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Roles of triglyceride and phosphate in atherosclerosis of diabetic hemodialysis patients

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Abstract

Background: A growing number of patients with End-Stage Renal Disease (ESRD) are undergoing long-term hemodialysis (HD). HD needs a vascular access (VA) and complications of VA account for a sizable proportion of its costs. One of the important cardiovascular diseases (CVD) is atherosclerosis, which is a major cause of premature deaths in the world. So, it is essential to find the risk factors to treat them before they cause an obvious CVD.

Methods: We analyzed data from 174 ESRD patients who were candidate for Arterio Venous Fistula (AVF) creation from April 2008 to March 2009 in Hasheminejad Kidney Center by convenient sampling. X-ray images were used and C 4.5 algorithm of data mining techniques revealed the roles of two risk factors for atherosclerosis of diabetic ESRD patients. Pearson coefficient was also used to measure the correlation between the parameters.

Results: Diabetic patients had significantly more calcified arteries in their forearm X-ray than other patients ($p<0.001$). Occurrence of atherosclerotic CVD in diabetic HD patients has an adverse relation compared with the controlled levels of their plasma levels of Triglyceride (TG) and Phosphorus. We found an inverse effect of TG and phosphorus plasma levels on the atherosclerotic involvement of radial and ulnar arteries in diabetic HD patients. We observed that the prevalence of radial and ulnar arteries calcification in these patients is lower when they have higher plasma levels of TG and phosphorous.

Conclusion: This study investigates the role of high plasma levels of TG and phosphorous in the development of atherosclerosis in diabetic HD patients. Although many studies showed that hypertriglyceridemia plays a promoting role in the development of CVD, our study also found an inverse effect of plasma levels of TG on the atherosclerotic involvement of radial and ulnar arteries in diabetic patients, and therefore our results support this suspicion that hypertriglyceridemia plays a significant role in developing atherosclerosis.

Keywords: Image Mining, X-ray, Arterial Calcification, Atherosclerosis, Diabetes Mellitus, Triglyceride, Phosphorus, inverse effect

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Introduction

A growing number of patients with End-Stage Renal Disease (ESRD) are undergoing long-term hemodialysis (HD). In the US, more than 871,000 persons were treated for ESRD in 2009, which represented an increase of nearly 600% between 1980 and 2009, and accounted for 6% of the 2009 Medicare budget ($29 billion) (1). Complications of HD access account for a sizable proportion of these costs (1, 2).

Reducing morbidity and costs of vascular access (VA) maintenance is a challenge in HD patients. Arterio Venous Fistula (AVF) has least complications and AVF is preferred VA method. In Iran, AVF remains the first choice

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↑What is "already known" in this topic:
Atherosclerosis is an important cardiovascular disease (CVD) and is a major cause of premature deaths in the world. Specially, vascular calcification - as a representative of atherosclerosis - is a risk factor for mortality due to CVD in End-Stage Renal Disease (ESRD) patients.

→What this article adds:
There is an adverse relation in atherosclerosis formation in diabetic ESRD patients such that the prevalence of radial and ulnar arteries calcification is lower when they have higher plasma levels of Triglyceride (TG) and Phosphorus.

for VA and rate of AVF has increased remarkably, reaching up to 93.4% and comparable to other VA methods (3).

The total number of ESRD patients undergoing renal replacement therapy (RRT) in 2007 was 32,686, which denotes a prevalence of 435.8 per million population (PMP). This number is very high compared with 1997, 2000 and 2006, when the prevalence of ESRD was 137 pmp, 238 pmp and 357 pmp, respectively. The incidence of ESRD patients also seems to be increased, from 13.82 pmp in 1997 to 49.9 pmp in 2000 and 63.8 pmp in 2006. It is possible that the increase is due to the increased recognition of the disease due to the increase in the number of HD centers (150 in 1997, 227 in 2000 and 316 in 2006), kidney transplantation centers, transplantations (22.8 pmp in 1997 to 26.5 pmp in 2006) and nephrologists in our country. Also, the number of patients on HD increased from 587 (106.7 pmp) in 1991 in Tehran to 12500 (179 pmp) in 2006 (4-7). Moreover, the statistics of ESRD incidence and prevalence in years 2008-2012 has been published by USRDS (8).

