 2003;64(3):1101–1107

81 Lin CC, Yang WC, Lin SJ, et al. Length polymorphism in heme oxygenase-1 is associated with arteriovenous fistula patency in hemodialysis patients. Kidney Int 2006;69(1): 165–172

82 Sener EF, Taheri S, Korkmaz K, et al. Association of TNF-α -308 G > A and ACE I/D gene polymorphisms in hemodialysis patients with arteriovenous fistula thrombosis. Int Urol Nephrol 2014;46(7): 1419–1425

83 Wu JH, Zhang DW, Cheng XL, Shi H, Fan YP. Platelet glycoprotein IIb HPA-3 a/b polymorphism is associated with native arteriovenous fistula thrombosis in chronic hemodialysis patients. Ren Fail 2012; 34(8):960–963