Impact of type 2 diabetes on the plasma levels of vascular endothelial growth factor and its soluble receptors type 1 and type 2 in patients with peripheral arterial disease[*]

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Abstract: Objective: Type 2 diabetes coexistent with lower extremity artery disease (peripheral arterial disease (PAD)) can be observed in numerous patients. The mechanism compensating for ischemia and contributing to healing is angiogenesis—the process of forming new blood vessels. The purpose of this study was to assess the likely impact of type 2 diabetes on the plasma levels of proangiogenic factor (vascular endothelial growth factor A (VEGF-A)) and angiogenesis inhibitors (soluble VEGF receptors type 1 and type 2 (sVEGFR-1 and sVEGFR-2)) in patients with PAD. Methods: Among 46 patients with PAD under pharmacological therapy (non-invasive), we identified, based on medical history, a subgroup with coexistent type 2 diabetes (PAD-DM2+, n=15) and without diabetes (PAD-DM2−, n=31). The control group consisted of 30 healthy subjects. Plasma levels of VEGF-A, sVEGFR-1, and sVEGFR-2 were measured using the enzyme-linked immunosorbent assay (ELISA) method. Results: The subgroups of PAD-DM2+ and PAD-DM2− revealed significantly higher concentrations of VEGF-A (P=0.000007 and P=0.0000001, respectively) and significantly lower sVEGFR-2 levels (P=0.02 and P=0.00001, respectively), when compared with the control group. Patients with PAD and coexistent diabetes tended to have a lower level of VEGF-A and higher levels of sVEGFR-1 and sVEGFR-2 comparable with non-diabetic patients. Conclusions: The coexistence of type 2 diabetes and PAD is demonstrated by a tendency to a lower plasma level of proangiogenic factor (VEGF-A) and higher levels of angiogenesis inhibitors (sVEGFR-1 and sVEGFR-2) at the same time. Regardless of the coexistence of type 2 diabetes, hypoxia appears to be a crucial factor stimulating the processes of angiogenesis in PAD patients comparable with healthy individuals, whereas hyperglycemia may have a negative impact on angiogenesis in lower limbs.

Key words: Angiogenesis, Peripheral arterial disease, Soluble receptors, Type 2 diabetes mellitus, Vascular endothelial growth factor

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1 Introduction

Type 2 diabetes and atherosclerosis can be regarded as epidemic diseases at the turn of the 20th and 21st centuries. Coexisting complications of diabetes

and lower extremity artery disease (peripheral arterial disease (PAD)) account for the most common causes of lower limb amputation, whereas the frequency of amputations in patients with diabetes is five- to ten-fold higher than that in non-diabetic individuals. Macroangiopathic and microangiopathic complications are a major cause of mortality in diabetes. Symptoms like intermittent claudication occur twice as often in individuals with diabetes, which increases the risk of PAD three to four times (Norgren *et al.*, 2007; Jude *et al.*, 2010).

Vascular endothelial growth factor A (VEGF-A) is considered to be the main proangiogenic factor as it participates in the formation of new blood vessels. In patients with PAD, an angiogenic impulse is ischemia of tissues caused by narrowed vessels as a result of atherosclerotic plaque. Through hypoxia inducible factors (e.g. hypoxia inducible factor 1α (HIF-1α)), endothelial cells produce VEGF-A which participates in several angiogenesis stages. For example, VEGF-A leads to the activation and migration of endothelial cells and inhibits their apoptosis. Additionally, VEGF-A mobilizes endothelial progenitor cells (EPCs) which migrate to ischemic tissues, where they differentiate to endothelial cells and proliferate rapidly (Bao *et al.*, 2009). As clinical and laboratory data indicate, impaired angiogenesis can be observed in, for example, patients with diabetic foot syndrome (DFS) (Drela *et al.*, 2014). Therefore, it is necessary to investigate factors that have an influence on angiogenesis in PAD and diabetes alike. The practical use of discovered mechanisms is emphasized in effective attempts to apply VEGF-A and bone marrow mononuclear cells, for example, in the treatment of critical limb ischemia coexistent with diabetes (Kusumanto *et al.*, 2006; Skóra *et al.*, 2013).

