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Vascular pathology of diabetic foot: A review article

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Abstract:

Background: The frequency of diabetes has increased significantly during the past decade.Although diabetic complications diabetic foot is the most serious diabetic complication, its pathophysiology has not been well recognizedby the medical community. Medical publications have introduced etiologies for diabetic foot. With this in mind,this review article was performed to evaluate vascular pathology of diabetic foot in diabetic patients.

Methods: We searched for articles published between January 1986 and June 2016 (30 years). Out of389 articles, we excluded 381 articles based on exclusion criteria and retained 7 for data extraction. From these 7 articles, 4 articles were observational, and 3 articles were used as a randomized controlled trial (RCT).

Results:5 out of these 7 selected articles showed that atherosclerosis is the etiology of vasculopathy, including anincrease in ox-LDL and ischemia-modified albumin, a decrease in paraoxonase 1, anincrease in the number of mature dendritic cells, and decrease in the number tolerogenic dendritic cells. Only one case report found that thrombosis may be involved in the development of diabetic foot, and states that this is the first time that deep vein thrombosis has been reported as the etiology of diabetic foot. In only one case report itwas found that leukocytoclastic vasculitis may cause diabetic foot.The other etiologies that have been mentioned as other factors causing diabetic foot (etc. vasospasm), no study has been done to verify these claims.

Conclusion: According to the 7 mentioned studies, we can prescribe medicines tailored forthese mechanisms in diabetic patients in order to prevent diabetic foot.

Ethical number registration: IR.SSU.MEDICINE.REC.1394.310.

Keywords: Diabetic foot, Pathology,Vasculitis, Atherosclerosis, Vascular diseases

I. Introduction

The International Diabetes Federation (IDF) published that global diabetes prevalence reached 246 million in 2007 [1] and has increased significantly during the past decade. The IDF further states that it will reach 380 million in 2025 [2]. The most serious diabetic complication is diabetic foot,which causes non-traumatic amputations [3]. The risk of amputation in diabetic patients is higher than non-diabetic patients [4]. Diabetic foot gangrene results from peripheral arterial disease with or without foot sepsis, which increasesmortality rate in diabetic patients [5].Due to the seriousness, early primary and paraclinicalevaluations are crucial to treating the underlying causes of diabetic foot, and reduce the risk of amputations as well as treatment costs.[6]. The this end, it is necessary to know the pathophysiology of diabetic foot. This review article was designed to evaluate vascular pathology of diabetic foot in diabetic patients.

II. Methods

Data sources and search strategy

The authors conducted a review based on relative search terms including combinations of "diabetic foot", "gangrene", "ischemia", "necrosis", "vasculitis", "atherosclerosis", "thrombosis", "vasospasm", "PDA", "vascular pathology" through online databases: PubMed, Web of Science, Cochrane Databases, covering Jan 1986 toward 4/20/2017 (Last checked: 5/6/17). Results with English abstracts were included and no constraints were applied relating to the type of publication.

