

Vascular Access in Diabetics

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**CONTROVERSIES & UPDATES IN VASCULAR SURGERY JANUARY 19-21 2017
MARRIOTT RIVE GAUCHE & CONFERENCE CENTER PARIS, FRANCE**

Disclosure

Speaker name:

SELCUK BAKTIROGLU...

I have the following potential conflicts of interest to report:

- Consulting
- Employment in industry
- Shareholder in a healthcare company
- Owner of a healthcare company
- Other(s)
- I do not have any potential conflict of interest

AGING POPULATION

- The incident hemodialysis (HD) population is aging
- Currently, the definition of the elderly in the hemodialysis population is described as those >80 years.
- Patients aged 65–74 years and >75 years represent, 22 and 20% of the total prevalent renal replacement therapy population.
- Almost half of 65–74 year-olds have five or more chronic health conditions (comorbidities), and this figure may reach 70 % in patients over 85 years

Fassett RG (2014) Current and emerging treatment options for the elderly patients with chronic kidney disease. *Clin Interv Aging* 9:191–199

Renal replacement therapy in Europe (2015) a summary of the 2012 ERA-EDTA Registry Annual Report. *Clin Kidney J* 8(3):248–261

C Lomonte, G Forneris, M Gallieni et al. The vascular access in the elderly: a position statement of the Vascular Access Working Group of the Italian Society of Nephrology *J Nephrol* (2016) 29:175–184.

Hicks CV, Canner JK, Arhuidese I et al (2015) Mortality benefits of different hemodialysis access type are age dependent. *J Vasc Surg* 61:449–456

Therefore, when we are talking on

VASCULAR ACCESS in DIABETICS,

we must be aware that mostly we are talking on elderly with many comorbidities. And diabetes is only one of them.

Comorbidities should be the main subject **when deciding the VA type in these patients.**

Even before the choice of VA type, the nephrologist faces the dilemma of whether or not to initiate hemodialysis (HD) in elderly patients with important comorbidities and poor functional status.

TJ. Vachharajani, S Moossavi, JR. Jordan, et al. Re-evaluating the Fistula First Initiative in Octogenarians on Hemodialysis *Clin J Am Soc Nephrol* 6: 1663–1667, 2011.

C Lomonte, G Forneris, M Gallieni et al. The vascular access in the elderly: a position statement of the Vascular Access Working Group of the Italian Society of Nephrology *J Nephrol* (2016) 29:175–184

-There are conflicting reports on the effects of diabetes on the outcomes of hemodialysis access procedures.

-While some authors reported deleterious effects of diabetes on vascular access outcomes [1-4], others found no negative effects [5-7], even there are reports of beneficial effects of some lesions frequently seen in diabetic vasculature.

1. Sedlacek M, Teodorescu V, Falk A et al. 2001. Hemodialysis access placement with preoperative noninvasive vascular mapping: Comparison between patients with and without diabetes. *Am J Kidney Dis.*;38(3):560-4.
2. Lin SL, Huang CH, Chen HS et al.1998. Effects of age and diabetes on blood flow rate and primary outcome of newly created hemodialysis arteriovenous fistulas. *Am J Nephrol.* ;18(2): 96-100.
3. Murphy GJ, Nicholson ML. 2002. Autogeneous elbow fistulas: the effect of diabetes mellitus on maturation, patency, and complication rates. *Eur J Vasc Endovasc Surg.*; 23(5):452-457.
4. Lauvao LS, Ihnat DM, Goshima KR, et al. 2009.Vein diameter is the major predictor of fistula maturation. *J Vasc Surg.* 2009;49(6):1499-1504.
5. Adams MB, Majewski JT, Kiselow MC et al. 1986. Diabetic vascular access. *Dial Transplant.*;15(6):307-308.
6. Coentrão L, Biesen WV, Nistor I et al. 2015. Preferred haemodialysis vascular access for diabetic chronic kidney disease patients: a systematic literature review. *J Vasc Access* ;16(4): 259-264.
7. Kalman PG, Pope M, Bhola C et al. 1999. A practical approach to vascular access for hemodialysis and predictors of success. *J Vasc Surg.* 1999;30(4):727-733

- Why is there concern about diabetes and related vascular problems on vascular access procedures?
- What are the differences of diabetic patients and their vasculature from that of nondiabetics?
- Do they have an effect on hemodialysis vascular access outcomes?
- I will try to find answers to these questions in light of the available evidence.