We summarized these rates in Table 1 and illustrated their trends in Fig. 1.

Moreover, atherosclerosis is a chronic inflammatory disease of large- to medium-sized arteries and is the main underlying cause of death worldwide (9). Cardiovascular diseases (CVD) due to atherosclerosis are one of the major reasons for disease burden in developed countries (10). Atherosclerosis causes obvious CVD, and CVD is one of the causes of premature deaths. Since atherosclerotic plaque grows slowly, it does not lead to symptoms, and affected individuals usually remain asymptomatic. For instance, patients mostly have no cardiac symptoms until the lesion causes 70-80% narrowing of the coronary vessels (11). However, several myocardial infarctions are the consequences of an atherosclerotic plaque, which does not cause a high-grade stenosis and therefore does not yet restrict the coronary arteries blood flow (12, 13). Also, elevated LDL cholesterol, high triglyceride (TG), low high-density lipoprotein (HDL) cholesterol, smoking, hypertension and diabetes mellitus, are known risk factors for vascular diseases, including atherosclerosis (14-16).

Furthermore, vascular calcification is a representative of atherosclerosis, and it is also known as a risk factor for mortality due to CVD in ESRD patients. Vascular calcification is detectable by radiography and X-ray computed tomography (CT) (17, 18).

Some studies revealed that classic risk factors for atherosclerosis such as age, sex, hypertension, high blood glucose level and dyslipidemia are the most common causes of atherosclerosis, which are responsible for even more than 50% cases of atherosclerosis (19-23).

Imaging plays a critical role in early diagnosis and treatment of VA failure (24). However, catheter fistulography cannot evaluate extravascular structures,

Table 1. The incidence and prevalence of patients with ESRD in Iran (1997-2012)

Year (s)	ESRD Incidence (PMP)	ESRD Prevalence (PMP)
1997	13.82	137
2000	49.9	238
2006	63.8	357
2007	-	435.8
2008	99	491
2009	101	529
2010	106	556
2011	108	586
2012	105	621

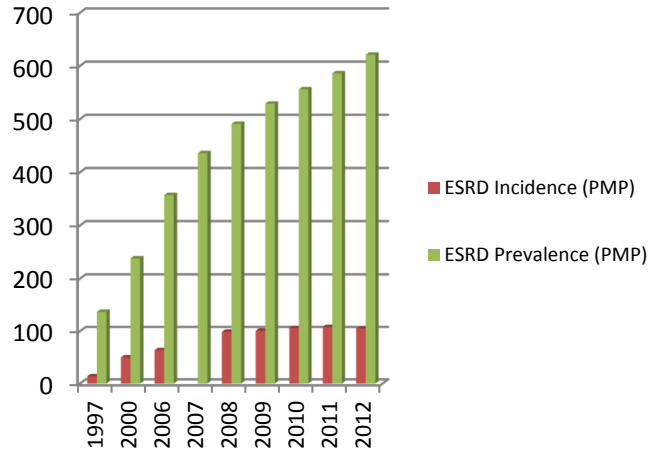

Fig. 1. The trends of incidence and prevalence rates of ESRD in Iran (1997-2012)

Table 2. The parameters of calcification detection by radiologist and surgeons

Parameters in Figures 3, 4	Comment	Range1	Range2
Calcification	Dose patient have calcification in X-ray?	'1'= Seen	'2'= Not Seen
Radiologist	Detecting calcification by radiologist	'1'= Seen	'2'= Not Seen
Expert	Detecting calcification by surgeons	'1'= Seen	'2'= Not Seen
Length	The length of Arterial Calcification	It is measured by centimeters & is denoted with the colors (Figures 3, 4).	