Inclusion and exclusion criteria

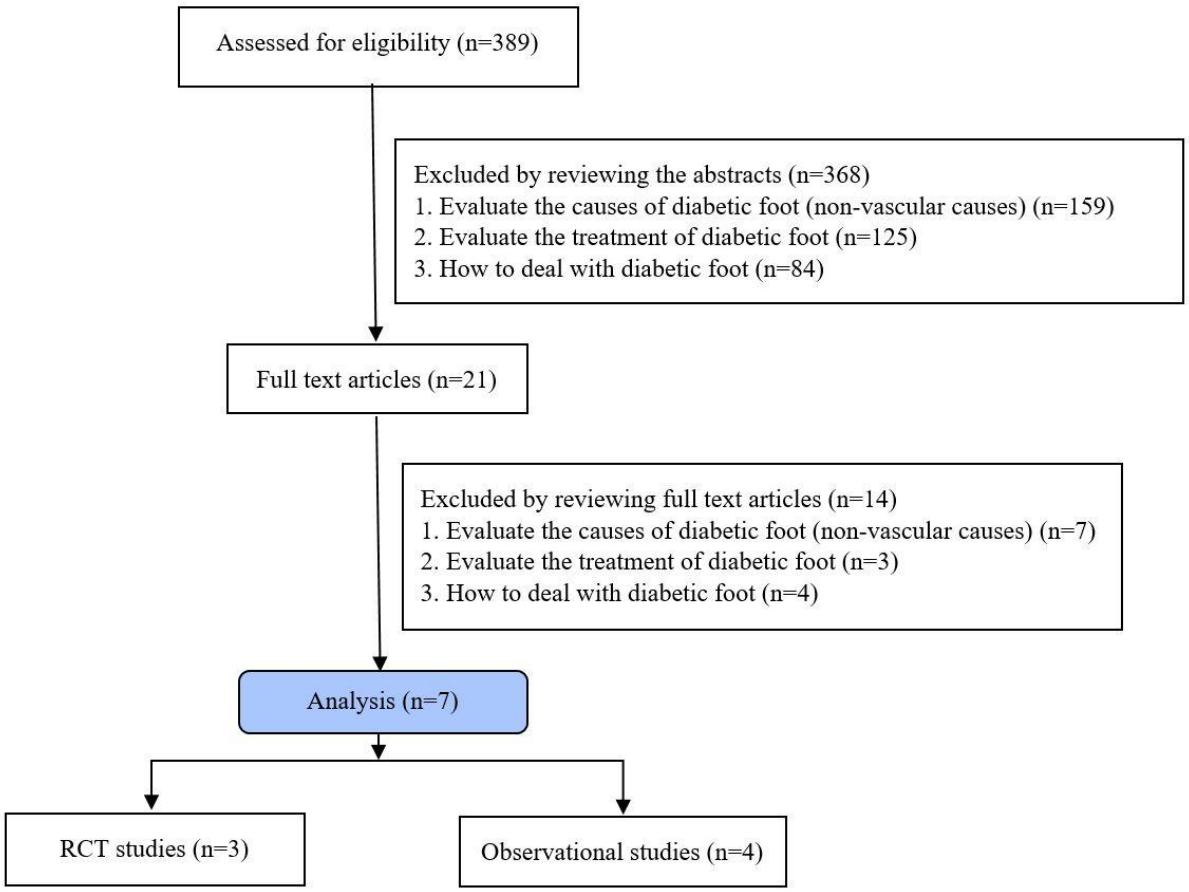
Eligibility criteria for inclusion encompassed studies presenting histopathological findings of diabetic foot ulcers or any vascular changes of (either small- or medium- sized) arteries of the lower limbs as measure outcomes in patients with diabetes mellitus. Studies lacking abstracts were excluded.

Study selection

Two authors, KK and MO, screened titles, abstracts, and then–for the studies meeting the criteria mentioned above–reviewed full-text articles independently, describing the reason for exclusion of each. Any discrepancies between included studies were resolved by the author MO,which led to a group consensus. As no results fulfilling the abovementioned criteria were found in the databases, for confirmation, several experts in the field (not in the list of authors of this article) were asked toassist in the search, sticking to the eligibility criteria. Conclusively, for the purpose of this study, any studies designating etiologies of the vasculopathy have been included into this study (at the level of reviewing full-text articles), yet still with the same keywords and databases.

We searched for articles published between January 1986 and June 2016 (30 years), then evaluated 389 studies and checked them in 3 steps. Before reading the studies themselves, we first checked the abstracts.Out of these 389articles found,21 manuscripts had inclusion criteria, and the other 368 were excluded **(Figure 1)**.

Figure title and legend
Figure 1. Study flowchart



Once this shortlist was created, westudied articles the selected.Out of21 articles, 7 were retained, and the other 14 were excluded. After more review, 7 were settled on for data extraction. From these 7 articles, 4 articles were observational, and 3 articles were randomized controlled trials (RCTs). Moreover, we mailed all corresponding authors of the 7 studies asking that theyinform us if they have any additional findings.However, we did not receive any response.

Data extraction
From each study, the following parameters were extracted: Name of authors, year of the publication, country where the study took place, name of departments authors are affiliated with, histopathologic findings of lower limb arteries, study population, type of study, age, and gender of patients.

III. Results

From the 389 articles written in the last 30 years, only 7 articles studied the etiology of vasculopathy onpatients with diabetic foot. Five articles out of these 7 articles showed that atherosclerosis is the etiology of vasculopathy, including increase in ox-LDL and ischemia-modified albumin and decrease in paraoxonase 1 activity [10], increase in mature dendritic cell numbers, and decrease in tolerogenic dendritic cells [11]. Only one case report, which was published in 2016, found that thrombosis may be involved in the development of diabetic foot, and states that this is the first time that deep vein thrombosis have been reported as the etiology of diabetic foot [12]. In another case report, it was also found that leukocytoclastic vasculitis may cause diabetic foot [13]. The other etiologies have been mentioned as other factors causing diabetic foot (etc. vasospasm), although no study has been done to verify these claims.