Diabetes and vascular disease

NO; ROS; Endothelial Dysfunction

-Hyperglycemia, insulin resistance, and elevated free fatty acids trigger systemic inflammation and impair nitric oxide (NO) bioavailability, leading to impaired endothelial function.

- Metabolic abnormalities cause overproduction of reactive oxygen species (ROS), leading to endothelial dysfunction.

-Endothelial dysfunction is a pathological state and due to impairment or loss of normal homeostatic properties, a vasospastic, prothrombotic, and proinflammatory atherogenic milieu exists.

Oxidative stress resulting from either the increased production or inadequate removal of (ROS) plays a key role in the pathogenesis of diabetic vascular complications.

Beckman JA, Creager MA. 2016. Vascular Complications of Diabetes. *Circ Res.*;118: 1771-1785

Evans JL, Goldfine ID. 2016. A New Road for Treating the Vascular Complications of Diabetes: So Let's Step on the Gas Diabetes; 65:346-348

Tousoulis D, Papageorgiou N, Androulakis E et al. 2013. Diabetes Mellitus-Associated Vascular Impairment Novel Circulating Biomarkers and Therapeutic Approaches. *J Am Coll Cardiol* ;62:667-76

-Endothelial dysfunction may impair vasodilation and increase the risk for thrombosis and intimal hyperplasia (IH) after AVF creation.

-The intima of the radial artery was found to be 39% thicker in patients with end-stage renal disease, compared to healthy subjects.

Paneni F, Beckman JA, Creager MA, Cosentino F. 2013. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Eur Heart J.* ;34(31); 2436-2443.

Vazquez-Padron RI, Allon M. 2016. New Insights into Dialysis Vascular Access: Impact of Preexisting Arterial and Venous Pathology on AVF and AVG Outcomes *Clin J Am Soc Nephrol* 11: 1495–1503

Johansson M, Myrdal A, Friberg F. 2010. High-resolution ultrasound showing increased intima and media thickness of the radial artery in patients with end-stage renal disease. *Atherosclerosis* Jul;211(1):159-63

Atherosclerosis and arteriosclerosis

- Atherosclerosis and arteriosclerosis are the major causes of cardiovascular disease in end-stage renal disease (ESRD).
- Atherosclerosis is an intimal disease characterized by plaques and occlusive lesions.
- In contrast, arteriosclerosis in ESRD is largely a disease of the medial layer characterized by increased collagen content, calcification, and both hypertrophy and hyperplasia of vascular smooth muscle cells.

- These changes result in increased thickness and stiffness of the arterial wall.
- Arteriosclerosis can be considered the vasculopathy of ESRD.



- Concomitant presence of diabetes mellitus can contribute to these abnormalities through accumulation of inelastic material in the arterial wall (stiffening).

- Arterial calcification develops in two distinct sites: the intima and media layers of the arterial wall.
- These two forms are frequently associated. While media calcification is frequently observed with aging in the general population, it is significantly more pronounced in patients with metabolic disorders, such as metabolic syndrome, diabetes or chronic kidney disease (CKD).
- Typically, media calcification is concentric, and does not extend into arterial lumen. It can easily be seen on plain x-ray as “rail-road track” type linear calcifications .



London GM. 2011 Arterial calcification: cardiovascular function and clinical outcome. *Nefrologia*.;31(6):644-647.

*Wang N, Yang J, Yu X, et al. 2008. Radial artery calcification in endstage renal disease patients is associated with deposition of osteopontin and diminished expression of alpha-smooth muscle actin. *Nephrology (Carlton)*.;13(5):367-375

-Almost one-third of radial arteries in uremic patients had arterial calcification predominantly in the media of the vessel.

