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ARTIFICIAL NEURAL NETWORK BASIS FOR LONG-TERM VIABILITY PREDICTION OF VASCULAR ACCESS IN HEMODIALYSED POPULATION

Abstract. *The important number of end-stage renal disease population and subsequently, the modality of performing an optimal vascular access adequate for dialysis represent important healthcare problems that are on continuous debate. Additionally, considering that only half of the newly created arteriovenous fistula are well-developed and even a smaller number is free of related complications, there is an increased interest in achieving a suitable vascular access. Therefore, the aim of the present study was to create a computational model to monitor hemodialysed patients and to predict arteriovenous fistula evolution. The research included 52 newly initiated hemodialysed patients on central venous catheter or arteriovenous fistula, followed along 1 year. The statistically analyzed data and also the described artificial neural models related to this particular category of individuals emphasized a correlation between various bioumoral factors, such as hemoglobin, creatinine, urea, uric acid, serum albumin, erythrocytes sedimentation rate, serum iron, and the future growth rate of the vein diameter, implicated in creating a patency fistula. Although the findings were promising, more complex researches are needed in the future designed to take into account several other aspects related to the underlying pathology or to the dialysis procedure itself and to study a larger number of hemodialysis patients to be followed for a longer period long.*

Key words: *end-stage renal disease, vascular access, hemodialysis, artificial neural network, prognosis.*

JEL Classification: I14, O15

1. Introduction

It is generally known that the increase of end-stage renal disease (ESRD) population and subsequently, the modality of performing vascular access (adequate for the dialysis therapy and free of related complications) represent important healthcare problems that are on continuous debate (**Bode et al (2011); Himmelfarb (2007); Lysaght (2002)**). Additionally, recent data reported that 24 months after the surgery only in 50% or less of the cases, well-developed arteriovenous fistulae were identified (**Caroli et al (2013); Field et al (2008); Fokou et al (2012); Huijbregts et al (2008)**); considering the multitude of kidney disease patients requiring renal replacement therapy (RRT), these results are not satisfactory.

An optimal vascular access for an adequate long-term hemodialysis (HD) requires several specific conditions that enhance the patency rate of the arteriovenous fistula (AVF) and improve the overall prognosis. As **Antiga et al (2009)** emphasized, once AVF is created, and mainly due to the increase of the blood flow in the newly developed fistula, a remodeling of the involved vessels structure is noticed associated with a decrease of the wall resistance. Consequently, these features induce a further increase of the blood stream rate and resistance drop-off, allowing a flow rate above 600 mL/min in a well-developed fistula (**Konner et al (2003); Wedgewood et al (1984)**). Nevertheless, the newly created fistula associated with decreased wall resistance and high blood flow can lead to several disorders: an inefficient peripheral vascularization in the distal limb and left ventricular hypertrophy development (**Bode et al (2011); MacRae (2006); Tordoir et al (2004)**).

Furthermore, according to **Valdivia et al (2013)** and **Jofré et al (2006)**, there are several prognostic factors (*e.g.*: severe anemia and malnutrition, uncontrolled hypertension, important inflammatory state) that are strongly correlated with vascular access failure and also with dialysed patients over-all poor outcome. Additionally, **Anees & Ibrahim (2009)** observed that decreased hemoglobin and albumin values at the moment of HD initiation, significantly elevate the mortality risk.

"Is this enough to comprehend the magnitude of the inner processes involved in creating an ideal arteriovenous fistula without complications?" still remains a matter of debate. Therefore, the aim of the study was to create a computational model to monitor hemodialysed patients (by a thoroughly assessment of various bioumoral parameters including duplex ultrasound of vascular capital before and after AVF creation), and to anticipate and define the individuals presenting high risk probability in developing vascular access complications with direct impact on their future prognosis.

2. Related work

Methods and Materials

A 1-year prospective clinical study (July 2014 – June 2015) was conducted, including a cohort of hemodialysed patients who initiated dialysis on native AVF or central venous catheter (CVC) in the Department of Nephrology and Dialysis. The following exclusion criteria were considered: acute kidney failure, neoplasia, immunological disorder, active chronic hepatic diseases, significant anemia (Hb < 8 g/dL) or malnutrition (serum albumin < 2.5 g/dL), BMI (body mass index) < 18.5, severe cardiovascular morbidity (heart failure NYHA class IV, arrhythmias, uncontrolled hypertension, recent myocardial infarction or stroke), recurrent infections episodes and the development of vascular access early complications in a 3 months

period since the HD initiation. Graft AVF were also excluded, because patients requiring prosthetic vascular access presented a poor clinical and bioumoral status.

At the beginning, 57 patients were considered suitable for the research, but considering also the 3 months period free of any complications, 5 subjects were excluded (4 cases of recurrent infections episodes due to CVC and 1 patient with AVF thrombosis).