Table 1. Features of selected studies

Author	Year	Department	Country	The etiology of vasculopathy	Study type	No. patients	Mean Age (year)	Gender (Male %)
Edmonds M, et al. [7]	1986	Radiology	England	Atherosclerosis	Clinical trial (RCT)	Not applicable	-	-
Ci He et al. [8]	2014	Radiology	China	Plaque and stenosis	Observational (Case-Control)	60 diabetic patients	69/42	77/2
						101 non-diabetic patients (controls)	68/5	78/3
Kokobelian AR et al. [9]	2006	Radiology	Russia	Atherosclerosis	Clinical trial (RCT)	390 diabetic patients	-	-
Muhta [10]	2016	Biochemistry	Turkey	Atherosclerosis (increasing ox-LDL and ischemia-modified albumin and decreasing in paraoxonase 1 activity)	RCT (Patients with DF divided into 2 groups: had or had not undergone lower extremity	30 patients with DF	67/58	56/7
						30 healthy controls	52/6	53/3
						30 diabetic patients	53/56	50
Fang Z et al. [11]	2014	Vascular Surgery	China	Atherosclerosis (increasing mature dendritic cell; and decreasing tolerogenic dendritic cell)	Observational (Case-Control)	18 patients with DF	66/35	55.5
						10 healthy controls	58/34	60
						30 patients with ASO	64/23	60
C.O. Ekpebegh et al. [12]	2016	Internal medicine	South Africa	Deep vein thrombosis	Case report (Observational)	one patient	75	Male
Barış Sarıakçalı et al. [13]	2013	Internal medicine	Turkey	Leukocytoclastic vasculitis	Case report (Observational)	one patient	64	Male

ASO: Patients with atherosclerosis occlusion syndrome; DF: Diabetic Foot; RCT: Randomized control trial

IV. Discussion

Possible mechanisms of vascular events are atherosclerosis, thrombosis, vasculitis and abnormal protein deposition (amyloidosis) or malignant cell infiltration (Lymphomatoid granulomatosis). It seems that atherosclerosis is the most described mechanism for common vascular events, especially in elderly people and commonly encountered devastating diabetic foot (DF). The role of immunologic reactions in atherosclerosis has been seen in recent years. However, according to our survey, frank vasculitis is rarely diagnosed in DF, though there has been no specific pathology study on vascular sections in DF.

Interestingly, when we specifically investigated on three DF in our center with emphasis on vascular pathology of these samples and surprisingly we found frank vasculitis in two among three patients with DF (unpublished data). We also previously observed that near all of our cases with temporal giant cell arteritis are either overt diabetic or have prediabetes. Many authors believe that diabetes is potentially a pro-inflammatory condition and many rheumatologic disorders are more frequent among diabetics or have more severe course in diabetic patients. Therefore,due to the lack of any strong evidence supporting the atherosclerosis as a default mechanism for DF, we concluded that vasculitis as a novel or neglected mechanism of vascular events in DF might be subject to underestimation and this denotes to the poor prognosis and very high rates of amputation in thispopulation.

He C et al. showed that diabetes leads to increased accumulation of plaque in the arteries(63.1% in diabetic patients compared with non-diabetic patients 46.9%), narrowing of the arteries, and stenosis in the distal parts of the leg. [8] AlthoughHe C et al. studied the prevalence of stenosis and atherosclerosis in diabetic patients was studied, therewas no mention of the mechanisms of atherosclerosis in diabetic foot.

According to Muhtaroğlu S et al., the low activity of paraoxonase 1 (PON1) as well as the high levels of oxidized low-density lipoprotein (ox-LDL) and serum ischemia-modified albumin (IMA) may be involved in the pathogenesis of diabetic foot.They found that serum PON1 activity was lower and ox-LDL levels were higher in the diabetic foot group than in the control and diabetes groups. Albumin-adjusted IMA values were higher in the diabetic foot group compared to the diabetes group. Moreover, the post-amputation levels of IMA were decreased compared to the pre-amputation condition [10]. This information may be applicable in the treatment of diabetic foot, making way for new medical interventions.