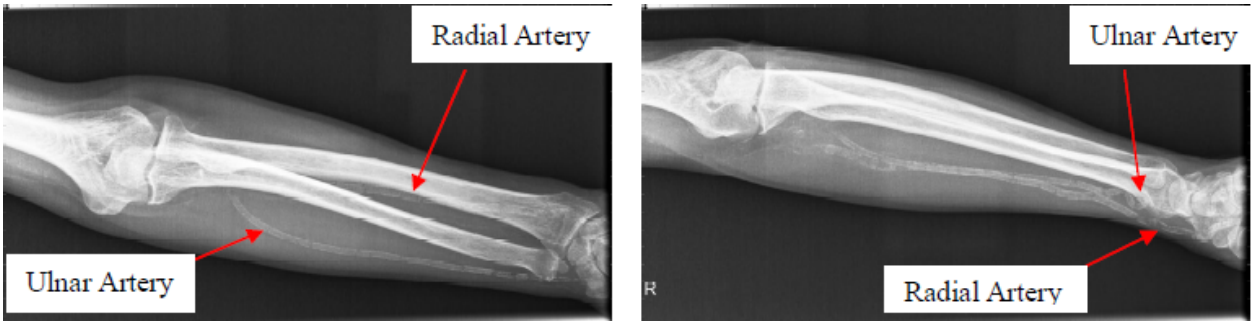

Fig. 2. Arterial calcification in their forearm Radiographies

such as in cases of stenosis or obstruction secondary to external compression. Delineation of the central vascular anatomy, including the aorta, subclavian artery, and superior vena cava, may require multiple injection runs and/or multiple punctures, which can create patient discomfort and add to the cost of the procedure (25).

These facts demonstrate that further consideration should be given to atherosclerosis and its risk factors.

Data mining is a process, which is used to extract potentially useful information from large amounts of data (26). Usual methods of statistical analysis cannot analyze and process some information because they are too abundant and complicated, but data mining is the technique, which can change these complex data into helpful information (27). Since medical data mining is an effective analytical technique for exploring previously unknown and potentially useful data, it is now becoming popular in healthcare system (28). In the field of medicine, data mining is a useful technique to extract information, which is helpful in decision making (29). Specially, the extracted information from data mining can help surgeons to detect and predict surgical complications (30, 31).

The goal of our study is to assess and report the correlation between different risk factors for atherosclerosis, using data mining technique. Thus the risk factors of atherosclerosis can be interpreted based on these possible correlations in future. Also, the maximum level of different risk factors might be adjusted based on these findings.

Methods

In the present study, we analyzed data from 174 patients with ESRD who were candidates for AVF creation. Patients were included from April 2008 to March 2009 in Hasheminejad Kidney Center by convenient sampling. Forearm X-ray (anteroposterior and lateral projection) was done for all individuals and reported by a radiologist before surgery. Clinical and laboratory data (including atherosclerosis risk factors) were obtained through checklists. Our approach was based on a standard process model, namely CRISP-DM (Cross-Industry Standard Process for Data mining) (32). We used Rapidminer software for analyzing data.

We used data mining techniques, as its applications have become increasingly essential for healthcare organizations to make decisions based on the analysis of huge amounts of clinical data generated by healthcare transactions (28). Nevertheless, running these techniques on low volume datasets is also useful (29). According to data mining approaches, Rezapour et al. (2017) have presented a system which controls outcomes of AVF surgery in ESRD patients (33).

Before running decision tree based on C 4.5 algorithm, we reviewed and compared the status of calcification detected by radiologists and surgeons. In this comparison we used some parameters as mentioned in Table 2.

From all patients with the mean age of 56±16.1 years (58.6% male and 41.4% female), 18% (n=34) had arterial calcification in their forearm radiographs (Fig. 2).