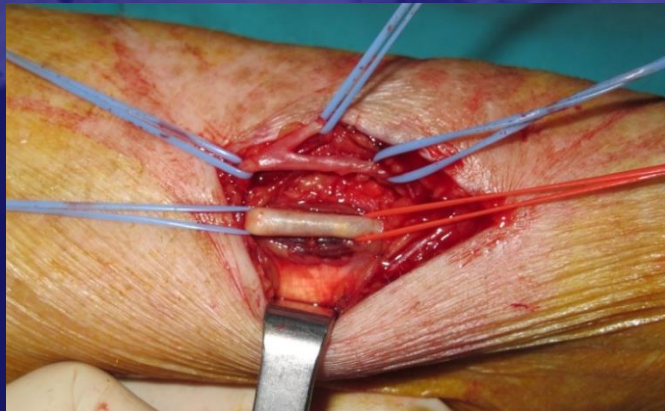
-Although it is expected by many that vascular calcification may influence successful vascular access creation, interestingly, it was found that distensibility and compliance of the radial artery are not reduced in patients with Type 2 diabetes mellitus.



Wang N, Yang J, Yu X, et al. 2008. Radial artery calcification in endstage renal disease patients is associated with deposition of osteopontin and diminished expression of alpha-smooth muscle actin. *Nephrology (Carlton)*.;13(5):367-375.
Catalano M, Scandale G, Minola M, et al. 2009. Elastic properties and structure of the radial artery in patients with type 2 diabetes. *Diab Vasc Dis Res*.;6(4):244-248

Effects of preexisting vascular pathology on vascular access outcomes

- There are conflicting and controversial reports on the effects of preexisting vascular problems due to diabetes and CKD on the outcomes of hemodialysis access procedures.
- Johansson et al. showed in their study with ultrasound biomicroscopy, patients with end-stage renal disease showed 39% thicker intima and 18% greater media in the radial artery compared to healthy subjects.



Johansson M, Myredal A, Friberg F. 2010. High-resolution ultrasound showing increased intima and media thickness of the radial artery in patients with end-stage renal disease. *Atherosclerosis* Jul;211(1):159-63₁₄

-Fistula failure was observed only in patients with preexisting intimal hyperplasia (IH) of radial artery in Kim et al. study. The incidence of diabetes mellitus was higher in patients with IH (60.0% vs. 28.6%).

-On the contrary, Allon et al found that none of the preexisting pathologies like medial fibrosis and calcification, arterial and venous intima thickening, were significantly associated with unassisted primary arteriovenous graft (AVG) survival, and all the trends favored longer unassisted primary AVG survival in patients with preexisting vascular abnormalities.

Diabetes was present in 59% of their study population.

Kim YO, Song HC, Yoon SA, et al. 2003. Preexisting intimal hyperplasia of radial artery is associated with early failure of radiocephalic arteriovenous fistula in hemodialysis patients. *Am J Kidney Dis.*;41(2):422-428.

Allon M, Litovsky S, Young CJ, et al. 2013. Correlation of pre-existing vascular pathology with arteriovenous graft outcomes in hemodialysis patients. *Am J Kidney Dis.* ;62(6):1122-1129.

- Arterial microcalcification (AMiC) of the vascular access was found a predictor for cardiovascular mortality (HR: 2.35).
- Diabetes (OR:16.49) was the only independent risk factor for (AMiC).
- Same group found greater AVF failure rate in 1 year in the (AMiC) group (53.5% vs. 31.0%)
- In another study, the frequency of AVF nonmaturation was found similar between patients with or without preexisting arterial microcalcification
- They also found only diabetes predicted arterial microcalcification ($p < 0.001$).

Yun YS, Choi SJ, Lee JY et al. 2014. Impact of arterial microcalcification of the vascular access on cardiovascular mortality in hemodialysis patients. *Hemodial Int* 18: 54–61

Choi SJ, Yoon HE, Kim YS et al. 2015. Pre-existing Arterial Micro-Calcification Predicts Primary Unassisted Arteriovenous Fistula Failure in Incident Hemodialysis Patients. *Semin Dial.* Nov-Dec;28(6):665-9

Allon M, Robbin ML, Umphrey HR, et al. 2015. Preoperative arterial microcalcification and clinical outcomes of arteriovenous fistulas for hemodialysis. *Am J Kidney Dis.*;66(1):84-90

Macrocalcification of the Arteries

- Macro calcification seen on x-ray examination, was found associated with worse late clinical outcomes and worse survival of native arteriovenous hemodialysis fistulas.
- On the contrary, in another study distensibility and compliance of the radial artery are found not reduced in patients with type 2 diabetes mellitus.