All the patients considered for the study underwent predialysis laboratory investigations (*e.g.*: hemoglobin, white blood cells, serum creatinine, urea, albumin and protein, calcium, hepatic enzymes, erythrocytes sedimentation rate – ESR, fibrinogen, sodium, potassium, uric acid, serum iron, diuresis, interdialitic gained weight, Kt/V) and imaging laboratory tests – Doppler ultrasound of the vascular capital and echocardiography which revealed a normal ejection fraction (EF > 50%) and no signs of left ventricular hypertrophy or vascular calcifications. Before the fistulae were created, tourniquet test was performed in all patients that started HD on CVC, showing a good response of the elected veins for anastomosis.

In addition, the 52 patients followed the same dialysis protocol:

- sessions of 4 hours, 3 times per week;
- high flux dialysis with a blood flow of at least 350 mL/min;
- other technical data: polysulfone membranes with an effective surface of 1.8 m^2, conductivity = 138 mmol/L, standard bicarbonate = 35 mmol/L, t^o = 36^{o}C;
- dialysis solution type *Infosol A 201,5* with the following biochemical composition: glucose = 0, Na = 138 mmol/L, K = 2 mmol/L, Ca = 1.5 mmol/L, Mg = 0.5 mmol/L, osmolarity = 286 mOsm/L;
- bolus administration of low molecular weight anticoagulant (3500 IU) at the beginning of each dialysis session;
- administration of erythropoietin stimulating agents (ESA) (5000 IU of epoetin beta every 2 weeks), iron supplementation 1 dose every week (a 5 mL ampoule contains 100 mg iron(III)-hydroxide sucrose complex) and 0.5 µg/day alfacalcidol (Alpha D_3).

Initially, the included individuals were grouped in diabetics and non-diabetics, but because of the small proportion of patients with diabetes mellitus – *n= 10* (considered statistically insignificant), a native AVF and respectively, a CVC group were formed with an equal patients' distribution.

The results were statistically analyzed and also introduced in a special computerized predictive program (artificial neural network – ANN) able to generate a viable model of future evaluation. ANN, based on the biological neural structure, perform 'reasoning tasks': the data are introduce in the input nodes, processed and then the output nodes produce the results (**Stancu & Constantin (2014)**). In other words, ANN represents a more reliable and advanced statistical method, being able to repeat the processes up to thousands of times until the target value is obtained (**Stancu &**

Constantin (2014)). The accuracy of the technique depends on several aspects: the training data sets must be correct and should be significant for the studied group, and the variables should be correlated with the outcome (**Stancu & Constantin (2014); Geddes et al (1998)**)

Statistical analysis

The findings were analyzed using Two Way ANOVA, a procedure that allows to analyze the relationship between several variables (irrespective if categorical type or factors are present) and a dependent parameter quantitatively expressed. This technique tests different hypothesis underlining the effects of the monitored variables: globally, separately (principal effect) and cumulatively. In addition, the impact of these effects is calculated using η^2 coefficient (a value > 0.500 correlates with an important level of interaction). A significant level below 0.05 ($\alpha < 0.05$) was considered statistically meaningful. The data were analyzed using Excel and IBM SPSS Statistics v. 20.

Results

At the end of the research, the assessed information highlighted the following characteristics (Table 1):

Table 1. Specific characteristics of the included HD patients

N = 52	**Characteristics**
An equal distribution of patients starting dialysis on native AVF and CVC	
Type of fistulae of the patients starting HD directly on AVF	7.69% radiocephalic
	15.38% brachiobasilic
	76.92% brachiocephalic
Type of created fistula after initiating HD on CVC	22 brachiocephalic
	4 radiocephalic
Mean age (years)	68.82
Gender	40.38% female patients
	59.62% male patients
BMI – mean value	24.5
Height – mean value (cm)	168.5
Weight – mean value (kg)	69.56
Diabetes mellitus	7.69% cases initiating HD directly on preexistent brachiobasilic AVF
	30.77% cases starting HD on CVC
Cephalic vein diameter at the end of the study – mean value (mm)	6.69
Basilic vein diameter at the end of the study – mean value (mm)	6.92

After performing Two Way ANOVA analysis, statistically significant differences between AVF and CVC group were noticed regarding the value of some bioumoral parameters that certified the fact that the patients initiated on CVC had a poorer clinical condition – $p < 0.001$, highlighting the importance of the modality of HD initiation (Table 2). Furthermore, at the end of the study, in both groups, the correction of malnutrition, inflammation, potassium, iron and calcium deficiency, and acidosis was noticed ($\eta^2 < 0.500$), emphasizing the need for an adequate dialysis dose and active medical management.

Table 2. The correlation between bioumoral variables and the modality of HD initiation (η^2 values)

	Corrected model	Global effect (Moment)	Principal effect (AVF, CVC)	Cumulative effect (Moment x group)
Hb	0.936	0.915	0.609	0.700
Albumin	0.992	0.992	**0.304**	**0.198**
ESR	0.998	0.998	**0.287**	**0.162**
K^+	0.877	0.838	**0.435**	0.543
Ca^{2+}	0.965	0.958	0.807	**0.160**
HCO_3^-	1	1	0.934	**0.167**
Iron	0.993	0.993	0.760	**0.310**
Creatinine	0.998	0.998	0.985	0.992
Urea	1	1	1	1
Uric acid	0.992	0.989	0.931	0.953

Legend: HD = hemodialysis; Hb = hemoglobin; ESR = erythrocytes sedimentation rate; K^+ = serum potassium; Ca^{2+} = serum calcium; HCO_3^- = bicarbonate; AVF = arteriovenous fistula; CVC= central venous catheter.

