A novel factor for primary arteriovenous fistula failure: hyperinsulinism

Davut Akin, Sehmus Ozmen and Ramazan Kaya

ABSTRACT

Introduction: Dysfunction of vascular access is an important reason of morbidity for dialysis patients and it is a major factor affecting the economical burden of hemodialysis. The preferred type of vascular access is creation of an arteriovenous fistula (AVF). However, the problem of fistula maturation rate is still a challenge. Herein, we tried to search the role of hyperinsulinism and insulin resistance as a new predictor of primary AVF failure (pAVFF) that may be a cause of intimal damage.

Methods: We included 119 patients (73 male and 46 female) with a diagnosis of end-stage renal disease (ESRD) who had undergone an AVF operation by a vascular surgeon. The AVF was examined for presence of thrill on the first postoperative day. A successful cannulation with two fistula needles with a blood flow of 250 mL/min for at least one complete dialysis session, after 4 weeks of AVF surgery was defined as functioning access. Insulin resistance in our patients was determined by the standard homeostasis model assessment (homa-IR). A logistic-regression analysis was performed to investigate the independent factors related with pAVFF.

Findings: Detection of pAVFF occurred in 27 (22.7%) patients. The presence of thrill, amount of daily proteinuria, insulin levels, homa-IR, and serum albumin levels were found to be significantly different between patients with fistula failure and those without pAVFF. The logistic-regression analysis of preoperative factors revealed the following OR (odds ratio) and 95% CI values: homa-IR 1.205 (1.063–1.366) (p = 0.004), serum albumin 0.398 (0.178–0.892) (p = 0.025), and the amount of daily proteinuria 1.307 (1.012–1.688) (p = 0.041). Even after addition of the presence of postoperative thrill on AVF, which was a postoperative strong clinical factor to the analysis, mean homa-IR and mean serum albumin continued to be independent predictors of pAVFF.

Discussion: Insulin resistance or hyperinsulinism may be a significant cause of pAVFF, which emphasizes the role of endothelium in fistula dysfunction.

Introduction

Dysfunction of vascular access is an important reason of morbidity for dialysis patients and it is a major factor affecting the economical burden of hemodialysis. The preferred type of vascular access is creation of an arteriovenous fistula (AVF). However, the problem of fistula maturation rate is still a challenge. The risk of access failure differs among individuals; vascular anatomy is not the sole factor in a significant number of patients. Many other risk factors of fistula dysfunction include hypertension, presence of diabetes mellitus, hypoalbuminemia, antithrombin III deficiency, increased serum levels of lipoprotein. A significant proportion of vascular access dysfunction cases, however, have been still unexplained. This suggests that there are additional predisposing factors that are still undiscovered.

We may propose hyperinsulinism as a risk factor for vascular access dysfunction by the way of its damage to the endothelium. Endothelial dysfunction may lead to vascular access dysfunction by the different mechanisms. Insulin-like growth factor-1 (IGF-1) and transforming-growth factor-B are growth factors with local activity which may play a role in the development of intimal hyperplasia. The stenosis of AVF can thus be accepted as a model of accelerated vascular atherogenesis. IGF-1 has a role in many vasculopathies, such as hypertension, atherosclerosis, angiogenesis, vascular restenosis, and diabetic vasculopathy. In failing AVF of hemodialysis patients, IGF-1 and IGF-binding proteins-1 immunoreactivity in the neointimal and the medial layers have been demonstrated. The major problem with AVF is the high rate of primary failure, which may be due to early thrombotic event and/or maturation arrest. AVF endothelium is activated by the surgery and exhibits augmented permeability, offering a targeting mechanism for retention in pathological endothelium.
High plasma levels of factor VII, von Willebrand's factor, D-dimer, fibrinogen, thrombin-ATIII complex, and plasma activator inhibitor type 1 have been demonstrated in patients with ESRD and endothelial damage. In addition, these patients often have low predialysis values of protein C, a natural coagulation inhibitor whose deficiency is related with a high risk of venous thrombotic events.7–10

Herein, we tried to search the role of hyperinsulinism and insulin resistance as a new predictor of primary AVF failure that may be a cause of intimal damage.

Methods

We included 119 patients (73 male and 46 female) with a diagnosis of end-stage renal disease (ESRD) who had undergone an AVF operation by a vascular surgeon. The etiology of ESRD was hypertension (n = 47 subjects), diabetes mellitus (n = 29), urologic disorders (n = 13), glomerular disease (n = 8), unknown (n = 14), and others (n = 8). The patients older than 18 years, enclosing Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease 2012 Guidelines11 kidney disease definitions, were enrolled into the study. Preliminary results were presented at the World Congress of Nephrology 2009, in Milan, Italy. The AVF was examined for presence of thrill on the first postoperative day. A successful cannulation with two fistula needles with a blood flow of 250 mL/min for at least one complete dialysis session, after 4 weeks of AVF surgery was defined as functioning access. We used turbidimetric assay with benzethonium chloride to determine proteinuria in urine collected after 24 h by an Abbots Aeroset Analyzer (Toshiba, Tochigi-Ken, Japan).