Results

As illustrated in Fig. 3, the scatter plot shows the diagnosis errors of radiologists in the northwest corner of the plot. In the northeast of this plot, when calcification was not apparent in X-Ray (no points at the southeast area), the radiologists did not reported its existence; but in the northwest corner of it, some errors have occurred: there are cases of existing calcifications in X-Ray (the red points in southwest area) which radiologists could not diagnosed them (there is no red point in northwest area).

On the other hand, Figure 4 shows that surgeons had more diagnosis errors if the decision was made without radiography; In addition to radiologist's diagnostic errors (Northwest corner of Fig. 3), surgeon had made two mistakes of another kind (Southeast corner of Fig. 4): two patients were diagnosed with atherosclerosis whereas they have not any evidence of calcification in X-Ray.

So we saw that using X-rays helps surgeons to make more accurate diagnosis.

Furthermore, Pearson correlation test showed that diabetic patients had significantly more calcified arteries in forearm X-ray than other patients ($p<0.001$). Noticing this fact, after running decision tree on our gathered data, we

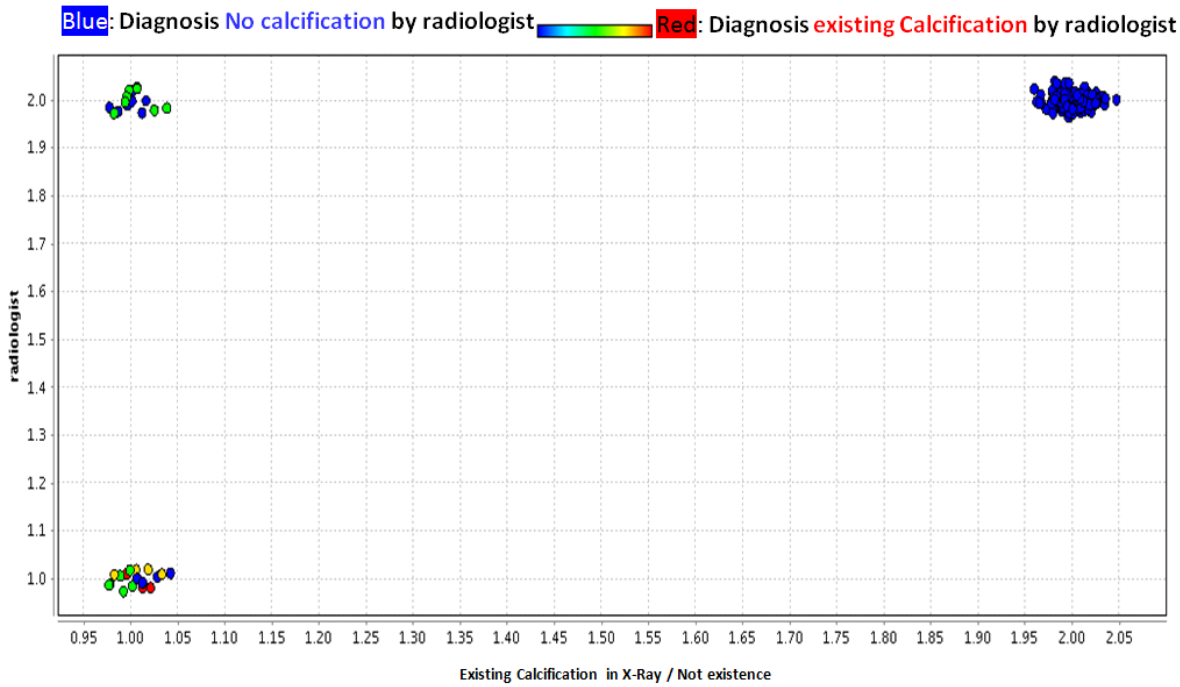

Fig. 3. Forearm arterial calcification in radiography and calcification cases reported by radiologists: the diagnosis errors in the northwest corner