When diuresis effect on dialysed subjects' evolution was analyzed no statistically differences between the moments of evaluation were noticed – $p = 0.025$, $\eta^2 = 0.148$, highlighting the fact that the patients preserved their initial residual diuresis on the entire 1-year study. In contrast, the cumulative effect was significant, proving one more time the importance of the timing of RRT initiation ($p < 0.001$, $\eta^2 = 0.998$). Additionally, regarding interdialytic weight gain, no statistically differences between the three moments (initial, 6-months and 12-months, respectively) was observed ($p = 0.034$, $\eta^2 = 0.123$), emphasizing that the studied HD individuals were extremely compliant to the medical advices.

At 12-months, some variable levels were close, but a statistical difference between them was observed, emphasizing that HD initiation on CVC may have a negative influence on the future prognosis – $p < 0.001$ (Figure 1).

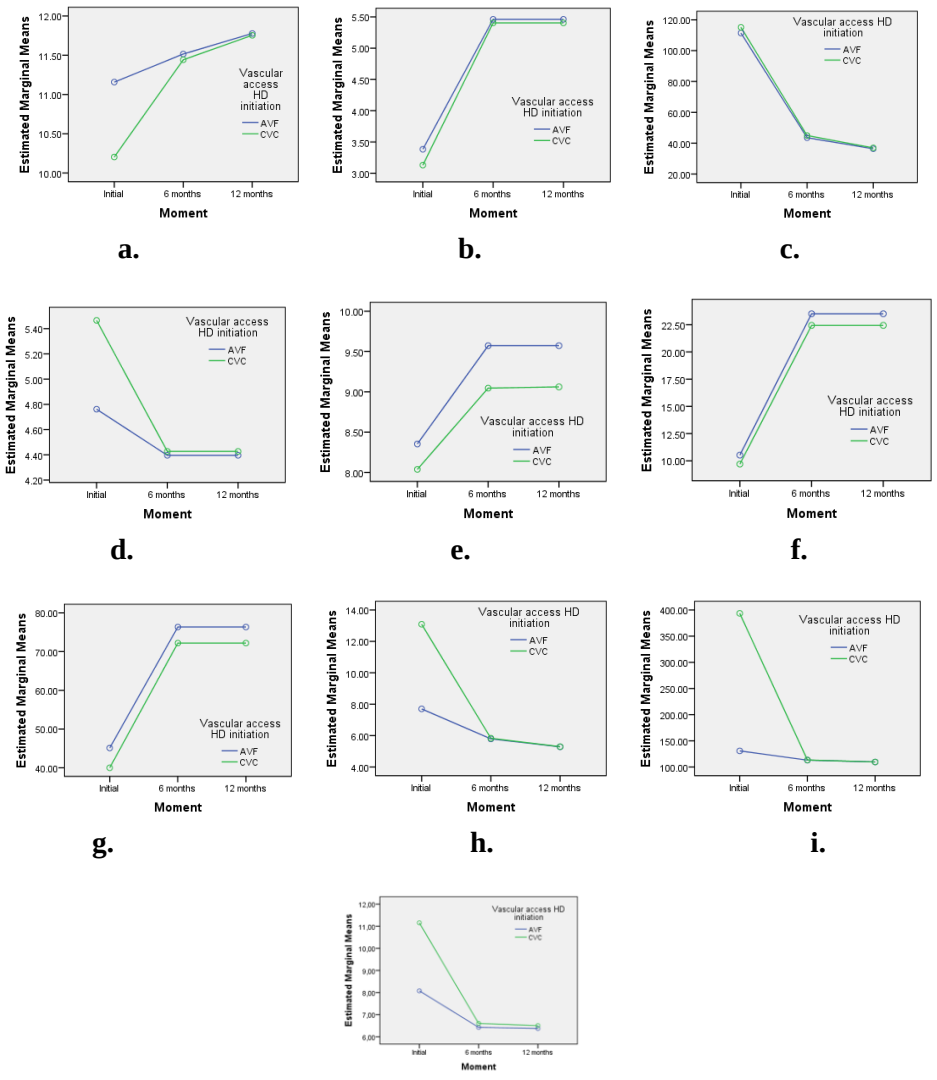

Figure 1. Bioumoral variables evolution depending on the modality of RRT initiation (a. hemoglobin; b. serum albumin; c. ESR; d. serum potassium; e. serum calcium; f. bicarbonate; g. serum iron; h. serum creatinine; i. urea; j. uric acid)

When correlating the increase of AVF growth (cephalic vein above 6 mm) with the correction of anemia, malnutrition, acidosis, nitrogenous waste products, iron and calcium deficiency, a clear association was emphasized ($p < 0.001$) in both groups (Figure 2 and 3).