Insulin resistance in our patients was determined by the standard homeostasis model assessment (homa-IR): homa-IR = fasting insulin [mU/L] × fasting glucose [mg/dL]/405.

The patients under age of 18 years, with previous fistula creation, and those on any kind of insulin treatment were not included.

Statistical analysis

All results were expressed as means ± SD and p values < 0.05 were considered statistically significant. Student's t-test was used for comparison of parametric values of groups and chi-square for frequencies. A logistic-regression analysis was performed to investigate the independent factors related with pAVFF. The factors found to be significantly different between patients with and without pAVFF were included in logistic regression analysis.

Findings

Primary AVF was detected in 27 (22.7%) of the patients. The significantly different parameters between patients with and without pAVFF are demonstrated in Table 1. The other parameters (serum hemoglobin, urea, creatinine, calcium, phosphorus, age, sex, DM, HT, BMI, PTH, and presence of catheters) were similar (Table 2).

The logistic regression analysis of preoperative parameters revealed the following OR and 95% CI values: homa-IR 1.205 (1.063–1.366) (p = 0.004), serum albumin 0.398 (0.178–0.892) (p = 0.025), and daily proteinuria 1.307 (1.012–1.688) (p = 0.041). When the presence of postoperative thrill on AVF, which was a postoperative strong clinical factor, was added to analysis, homa-IR and serum albumin remained as an independent predictor of pAVFF.

### Table 1. Comparison parameters between with and without pAVFF.

| Parameter                          | pAVFFa present (n: 27) | pAVFFa absent (n: 92) | p Value |
|------------------------------------|------------------------|-----------------------|---------|
| Postoperative thrill (%)           | 33.3                   | 83.7                  | <0.0001 |
| Daily proteinuria (g/d)            | 3.0 ± 2.4              | 1.5 ± 1.7             | 0.001   |
| Insulin (μU/mL)                    | 22.7 ± 19.9            | 11.7 ± 9.2            | <0.0001 |
| Homa-IRb                           | 6.1 ± 5.3              | 3.2 ± 2.7             | <0.0001 |
| Serum albumin (mg/dL)              | 2.7 ± 0.9              | 3.2 ± 0.7             | 0.004   |
| BMI (kg/m²)c                       | 24.4 ± 5.3             | 23.9 ± 5.4            | ns      |

Note: aPAVFF: primary arteriovenous fistula failure.

bHoma-IR: insulin resistance was evaluated by homeostasis model assessment.

### Table 2. Comparison of other parameters between with and without pAVFF.

| Parameter                          | pAVFFa present (n: 27) | pAVFFa absent (n: 92) | p Value |
|------------------------------------|------------------------|-----------------------|---------|
| Age                                | 54.48 ± 18             | 57.10 ± 17            | nsb     |
| Female/male                        | 12/15                  | 34/58                 | nsb     |
| Urea (mg/dL)                       | 198.85 ± 76            | 200.83 ± 78           | nsb     |
| Creatinine (mg/dL)                 | 7.12 ± 3.2             | 7.53 ± 3.0            | nsb     |
| Presence of DM                     | 9/27                   | 20/92                 | ns      |
| Presence of HT                     | 14/27                  | 60/92                 | ns      |
| BMF (kg/m²)                        | 24.4 ± 5.3             | 23.9 ± 4.4            | ns      |
| Glucose (mg/dL)                    | 107 ± 41               | 108 ± 36              | ns      |
| Total cholesterol (mg/dL)          | 167 ± 56               | 155 ± 47              | ns      |
| HDL cholesterol (mg/dL)            | 30.5 ± 11.6            | 33.6 ± 11.9           | ns      |
| LDL cholesterol (mg/dL)            | 100 ± 41               | 93 ± 38               | ns      |
| TG (mg/dL)                         | 183 ± 159              | 144 ± 90              | ns      |
| Hemoglobin (g/dL)                  | 9.63 ± 1.3             | 9.78 ± 1.8            | nsb     |
| PTH (pg/mL)                        | 339.62 ± 187.76        | 309.91 ± 206.56       | nsb     |
| Calcium (mg/dL)                    | 7.8 ± 1.1              | 9.5 ± 1.9             | ns      |
| Phosphorus (mg/dL)                 | 5.641 ± 1.53           | 5.210 ± 1.45          | ns      |
| Presence of catheter               | 22/27                  | 64/92                 | nsb     |

Note: aPAVFF: primary arteriovenous fistula failure.
bns: non-significant.
Discussion

To date, the risk factors of pAVFF include hypotension, diabetes mellitus, hypoalbuminemia, presence of anti-cardiolipin antibodies, increased concentrations of lipoprotein(a), and fibronectin.\textsuperscript{2,12} However, the role of hyperinsulinism or insulin resistance, which is important in intimal hyperplasia or injury, has not been investigated.

Insulin resistance results in increased cardiovascular events by metabolic vasculopathy and may lead to increased inflammation, endothelial damage, dyslipidemia, and hypercoagulability that can influence the cardiovascular diseases (CVD) risk.\textsuperscript{13} We found hyperinsulinism or insulin resistance as an independent predictor of pAVFF.