Available studies suggest that soluble vascular endothelial growth factor receptors type 1 and type 2 (sVEGFR-1 and sVEGFR-2) may be regarded as angiogenic inhibitors. The studies by Liu *et al.* (2014) indicated that sVEGFR-2, when forming complexes with VEGF-A, decreased bioavailability of VEGF-A to endothelial receptors, thus affecting a decreased biological activity of VEGF-A.

In blood of patients with atherosclerosis and diabetic individuals, higher levels of VEGF-A caused by tissue hypoxia can be found (Botti *et al.*, 2012). However, the role of different concentrations of sVEGFR-1 and sVEGFR-2 in the process of angio-

genesis is still unknown. The aim of this study was to assess the likely impact of type 2 diabetes on the levels of VEGF-A, sVEGFR-1, and sVEGFR-2 in plasma of patients with PAD.

2 Materials and methods

Among 46 patients (28 males and 18 females), treated in the Clinic of Vascular and Internal Medicine of Dr. Jan Biziel University Hospital No. 2 in Bydgoszcz (Poland) for symptomatic PAD, we identified, based on medical history, a subgroup of 15 patients (8 males and 7 females) with PAD and co-existing diabetes (PAD-DM2+) and a subgroup of 31 non-diabetic individuals (20 males and 11 females) with PAD (PAD-DM2−). Exclusion criteria for participation in the study were a history of neoplastic disease, diabetic retinopathy, and a lack of a patient consent. PAD severity was determined based on the Fontaine classification. The control group consisted of 30 healthy volunteers (15 males and 15 females, average age (55.9±7.7) years), without clinically manifested atherosclerosis, neoplastic disease, or abnormal carbohydrate metabolism.

Venous blood plasma samples were collected to determine concentrations of VEGF-A and its soluble receptors sVEGFR-1 and sVEGFR-2. The enzyme-linked immunosorbent assay (ELISA) method was applied, using Quantikine reagents (R & D Systems, USA). Approval of the study was obtained from the local Bioethics Commission of Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń (CM UMK; Document No. 509/2011), and the clinical investigations were carried out in accordance with the Helsinki Declaration. The consent for participation in the study was freely given, informed, and expressed in writing on a relevant form. The results were statistically analyzed using Statistica Ver. 10.0 software (StatSoft, USA) and Excel (Windows, USA). The significance level was set at *P*=0.05.

3 Results

Table 1 demonstrates the characteristics of the study group (PAD, *n*=46). Among the PAD patients, 15 had coexisting type 2 diabetes, accounting for ca.

33% of the subjects, whereas 67%, i.e. 31 individuals, had no history of diabetes. Average glycated haemo-globin (HbA1c) level in patients with PAD and diabetes was (8.0±1.0)%. Average ankle brachial index in all subjects was 0.48±0.25 and mean intermittent claudication (IC) distance was (91.9±88.7) m. These patients also suffered from coexisting arterial hypertension (89.1%) or ischemic heart disease (43.5%), and were smokers in the vast majority (93.5%), with mean body mass index of (26.5±4.2) kg/m^2.

Fig. 1 shows the number of patients in the PAD-DM2+ subgroup and the PAD-DM2− subgroup depending on the degree of ischemia according to Fontaine classification. The PAD-DM2+ subgroup (*n*=15) included 1 patient classified in IIa, 10 in IIb, and 4 in IV based on Fontaine classification. In the PAD-DM2− subgroup (*n*=31), there were 4 patients in IIa, 20 in IIb, 2 in III, and 5 in stage IV of disease severity.

Table 2 displays mean concentrations of analyzed factors in the PAD-DM2+ and PAD-DM2− subgroups and in the control group. Both subgroups revealed significantly higher VEGF-A levels and lower concentrations of sVEGFR-2 than the healthy subjects.