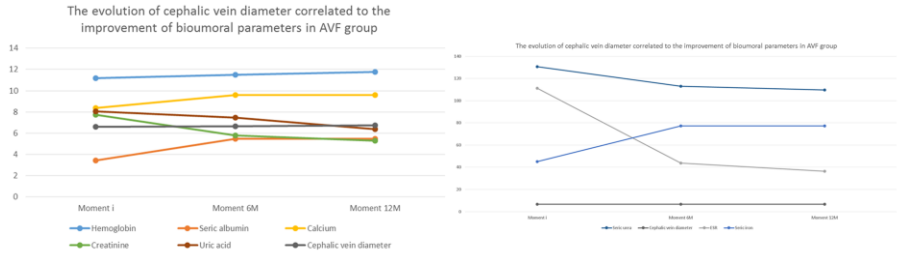

Figure 2. The correlation between the improvement of bioumoral parameters and cephalic vein growth in AVF group

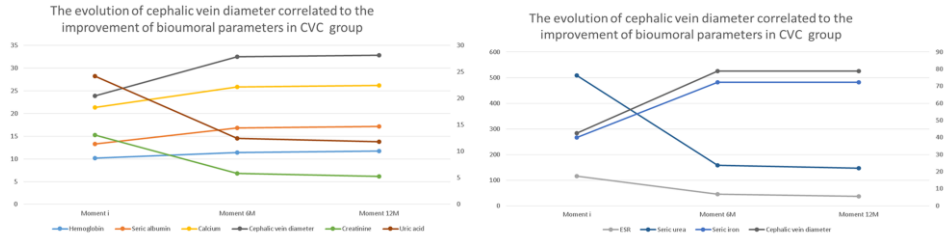

Figure 3. The correlation between the improvement of bioumoral parameters and cephalic vein growth in CVC group

In addition, analyzing the growth rate of cephalic vein in CVC group – $p < 0.001$, meaningful statistic differences were observed among the 3 moments of evaluation (Figure 4). Basilic vein cases could not have been statistically analyzed (only 4 brachiobasilic fistulae in AVF group).

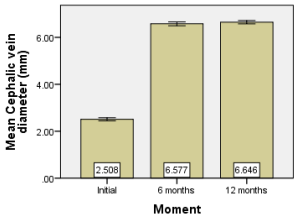

Figure 4. Cephalic vein growth in CVC group

These data underlined the idea of the possibility of developing a computerized prediction model to evaluate dialysed patients' outcome, including the success of a viable vascular access, depending on clinical condition, bioumoral factors and high compliance to the treatment.

Arteriovenous fistula model

Using an already trained and validated ANN, the evolution of a group of patients undergoing HD on native vascular access with optimal clinical and bioumoral conditions was simulated, in order to develop a computational model to accurately predict the long-term prognosis of dialysed population and emphasize the risk factors. A GMDH Shell 3 prognostic program has been applied, based on multi-layer perceptron algorithm – feedforward type of ANN (**Stancu & Constantin (2014)**). In this manner, the influence of various bioumoral parameters on the growth rate of cephalic vein diameter has been emphasized in the included ESRD patients.

For a better assessment of the results, 2 neural models have been designed in both groups (CVC and AVF patients):

- at 6 months, based on the initial levels of the parameters;
- at 12 months, based on the 6 months values of the considered factors.

At 6 months since the dialysis initiation, the artificial network presented the following structure in the CVC group:

- 8 entry neurons corresponding to each parameter (hemoglobin, serum albumin, ESR, calcium, serum iron, creatinine, urea, uric acid);
- 5 hidden neurons responsible for data modeling;
- 1 exit neuron – predicted value of cephalic vein diameter.

This computational model highlighted that factors such as creatinine, uric acid, ESR significantly influenced the growth rate of cephalic vein diameter (Figure 5):

- the initial values of the evaluated parameters have been marked as: a_i = hemoglobin; b_i = serum albumin; c_i = ESR; d_i = calcium; e_i = serum iron; f_i = creatinine; g_i = urea; h_i = uric acid.

PREDICTION GROWTH RATE OF CEPHALIC VEIN DIAMETER$_{6\ MONTHS}$ = $N_6 \times N_7 \times 0.1523$, where

N_i = the model corresponding to neuron$_i$ ($_i$ = 6, 7)

$N_6 = f_i \times (-0.384)$

$N_7 = c_i \times 0.04127 + h_i \times 0.1627$

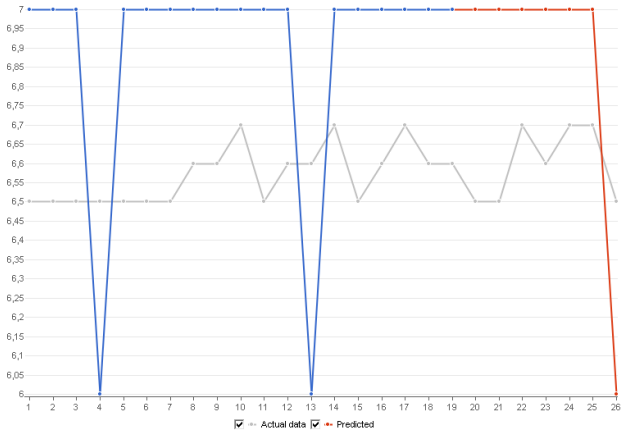

Figure 5. Prediction growth rate of cephalic vein diameter in CVC group at 6 months