Endothelial dysfunction is proposed as the mechanism linking proteinuria and atherosclerosis. It is an early event in atherogenesis process and may accelerate atherosclerotic plaque formation.\textsuperscript{14} We found that the amount of daily proteinuria, serum insulin levels, and homa-IR values were significantly higher in the pAVFF group than non-pAVFF group. However, serum albumin levels were lower in the pAVFF group than they were in those without pAVFF.

Stracke’s study demonstrated that IGF-1 is a growth factor that binds to its receptor on many cell types. IGF-1 receptors are shown on both vascular smooth muscle cells and endothelial cells. IGF-1 plays a role in many vasculopathies including diabetic vascular disease, atherosclerosis, hypertension, restenosis, and angiogenesis. Vascular smooth muscle cells and macrophages and lymphocytes within the stenotic lesions of fistulas in hemodialysis patients are found to be the sources of IGF-related peptides in this study.\textsuperscript{4}

In addition, insulin resistance assessed by homa has been demonstrated to be an independent predictive factor for CVD, a unit increase in insulin resistance is found to be related with a 5.4% increase in CVD risk.\textsuperscript{2} The Study of Inherited Risk of Coronary Atherosclerosis (SIRCA) reported the homa-IR index as the independent predictor of coronary artery calcification.\textsuperscript{15,16}

This study demonstrated for the first time a relationship between homa-IR and primary AVF failure in patients’ chronic kidney disease. This relationship is independent of conventional cardiovascular risk factors, parameters of renal failure, and even the postoperative factor such as presence of a thrill. In this study, we showed the influence of hyperinsulinemia primary AVF maturation. Hyperinsulinemia by elevated levels of growth factors that may enhance VSMC and endothelial cells may be the contributing factor to the development of neointimal hyperplasia. This idea warrants further studies investigating the vascular tissue of pAVFF.

Conclusion

To our knowledge, this is the first study that has investigated the role of hyperinsulinism in pAVFF. Our study indicates that hyperinsulinism or insulin resistance may be metabolic reasons for pAVFF, which emphasizes the role of endothelium. We also found that hypoalbuminemia is an undetermined significant risk factor of pAVFF.

Disclosure statement

The authors report no conflicts of interest.

References

1. Porile JL, Richter M. Preservation of vascular access. J Am Soc Nephrol. 1993;4:997–1003.
2. Goldwasser P, Avram MM, Collier JT, Michel MA, Gusik SA, Mittman N. Correlates of vascular access occlusion in hemodialysis. Am J Kidney Dis. 1994;24:785–794.
3. Windus DW, Jendrisak MD, Delmez JA. Prosthetic fistula survival and complications in hemodialysis patients: Effects of diabetes and age. Am J Kidney Dis. 1992;19:448–452.
4. Stracke S, Konner K, Köstlin I, et al. Over-expression of IGF-related peptides in stones of native arteriovenous fistulas in hemodialysis patients. Growth Horm IGF Res. 2007;17:297–306.
5. 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;64:1101–1107.
6. Delafontaine P, Song YH, Li Y. Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels. Arterioscler Thromb Vasc Biol. 2004;24:435–444.
7. Vaziri ND, Gonzales EC, Wang J, Said S. Blood coagulation, fibrinolytic, and inhibitory proteins in end-stage renal disease: Effect of hemodialysis. Am J Kidney Dis. 1994;23:828–835.
8. Sagripanti A, Cupisti A, Baicchi U, Ferdeghini M, Morelli E, Barsotti G. Plasma parameters of the prothrombotic state in chronic uremia. Nephron. 1993;63:273–278.
9. Griss JC, Branger B, Vécina F, al Sabadani B, Fourcade J, Schved JF. Increased cardiovascular risk factors and features of endothelial activation and dysfunction in dialyzed uremic patients. Kidney Int. 1994;46:807–813.
10. Lai KN, Yin JA, Yuen PM, Li PK. Effect of hemodialysis on protein C, protein S, and antithrombin III levels. Am J Kidney Dis. 1991;17:38–42.
11. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.
12. Goldwasser P, Michel MA, Collier J, et al. Prealbumin and lipoprotein(a) in hemodialysis: Relationships with
patient and vascular access survival. Am J Kidney Dis. 1993;22:215–225.

13. Stocker R, Keaney JF Jr. Role of oxidative modifications in atherosclerosis. Physiol Rev. 2004;84:1381–1478.

14. Reddy KJ, Singh M, Bangit JR, Batsell RR. The role of insulin resistance in the pathogenesis of atherosclerotic cardiovascular disease: An updated review. J Cardiovasc Med (Hagerstown). 2010;11:633–647.

15. Banerjee D, Recio-Mayoral A, Chitalia N, Kaski JC. Insulin resistance, inflammation, and vascular disease in nondiabetic predialysis chronic kidney disease patients. Clin Cardiol. 2011;34:360–365.

16. Qasim A, Mehta NN, Tadesse MG, et al. Adipokines, insulin resistance, and coronary artery calcification. J Am Coll Cardiol. 2008;52:231–236.