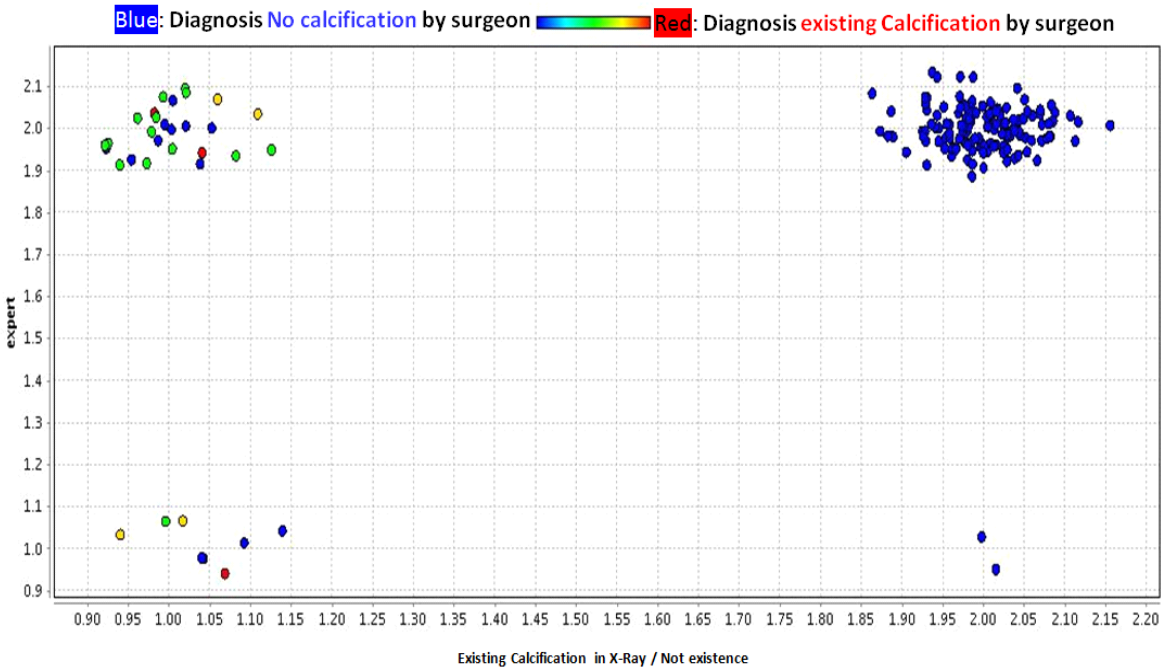

Fig. 4. Forearm arterial calcification in radiography and calcification cases reported by surgeons: the diagnosis errors in the northwest and southeast corners

focused on the extracted laws which explain more properties of this group of patients. As shown in Fig. 5, occurrence of atherosclerosis disease in diabetic patients has an adverse relation with controlled levels of their plasma levels of TG and Phosphorus. The extracted rules from Fig. 5 are summarized in Table 3.

Discussion

Our analysis on the role of hyperphosphatemia in atherosclerosis shows different results from some previous studies, which reported hyperphosphatemia as a risk factor for atherosclerosis. In the present study we found an inverse effect of plasma levels of TG on atherosclerotic involvement of radial and ulnar arteries in diabetic patients, and therefore our results support this suspicion that hypertriglyceridemia plays a significant role in developing atherosclerosis. Also, the present study shows that the prevalence of radial and ulnar arteries calcification in patients with 9.5-21 years' history of diabetes mellitus who have ESRD and normal level of Triglyceride (TG) is lower when plasma level of phosphorous is higher than 6 mg/dL.