The graphic showed that in only 2 situations (case 4 and 13) the cephalic vein diameter presented a lower limit value. In addition, the prediction included constant values, and after 5 cases, an inferior limit level of cephalic vein diameter should be emphasized. Furthermore, at 6 months since the dialysis initiation, considering the same clinical and bioumoral state regarding creatinine, uric acid and ESR values, the patients would present a cephalic vein diameter of: 6.664, 6.584, and 6.555 mm, respectively.

At 12 months since the dialysis started, the artificial network presented the following structure in the CVC group:

- 8 entry neurons corresponding to each parameter (hemoglobin, serum albumin, ESR, calcium, serum iron, creatinine, urea, uric acid);
- 11 hidden neurons responsible for data modeling;
- 1 exit neuron – predicted value of cephalic vein diameter.

This computational model highlighted that factors such as calcium, creatinine, urea, ESR, serum iron significantly influenced the growth rate of cephalic vein diameter (Figure 6):

- the 6 months values of the evaluated parameters have been marked as: a_6 = hemoglobin; b_6 = serum albumin; c_6 = ESR; d_6 = calcium; e_6 = serum iron; f_6 = creatinine; g_6 = urea; h_6 = uric acid.

PREDICTION GROWTH RATE OF CEPHALIC VEIN DIAMETER$_{12\ MONTHS}$ = N_{10} x N_4 x 0.1512, where

N_i = the model corresponding to neuron$_i$ ($_i$ = 4, 8, 10, 12, 13)

$N_{10} = N_{12}$ x N_{13} x 0.4902

$$N_{12} = d_6 \times f_6 \times (-0.002742)$$
$$N_{13} = c_6 \times e_6 \times 0.0000134$$
$$N_4 = d_6 \times N_8 \times 0.01507 + N_8 \times N_{10} \times 0.1307$$
$$N_8 = g_6 \times N_{12} \times (-0.03252) + N_{12} \times N_{13} \times 0.7103$$

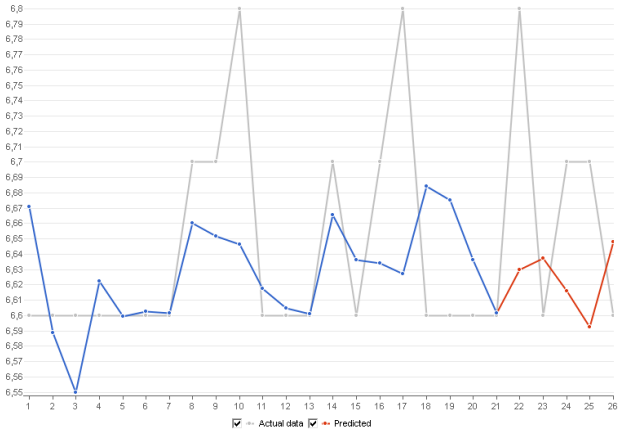

Figure 6. Prediction growth rate of cephalic vein diameter in CVC group at 12 months

Between 6 and 12 months, a significant difference of cephalic vein diameter among cases is noted, emphasizing the vulnerability of diameter vein evolution related to the assessed parameters. Additionally, at 1 year since dialysis started, considering the same clinical and bioumoral state regarding calcium, creatinine, urea, ESR, serum iron levels, the patients would present a cephalic vein diameter of: 6.638, 6.637, and 6.616 mm, respectively.

At 6 months since the dialysis initiation, the artificial network presented the following structure in the AVF group:

- 8 entry neurons corresponding to each parameter (hemoglobin, serum albumin, ESR, calcium, serum iron, creatinine, urea, uric acid);
- 34 hidden neurons responsible for data modeling;
- 1 exit neuron – predicted value of cephalic vein diameter.

This computational model highlighted that factors such as serum albumin, calcium, ESR, uric acid, urea, hemoglobin, and serum iron significantly influenced the growth rate of cephalic vein diameter (Figure 7):

- the initial values of the evaluated parameters have been marked as: a_i = hemoglobin; b_i = serum albumin; c_i = ESR; d_i = calcium; e_i = serum iron; f_i = creatinine; g_i = urea; h_i = uric acid.