Moreover, Fang Z et al. showed that tolerogenic dendritic cells (TDCs) and mature dendritic cells (mDCs) are assembled in the process of lower limb atherosclerosis occlusion syndrome (ASO), and the progression of the disease might be aggravated by DC-maturation. It is also possible that high glucose levelsare closely relatedto

the progression of atherosclerosis. The study demonstrated that immunogenicity of mDCs was significant in intima plaque and around the small vessel of adventitia on artherosclerotic aorta of lesion group, and this condition of mDCs are associated with disease progression. However, there was low expression of TDC and it was negatively correlated withthe progress of the disease. They further found that there is a close relationship between high glucose levels and disease progression. Further, TDC expressed high levels of IL-10 and TGF-β1 and decreased the percentage of CD4 (+) IL-17(+) Th17, IL-17 mRNA and IL-17 levels in vitro. [11]

Therefore, we can conclude an increase in ox-LDL and ischemia-modified albumin and a decrease in paraoxonase 1 activity [10], increase in the numbers mature dendritic cells and decreasein the numbers of tolerogenic dendritic cells [11] are known etiologies of diabetic footwhich increase the risk of atherosclerosis.

Various studies report higher risk of thrombosis in the veins of patients with diabetes in the liver and central nervous system, among other parts of the body [14, 15]. One case report demonstrateddeep vein thrombosis as an etiologic factor for diabetic foot. C.O. Ekpebegh et al. reported on a 75- year-old male with type 2 diabetes,as well as peripheral vascular disease. It was thought that his leg vein thrombosis was associated withhis gangrenous leg. [12] Deep venous thrombosis leads to increased venous pressure in the distal region, while the peripheral arterial disease leads to a reduction in pressure at the end of his organs. A Gangrenous leg is likely to further reduce capillary pressure of arterial pressure obtained [12]

Barış Sarıakçalı et al. reported on a type 2 diabetic patient who had purpuric skin lesions predominantly on the lower limbs and acute renal failure from underlying chronic kidney disease. All this was, according to the study, due to leukocytoclastic vasculitis associated with radiocontrast administration. He was initially diagnosed as having diabetic foot ulcer at outpatient clinic. After single dose of betamethasone depot (9.6 mg i.m.), skin eruptions paled and improved.Renal function showed an improvement on the following days. [13] This case study is the single study addressing vasculitis in DF. However, leukocytoclastic vasculitis is a small vessel vasculitis and cannot indicate deep tissue ischemia and foot gangrene.

It is important to note that publication of all most relevant aforementioned articles to our topic is by disciplines other than pathology (that is, radiology, biochemistry, vascular surgery and internal medicine).This could be seen as proof of a major shortage in the field of clinical pathology.

We must also state that, a brief assessment of study designs in included studies, revealed in many cases there are high risk of bias and or a low quality study design. This shows the need to perform better quality studies in future to assess the vascular pathology of diabetic foot.

V. Conclusion

Our review article showed that few studies, if any, have been published in the field of vascular pathology on diabetic foot, which many had low quality or high risk of bias. Since the incidence of diabetes mellitus as well as diabetic foot is increasing, with a high percentage of patients suffering foot amputations, further and extensive study in this area should be carried out to find out the etiologic factors and pathologies of diabetic foot.

Abbreviations

IDF:International Diabetes Federation
RCTs:Randomized Controlled Trials
PRISMA:Preferred Reporting Items for Systematic Reviews and Meta-Analyses ()
DF:Diabetic Foot
PON1: Paraoxonase 1
ox-LDL:oxidized Low-Density Lipoprotein
IMA:Ischemia-Modified Albumin
TDCs:Tolerogenic Dendritic Cells
mDCs:mature Dendritic Cells
ASO:Atherosclerosis Occlusion Syndrome

Declarations

Ethics approval and consent to participate

The ethics committee of Shahid Sadoughi University of Medical Sciences approved the study (IR.SSU.MEDICINE.REC.1394.310 / Date: Nov.25st, 2015).

Consent for publication

Not applicable

Availability of data and materials
Please contact author for data requests.

Competing interests
The authors declare that they have no financial and non-financial competing interests regarding the content of this article.

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Authors' contributions
All of the authors had full access to all the data. They all contributed to the study design, data interpretation and writing of the manuscript. They all take the responsibility for data acquisition and confirm that the tests followed guidelines and the results are valid. They also guarantee the integrity and accuracy of data analysis. KK and MO screened the articles. MM performed the main stages of statistical analysis. All authors read and approved the final manuscript.