Jankovic A, Damjanovic T, Djuric Z et al. 2015. Impact of Vascular Calcifications on Arteriovenous Fistula Survival in Hemodialysis Patients: A Five-Year Follow-Up *Nephron* ;129:247-252

Georgiadis GS, Georgakarakos EI, Antoniou GA, et al. 2014. Correlation of pre-existing radial artery macrocalcifications with late patency of primary radiocephalic fistulas in diabetic hemodialysis patients. *J Vasc Surg.*;60(2):462-470.

Catalano M, Scandale G, Minola M, et al. 2009. Elastic properties and structure of the radial artery in patients with type 2 diabetes. *Diab Vasc Dis Res.*;6(4):244-248.

MEDIAL FIBROSIS

-Arterial medial fibrosis is associated with older age and diabetes. Increased vascular stiffness caused by medial fibrosis has been proposed as a limiting factor for arterial dilation and AVF maturation.

-Kheda et al. found that low arterial elasticity is associated with stenosis and fistula maturation failure.

-Paulson also, concluded that poor elasticity is an important step in the cascade of events that leads to maturation failure and, vessel elasticity (stiffness) affects fistula maturation.

Vazquez-Padron RI, Allon M. 2016. New Insights into Dialysis Vascular Access: Impact of Preexisting Arterial and Venous Pathology on AVF and AVG Outcomes Clin J Am Soc Nephrol 11: 1495–1503

Kheda MF, Brenner LE, Patel MJ, et al. 2010. Influence of arterial elasticity and vessel dilatation on arteriovenous fistula maturation: a prospective cohort study. Nephrol Dial Transplant.; 25(2):525-531

Cameron JD, Cruickshank JK. 2007. Glucose, insulin, diabetes and mechanisms of arterial dysfunction. Clin Exp Pharmacol Physiol.;34(7):677-682

- On the contrary, Allon et al. found no association between preexisting arterial medial fibrosis and AVF nonmaturation.
- In their recent prospective study with patients undergoing arteriovenous fistula creation, Shiu et al. found preoperative arterial medial fibrosis was associated with greater 6-week arteriovenous fistula diameter and blood flow and a lower risk of clinical arteriovenous fistula nonmaturation.
- They concluded, this unexpected finding suggests that medial fibrosis promotes arteriovenous fistula development by yet undefined mechanisms.

Allon M, Litovsky S, Young CJ, et al. 2011. Medial fibrosis,vascular calcification, intimal hyperplasia, and arteriovenous fistula maturation. *Am J Kidney Dis.*;58(3):437-443.

Shiu YT,Litovsky SH, Cheung AK et al. 2016. Preoperative Vascular Medial Fibrosis and Arteriovenous Fistula Development. *Clin J Am Soc Nephrol.* 7;11(9):1615-23

-Recently, patients enrolled in the Hemodialysis Fistula Maturation Study underwent preoperative vascular function tests:

-Although, stiffness of the artery used for AVF creation expected to restrict arterial outward remodeling, in this study no relationship between stiffness and restriction of arterial outward remodeling was found.

Allon M, Green T, Dember LM et al. Hemodialysis Fistula Maturation Study Group. 2016. Association between Preoperative Vascular Function and Postoperative Arteriovenous Fistula Development. *J Am Soc Nephrol.* 27(12): 3788-3795

Hemodialysis Fistula Maturation (HFM) Study Group found 5.3% early thrombosis (ET) cases among 602 participants;

ET risk was surprisingly lower in diabetics (OR: 0.19).

Stiff, noncompliant feeding arteries paradoxically were associated with a lower frequency of ET.