PREDICTION GROWTH RATE OF CEPHALIC VEIN DIAMETER$_{6\ MONTHS}$ = N_8 x N_3 x 0.2545 + N_{13} x N_5 x (-0.1046), where

N_i = the model corresponding to neuron$_i$ ($_i$ = 3, 5, 7, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21)

$N_8 = b_i \times N_{21} \times 0.09766 + d_i \times N_{19} \times 0.0798$

$N_{21} = c_i \times h_i \times (-0.002079) + g_i \times 0.06522$

$N_{19} = a_i \times b_i \times (-0.02864) + c_i \times d_i \times 0.008316$

$N_3 = N_7 \times N_{12} \times (-0.1123) + N_9 \times N_{11} \times 0.2623$

$N_7 = b_i \times N_{21} \times 0.09766 + d_i \times N_{19} \times 0.0798$

$N_{12} = N_{17} \times N_{19} \times (-0.05986) + N_{20} \times N_{14} \times 0.21$

$N_{17} = a_i \times e_i \times 0.002303 + d_i \times 0.6586$

$N_{20} = b_i \times h_i \times (-0.006831) + c_i \times d_i \times 0.007349$

$N_{14} = g_i \times N_{17} \times 0.004124 + h_i \times N_{18} \times 0.05703$

$N_{18} = d_i \times 0.6212 + e_i \times 0.03266$

$N_9 = b_i \times N_{21} \times 0.08706 + d_i \times N_{20} \times 0.08411$

$N_{11} = g_i \times N_{13} \times 0.00263 + h_i \times N_{13} \times 0.08122$

$N_{13} = N_{15} \times N_{19} \times (-0.0968) + N_{16} \times N_{20} \times 0.247$

$N_{15} = c_i \times e_i \times 0.0002518 + d_i \times 0.6459$

$N_{16} = d_i \times 0.6095 + e_i \times h_i \times 0.004313$

$N_5 = b_i \times N_9 \times 0.03342 + N_7 \times N_8 \times 0.1329$

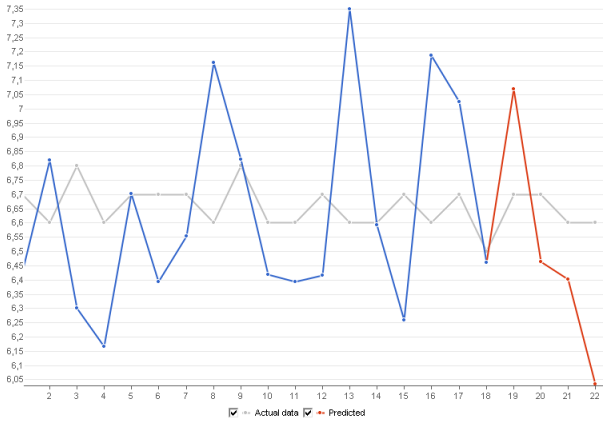

Figure 7. Prediction growth rate of cephalic vein diameter in AVF group at 6 months

In this situation, between the evaluated cases, significant variations of cephalic vein diameter were noticed, emphasizing the vulnerability of diameter vein evolution related to the initial parameters values, such as serum albumin, calcium, ESR, uric acid, urea, hemoglobin, and serum iron. A possible explanation of these findings could be that in this group of patients, hemodialysis should have had been initiated at an earlier moment. In addition, the lack of influence of the initial creatinine levels emphasizes that although creatinine value represents a useful marker of renal impairment, it does not provide complete data regarding the magnitude or kidney dysfunction, as its level may be influenced by several factors: age, nutritional status, weight *etc* (**Checheriță, Ciocâlteu et al (2013)**). At 6 months since dialysis initiation, considering the same clinical and bioumoral state regarding serum albumin, calcium, ESR, uric acid, urea, hemoglobin, and serum iron values, the patients would present a cephalic vein diameter of: 7.069, 6.463, and 6.40118 mm, respectively.

At 12 months since the dialysis started, the artificial network presented the following structure in the AVF group:

- 8 entry neurons corresponding to each parameter (hemoglobin, serum albumin, ESR, calcium, serum iron, creatinine, urea, uric acid);
- 12 hidden neurons responsible for data modeling;
- 1 exit neuron – predicted value of cephalic vein diameter.

This computational model highlighted that factors such as hemoglobin, ESR, serum albumin, urea, serum iron, calcium significantly influenced the growth rate of cephalic vein diameter (Figure 8):

- the 6 months values of the evaluated parameters have been marked as: a_6 = hemoglobin; b_6 = serum albumin; c_6 = ESR; d_6 = calcium; e_6 = serum iron; f_6 = creatinine; g_6 = urea; h_6 = uric acid.