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References

[1.] UNWIN N, GAN D, WHITING D.*The IDF Diabetes Atlas: providing evidence, raising awareness and action.* Diabetes Res Clin Pract. 2010;87(1):2–3. doi: 10.1016/j.diabres.2009.11.006

[2.] SCHOLTE AJ, SCHUIJF JD, KHARAGJITSINGH AV, JUKEMA JW, PUNDZIUTE G, VAN DER WALL EE, et al. *Prevalence of coronary artery disease and plaque morphology assessed by multi-slice omography coronary angiography and calcium scoring in asymptomatic patients with type 2 diabetes*. Heart.2008;94(3):290–295. doi: 10.1136/hrt.2007.121921.

[3.] OHNISHI H, SAWAYAMA Y, FURUSYO N, MAEDA S, TOKUNAGA S, HAYASHI J.*Risk factors for and the prevalence of peripheral arterial disease and its relationship to carotid atherosclerosis: the Kyushu and Okinawa Population Study (KOPS).* J Atheroscler Thromb. 2010;17(7):751–758. doi: 10.5551/jat.3731

[4.] NGUYEN LL, HEVELONE N, ROGERS SO, BANDYK DF, CLOWES AW, MONETA GL, LIPSITZ S, CONTE MS. *Disparity in outcomes of surgical revascularization for limb salvage: race and gender are synergistic determinants of vein graft failure and limb loss.* Circulation. 2009;119(1):123–130. doi: 10.1161/CIRCULATIONAHA.108.810341.

[5.] MOULIK PK, MTONGA R, GILL GV.*Amputation and mortality in New-onset diabetic foot ulcers y aetiology.* Diabetes Care. 26: 491-494, 2003.

[6.] HARRINGTON C, ZAGARI MJ, COREA J, KLITENIC J.*A cost analysis of diabetic lower-extremity ulcers*. Diabetes Care. 2000;23(9):1333–1338. doi: 10.2337/diacare.23.9.1333.

[7.] EDMONDS ME.*The diabetic foot: pathophysiology and treatment*. Clin Endocrinol Metab. 1986 Nov;15(4):889-916.

[8.] HE C, YANG JG, LI YM, RONG J, DU FZ, YANG ZG, GU M1.*Comparison of lower extremity atherosclerosis in diabetic and non-diabetic patients using multidetectorcomputed tomography.*BMC Cardiovasc Disord. 2014 Sep 24;14:125. doi: 10.1186/1471-2261-14-125.

[9.] KOKOBELIAN AR, ZIGMANTOVICH IUM. [*Syndrome of diabetic foot and atherosclerosis of the lower extremity arteries*]. Vestn Khir Im I I Grek. 2006;165(3):74-8. [Article in Russian]

[10.] MUHTAROĞLU S1, BARLAK KETI D2, ÜNLÜHIZARCI K3. *Investigation of ischemia-modified albumin levels and some atherosclerosis-related serum parameters in patients with diabetic foot*. Turk J Med Sci. 2016 Jan 5;46(1):126-32. doi: 10.3906/sag-1406-38.

[11.] FANG Z1, DENG Q1, HU H1, WANG X1, SUN X1, GE X1, et al. *Characteristics of immunogenic and tolerogenic dendritic cells within the arterial wall in atherosclerosis and in vitro*. Int J Clin Exp Med. 2014 Dec 15;7(12):4846-56. eCollection 2014.

[12.] C.O. EKPEBEGH 1, P. MUSOKE 2, A. AKINRIMADE. *Diabetic Foot Gangrene Precipitated by Deep Venous Thrombosis: A case report*. The Journal of Diabetic Foot Complications 2016; 1(2): 36-39.

[13.] BARIŞ SARIAKÇALIMURAT SERTMEHTAP EVRANTAMER TETIKER. *Radiocontrast-Related Leukocytoclastic Vasculitis Misdiagnosed as Diabetic Foot Ulcer in a Type 2 Diabetic Patient: A Case Report*. Turk J Endocrinol Metab 2013; 17: 78-80.

[14.] SCHWEIGART, JH. KLOTSAS, A. SCHELENZ, S. DHATARIYA, K. *Portal vein thrombosis despite anticoagulation in a person with diabetes*. J R Soc Med. 98: 161-163, 2005.

[15.] KEANE, S. GALLAGHER, A. ACKROYD, S. MCSHANE, MA. EDGE, JA. *Central venous thrombosis during diabetic ketoacidosis*. Arch Dis Child. 86: 204-206, 2002.