Surgeon factor and technical details in creating vascular access in calcified vessels

- There are different outcomes with the same patient characteristics among different centers and surgeons.
- Surgical skill, experience, careful patient selection, and preoperative evaluation of vascular anatomy by careful physical and ultrasound examination are all very important.
- Arterial and venous anatomy of the upper extremity may have significant amount of variations and these may affect AVF constructions and outcomes.
- During surgical exploration unexpected anatomical variations may still be found.

-Surgeon's intraoperative perceptions were found to be associated with early thrombosis of the vascular access.

-Surgeons' greater concern about maturation success was associated with higher thrombosis risk (OR, 8.09), as were absence vs presence of intraoperative thrill (OR, 21.0) and surgeons' reported frustration during surgery (OR, 6.85).

With this knowledge in mind, one can begin construction of avf as distally as possible (If there is no important contraindication).

The surgeon can decide intraoperatively, if he/she should continue on performing the anastomosis after seeing and palpating the vessels.

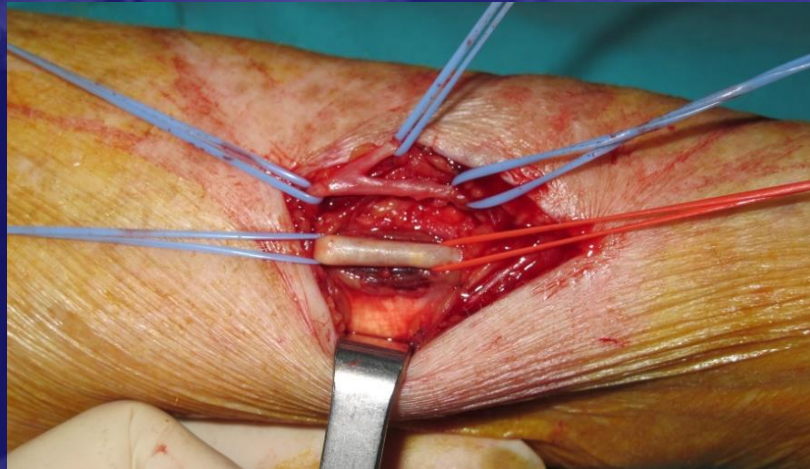
Or ,in case he/she is not satisfied with the result after the anastomosis is already done, may decide to go up to the elbow region,



Conclusions

- Diabetic vasculature, especially in patients with ESRD, has some specific problems, the most important of which seem to be the calcification and stiffening of the arteries.
- Although some authors report inferior outcomes of vascular access procedures in diabetics, others found no negative effects, even there are reports of beneficial effects of some lesions frequently seen in diabetic vasculature.
- Because most patients are elderly with many comorbidities, decision making should be based on individual life expectancy, functional status, and patient preferences, keeping in mind the best access is a distal avf.
- There is also evidence that most of the problems encountered can be dealt with multidisciplinary work, careful patient selection, surgical skill and experience.

THANK YOU FOR YOUR
ATTENTION



Diabetes and vascular disease

- Patients with diabetes are at heightened risk of adverse microvascular and cardiovascular events.
- Once cardiovascular disease develops, diabetes mellitus exacerbates progression and worsens outcomes.
- Diabetic vascular complications occur with a significantly greater frequency in hyperglycemic individuals with diabetes when compared with those with controlled diabetes .

Beckman JA, Creager MA. 2016. Vascular Complications of Diabetes. *Circ Res.*;118: 1771-1785

Evans JL, Goldfine ID. 2016. A New Road for Treating the Vascular Complications of Diabetes: So Let's Step on the Gas Diabetes; 65:346–348

Tousoulis D, Papageorgiou N, Androulakis E et al. 2013. Diabetes Mellitus-Associated Vascular Impairment Novel Circulating Biomarkers and Therapeutic Approaches. *J Am Coll Cardiol* ;62:667–76

Presence of vascular access calcification (VAC) significantly increases the risk for death (HR: 2.14) and, diabetic patients has a 3.43-fold risk for VAC compared with nondiabetic patients.



Schlieper G, Kruge T, Djuric Z et al. 2008. Vascular access calcification predicts mortality in hemodialysis patients *Kidney International* 74, 1582–1587