PREDICTION GROWTH RATE OF CEPHALIC VEIN DIAMETER$_{12\ MONTHS}$ = $c_6 \times N_{18} \times N_4 \times (-0.0002304) + N_4 \times 1.01$, where

N_i = the model corresponding to neuron$_i$ ($_i$ = 4, 7, 8, 9, 13, 14, 15, 18)

$$N_{18} = c_6 \times 0.004331 + d_6 \times 0.6822$$
$$N_4 = c_6 \times N_{14} \times 0.00557 + N_9 \times N_7 \times 0.1126$$
$$N_{14} = d_6 \times 0.6172 + d_6 \times e_6 \times 0.001115$$
$$N_9 = d_6 \times N_{15} \times (-0.3096) + N_{13} \times N_{18} \times 0.5903$$
$$N_{15} = b_6 \times g_6 \times 0.0003741 + d_6 \times 0.6778$$
$$N_{13} = b_6 \times e_6 \times 0.001388 + d_6 \times 0.6408$$
$$N_7 = a_6 \times N_9 \times (-0.04233) + N_8 \times 1.489$$
$$N_8 = d_6 \times N_{15} \times (-0.3096) + N_{13} \times N_{18} \times 0.5903$$

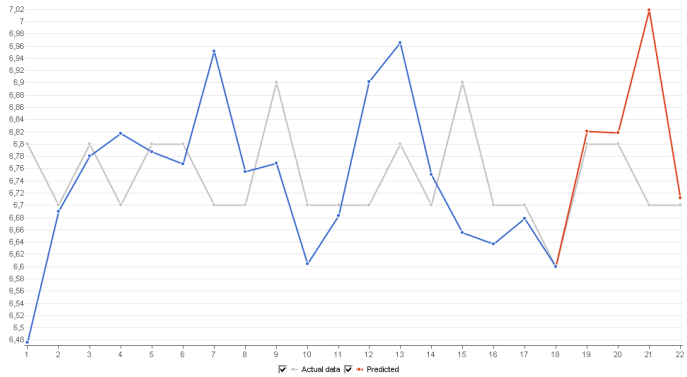

Figure 8. Prediction growth rate of cephalic vein diameter in AVF group at 12 months

Between 6 and 12 months, in most cases, diameter vein variations significantly decreased as the clinical and bioumoral status improved once hemodialysis was initiated. Additionally, the cephalic vein diameter presented a lower growth rate comparing to the previous period, possible because all the included individuals could be considered "ideal" dialysed patients – without comorbidities and complications specific of the hemodialysed population, compliant patients to the medical indications. At 12 months since dialysis started, considering the same clinical and bioumoral state regarding hemoglobin, ESR, serum albumin, urea, serum iron, calcium levels, the patients would present a cephalic vein diameter of: 6.8025, 6.8184, and 7.0184 mm, respectively.

3. Discussions

Over the years, significant steps forward have been made in decreasing AVF preoperative risks (such as a no suitable vessel capital) and consequently the possible complications (*e.g.*: thrombosis, stenosis), once duplex ultrasound was introduced in daily practice (**Bode et al (2011)**). Therefore, an adequate evaluation protocol of vascular access was achieved and according to KDOQI guidelines (**National Kidney Foundation (2006)**), a suitable AVF for an optimal dialysis treatment consists in the possibility of receiving a flow rate greater than 600 mL/min and the involved vein presenting a diameter above 6 mm and a depth of 0.6 mm from the skin surface. Furthermore, preoperatively, the elected artery should have a diameter higher than 2 mm (**National Kidney Foundation (2006)**).

Considering the significance of vasculature structure and size involved in the development of a well-developed AVF, most of the studies focused primarily in generating a viable preoperative AVF protocol in hemodialysed population.

In 1959, **Grodins (1959)** was the first who created a mathematical model for a better evaluation of the circulation hemodynamics, raising the scientific community interest for the assessment of various diseases based on computational method and the possibility of prediction of their progression (**Bode (2011)**). Therefore, most studies focused on hemodialysed population (especially on vascular access influence on over-all prognosis) have applied to mathematical methods in order to better explain the inner (patho-) physiological mechanisms generated once an anastomosis between an artery and a vein was performed.

The experimental and clinical trials conducted to determine the hemodynamics changes occurring at the newly created AVF concluded that both features related directly to the vessel ones ligatured (decrease of wall resistance and increase of blood stream) and the presence of local vascular remodeling near the anastomosis play a major role in the AVF future evolution (**Remuzzi & Ene-Iordache (2013)**). In addition, according to **Remuzzi & Ene-Iordache (2013)** and previously by **Wedgwood et al (1984)**, the suture procedure (end-to-side or end-to-end anastomoses) can also influence AVF hemodynamics, increasing the shear stress at this level which have a positive effect, but it may become harmful in long-term. Shear stress enhancement is beneficial for adapting the vascular structure to the newly present condition and to permit the flow of an elevated blood stream, but, on the other hand, in time it can be responsible for generating the onset of various vascular access related complications (*e.g.*: thrombosis, stenosis) (**Remuzzi & Ene-Iordache (2013)**).