Table 1 Characteristics of the PAD patients in the study group

Parameter	Value
Age (year)	63.0±8.5
Sex (F/M)	18 (39%)/28 (61%)
DM2+	15 (33%)
HbA1c in DM2+ subgroup	(8.0±1.0)%
DM2−	31 (67%)
Ankle brachial index	0.48±0.25
IC distance (m)	91.9±88.7
Fontaine IIa	5 (11%)
Fontaine IIb	30 (65%)
Fontaine III	3 (6.5%)
Fontaine IV	8 (17.4%)
Hypertension	41 (89.1%)
Coronary artery disease	20 (43.5%)
Smoking	43 (93.5%)
Body mass index (kg/m^2)	26.5±4.2
Waist-to-hip ratio	1.0±0.1

Data are expressed as mean±standard deviation (SD) or number (percentage), with a total of 46 patients. PAD: peripheral arterial disease; DM2: type 2 diabetes; IC: intermittent claudication
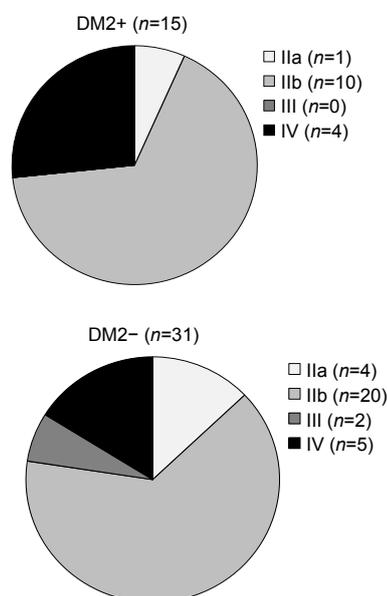

Fig. 1 Number of patients in the subgroup with PAD and type 2 diabetes (DM2+, *n*=15) and the non-diabetic subgroup with PAD (DM2−, *n*=31) according to Fontaine classification

Table 2 Plasma levels of VEGF-A, sVEGFR-1, and sVEGFR-2 in the study group (PAD) and the control group

Group	VEGF-A (pg/ml)	sVEGFR-1 (pg/ml)	sVEGFR-2 (pg/ml)
PAD (*n*=46)			
(a) DM2+ (*n*=15)	75.2±53.8	148.3±41.5	10987.6±3534.2
(b) DM2− (*n*=31)	88.8±84.8	127.5±33.6	8753.9±2277.3
(c) Control (*n*=30)	18.0±7.7	140.5±62.3	14481.5±3669.9
P-value	(a) vs. (c): **0.000007**	(a) vs. (c): 0.96	(a) vs. (c): **0.02**
	(b) vs. (c): **0.0000001**	(b) vs. (c): 0.8	(b) vs. (c): **0.00001**
	(a) vs. (b): 1	(a) vs. (b): 0.5	(a) vs. (b): 0.16

Date are expressed as mean±standard deviation (SD). The difference is considered to be significant at *P*-value of <0.05 (in bold)

Fig. 2 compares mean VEGF-A values of the PAD-DM2+ and PAD-DM2− subgroups and the control group. In the plasma of patients with PAD-DM2+, we found 4 times higher mean concentrations of VEGF-A when compared with healthy individuals (P=0.000007). Notably, the subgroup PAD-DM2− demonstrates nearly 5 times higher VEGF-A levels against the control group (P=0.0000001). The differences between the PAD-DM2+ and PAD-DM2− subgroups were not statistically significant.
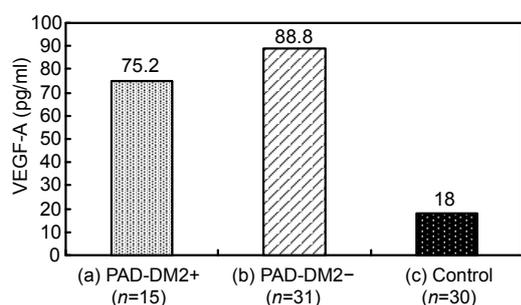