Since atherosclerosis is the major underlying cause of

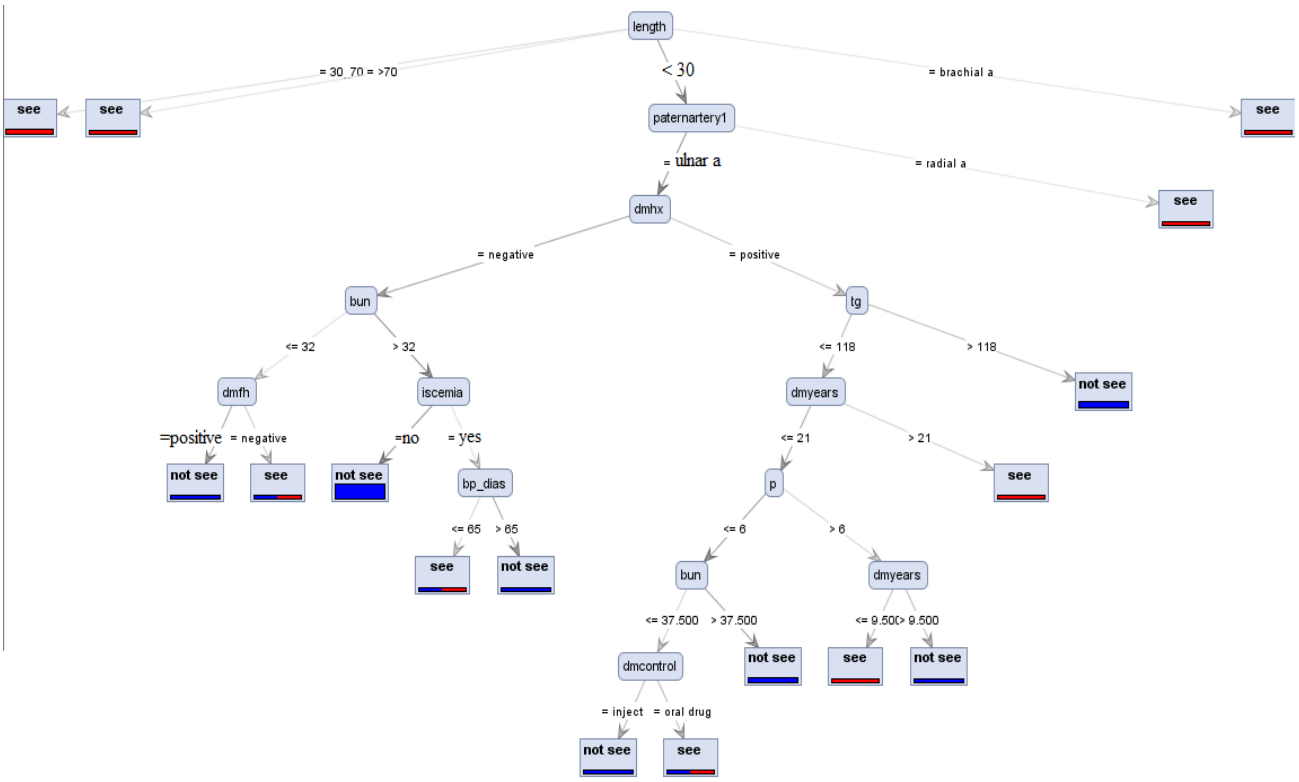

Fig. 5. In diabetic patients, atherosclerosis is not seen when their Triglyceride or Phosphorus is high

Table 3. The extracted rules on patients with diabetes history (dmhx=positive) from Figure 5

Rule I: When these patients have Triglyceride more than 118 (in figure 5: Triglyceride (TG) >118), then they do not have Arterial Calcification.
Rule II: If Triglyceride was equal or less than 118 (TG <=118), then diabetic patients with 21 years or more (dmyears>21) have Atherosclerosis Disease.
Rule III: If (TG <= 118) and (9.5 < dmyears <= 21) then for (Phosphorus>6) diabetic patients do not have Arterial Calcification.

mortality in the world (1), reduction and treatment of risk factors for atherosclerosis are the most effective ways to prevent cardiovascular diseases (CVD) (34) and it is essential to find the risk factors and to treat them effectively before they cause an obvious CVD. In this study, we try to find and interpret the correlations between these different risk factors.