Therefore, in a previous study (**Checheriță, Niculae et al (2013)**), the native AVF development using a mathematical approach was presented. It was hypothesized that the blood vessel could be imagined as a cylindrical shell characterized by radius (R), generator curve (L) and thickness (h) (considering the ratio $h/R<1$) (**Checheriță, Niculae et al (2013)**). Furthermore, it was considered that during AVF maturation, vessel stiffening could develop that might induce bending moments and shearing forces (**Checheriță, Niculae et al (2013)**). Therefore, the moment theory of cylindrical thin shells and also the effort method and canonical equation system for measuring these forces (Figure 9 and 10) were applied, presenting, in this manner, a brief explanation of the vascular remodeling onset (**Checheriță, Niculae et al (2013)**).

$$\begin{cases} X_1\delta_{11} + X_2\delta_{12} + \delta_{10} = 0 \\ X_1\delta_{21} + X_2\delta_{22} + \delta_{20} = 0 \end{cases}$$

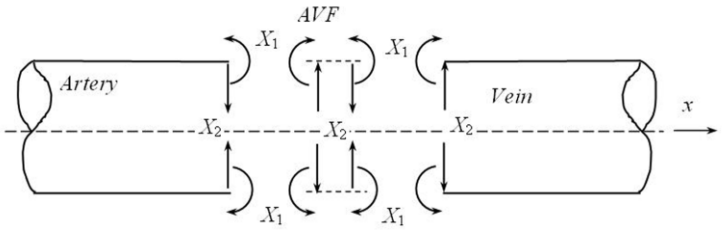

Figure 9. Sectional forces near the native AVF

$$w(x) = \frac{r^2}{Eh}\left(Z - \frac{\nu \cdot N_x}{r}\right)\left[1 - e^{-\beta \cdot x}\left(cos\,\beta \cdot x + sin\,\beta \cdot x\right)\right].$$

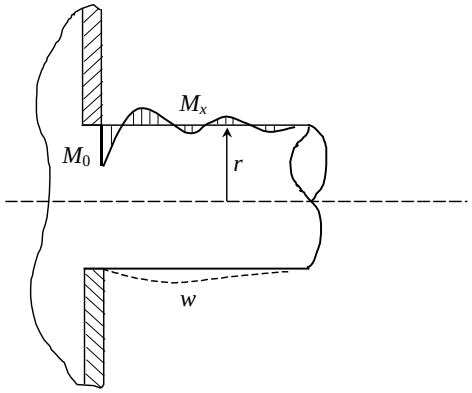

Figure 10. Vessel deformation after creating a native AVF

Once ANN was applied as a predictive medical tool, potentially risk factors incriminated for vascular access dysfunction were better emphasized. Nevertheless, there are still many gaps to be filled.

According to **Caroli et al (2013)** and **Fitts et al (2014)**, AVF failure is predominately related to vessel architecture and the implicated shear forces inducing endothelial changes, but the present research goes beyond this point emphasizing also the importance of the correct quantification of several bioumoral parameters specific to HD patients for an accurate prediction.

Therefore, in the present 1 year-study, only HD patients with "ideal" clinical and bioumoral condition were selected. The findings regarding various parameters evolution such as hemoglobin, nitrogenous waste products, iron and calcium

deficiency, inflammatory state are similar to other previous studies that emphasized the importance of these factors at the moment of RRT initiation (**Valdivia et al (2013)**; **Jofré et al (2006)**; **Anees & Ibrahim (2009)**).

The assessed data related to the modality of starting dialysis (on native AVF or CVC) – including the analyze of the 4 artificial neural models – are in accordance with previously results that suggested a decreased risks of complications in patients initiating HD directly on native fistulae *versus* CVC (**Lomonte & Basile (2015)**) with a better future evolution. The same authors underlined the importance of a thoroughly preoperative assessment for the creation of a well-developed fistula (**Lomonte & Basile (2015)**); in the present research, this surgical protocol was also applied.

Another aspect emphasized in the current study is the importance of residual diuresis in maintaining a long-term efficient hemodialysis that is in accordance with literature data emphasizing that preserved renal function decreases the risk of morbidity and mortality (**Nechita et al (2015)**).

Furthermore, although this predictive computational model of vascular access follow-up in hemodialysed patients represents an important step forward, the present study has some limitations as the number of included patients was small (52 cases with equal distribution between CVC and AVF groups), the short period of evaluation (only 1 year), the correlations only of some bioumoral factors with the growth rate of the cephalic vein diameter, the absence of specific comorbidities and complications of hemodialysed patients (insignificant statistically number of diabetic individuals, the lack of severe cardiovascular pathology or early and later complications related to the vascular access *etc*).

4. Conclusions

Considering these promising findings and also the above mentioned aspects, the study should be continued on a larger cohort of dialysed subjects (including also patients with different morbid conditions), followed for a longer period of time, and with the analysis of several other parameters for a better understanding of the factors influencing the evolution of arteriovenous fistula (*e.g.*: phosphates and parathormon values, protein and caloric daily intake, interdialytic weight gain *etc*). Furthermore, various other features should be correlated with the long-term prognosis of this group of patients: primary renal disease, echocardiography data, dialysis efficiency, the influence of drug therapy including the modifications of doses when the target-values are achieved (antihypertensive or hypolipidemic treatment, erythropoietin, iron sucrose, insulin, oral antidiabetic medication *etc*).

Chronic kidney disease, especially ESRD, due to the important associated morbid conditions and the high rate of mortality, remains a complex pathology with

many questions, not enough comprehended that represents the cornerstone of nephrology.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' contribution

All authors had equal contribution.

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