Our analysis on diabetic patients with ESRD who were candidates for AVF creation, shows an inverse effect of the role of high plasma levels of TG and phosphorous in the development of atherosclerosis. Although many studies showed that hypertriglyceridemia plays a promoting role in the development of atherosclerotic plaques (9-11), the outcome of our study differs from some of these studies.

Talayero et al. reported that hypertriglyceridemia is a risk factor for CVD and TG level is considered to be a biomarker of CVD risk given its association with atherogenic lipoproteins (35). Hotta et al. investigated the relation between hypertriglyceridemia and serum adipocyte-derived proteins and showed that hypertriglyceridemia plays an important role in the development of atherosclerosis and it causes abnormalities in plasma level of some adipocyte-derived proteins (36).

On the other hand, the role of TG in triggering the atherosclerotic lesions is still controversial (37). Some studies obtained contradictory evidence for the role of hypertriglyceridemia in promoting atherosclerotic lesions and its related vascular calcification.

For instance, Freitas et al. studied on healthy individuals who were 80 or over 80 years of age and have shown that there is no relation between TG and coronary calcium score (CCS) (38). Also, Kannel et al. in a study on lipid-induced coronary heart disease (CHD) reported that hypertriglyceridemia is not an independent risk factor for CHD (39). Moreover, despite Talayero et al. reported hypertriglyceridemia as an important risk factor for CVD, they found no evidence of any correlation between lowering TG level and reduced CVD risk (8).

Since TG is not water-soluble, it bounds to a lipoprotein to be transported in the blood in its lipoprotein-bound form. In many cases, hypertriglyceridemia is accompanied by high plasma levels of chylomicron and very low-density lipoprotein (VLDL). Chylomicron is metabolized and the remaining products of this metabolism play a role in developing of atherosclerosis (37, 40). Due to the small size of these remaining products they can simply infiltrate into sub-endothelial space and cause atherosclerotic lesions (41, 42).

Apart from this contradictory evidence, Qin et al. reported a significant correlation of traditional risk factors for carotid atherosclerosis with gender and age. According to

this study, the cut points and risk factors must be described based on specific sex and age categories. They also found that optimal range of fasting blood glucose as well as total cholesterol should be adjusted not only based on known optimal levels but also based on gender, age (34). As we found that the plasma level of TG is higher in diabetic patients with ESRDwith less radial and ulnar arteries calcification, the result of our study supports the above-mentioned study.

Moreover, another risk factor for coronary artery atherosclerosis is serum phosphorous level. (43). A study by Foley et al. shows that higher level of blood phosphorus, even in the normal range, might be a risk factor for coronary artery atherosclerosis not only in patients with advanced chronic kidney disease (CKD), but also in healthy individuals (43).

Since the outcome of our study differs from some of the previous studies, further research should be performed to observe the effect of hypertriglyceridemia and hyperphosphatemia on the incidence of atherosclerosis and vascular calcification in patients with other risk factors for vascular diseases.

Conclusion

As we have found an inverse effect on ESRD patients who were smoking (44) and an adverse effect in hypertensive patients on AVF failure (45), in the present study we found an inverse effect in diabetic patients with ESRD. The detected inverse effect is about triglyceride and phosphorus plasma levels on the atherosclerotic involvement of radial and ulnar arteries. We observed that the prevalence of radial and ulnar arteries calcification in diabetic patients who simultaneously suffer from renal failure is lower when they have higher plasma levels of TG and phosphorous. Finally, we recommend using data mining approaches to reveal unknown, useful and novel relations between medical variables.

Conflict of Interests

The authors declare that they have no competing interests.

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