Fig. 2 VEGF-A levels in the subgroup of patients with PAD and type 2 diabetes (PAD-DM2+, *n*=15), the non-diabetic subgroup with PAD (PAD-DM2−, *n*=31), and the control group (*n*=30)
(a) vs. (c): P=0.000007; (b) vs. (c): P=0.0000001; (a) vs. (b): P=1

Fig. 3 shows mean concentrations of sVEGFR-1 in the plasma of PAD-DM2+ patients, PAD-DM2− patients, and the control group, respectively. In the subgroup of PAD-DM2+, we observed slightly higher, and in the subgroup of PAD-DM2− moderately lower, levels of sVEGFR-1 in comparison with the control group. The comparative analysis of sVEGFR-1 levels between the subgroups of PAD-DM2+ and PAD-DM2− against the control group did not show any statistically significant differences.

Fig. 4 displays sVEGFR-2 levels in the subgroups of patients with PAD and in healthy subjects. In the PAD-DM2+ subgroup, we found significantly lower mean concentration of sVEGFR-2 by ca. 25% in comparison with the control group (P=0.02). The subgroup of PAD-DM2− demonstrated significantly lower sVEGFR-2 level by ca. 40% when compared with the control group (P=0.00001). Differences in sVEGFR-2 concentrations between the two subgroups of PAD-DM2+ and PAD-DM2− were not statistically significant, yet a tendency was noted towards higher concentrations of sVEGFR-2 in PAD-DM2+ patients compared with PAD-DM2− patients.
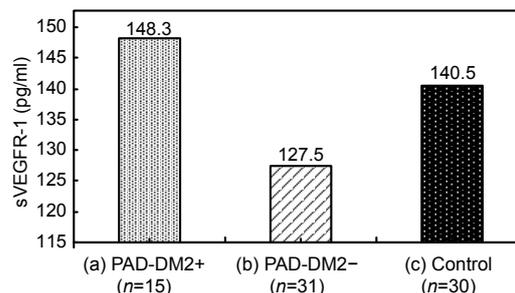

Fig. 3 sVEGFR-1 levels in the subgroup with PAD and type 2 diabetes (PAD-DM2+, *n*=15), the non-diabetic subgroup with PAD (PAD-DM2−, *n*=31), and the control group (*n*=30)
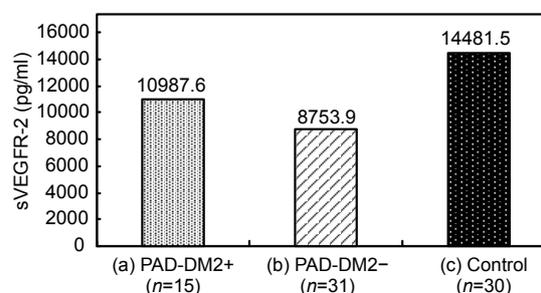(a) vs. (c): P=0.96; (b) vs. (c): P=0.8; (a) vs. (b): P=0.5

Fig. 4 sVEGFR-2 levels in the subgroup of patients with PAD and type 2 diabetes (PAD-DM2+, *n*=15), the non-diabetic subgroup with PAD (PAD-DM2−, *n*=31), and the control group (*n*=30)
(a) vs. (c): P=0.02; (b) vs. (c): P=0.00001; (a) vs. (b): P=0.16

Obtained levels of the above mentioned factors in uniform units (pg/ml) ensured the calculation of sVEGFR-1 to VEGF-A ratio as well as sVEGFR-2 to VEGF-A ratio. Table 3 shows the figures of sVEGFR-1/VEGF-A ratio and sVEGFR-2/VEGF-A ratio in the subgroups of PAD patients and in healthy subjects. Mean sVEGFR-1/VEGF-A ratio value in the subgroup PAD-DM2+ was 71% lower than that in the control group (P=0.0002). In the subgroup of PAD-DM2−, the figure was 73% lower than that in healthy individuals (P=0.00001). Differences between the subgroups of PAD-DM2+ and PAD-DM2− were not statistically significant. The sVEGFR-2/VEGF-A ratio was 75% lower in subgroup of PAD-DM2+ than that in the control group (P=0.000006), whereas in the subgroup of PAD-DM2−, the figure was 82% lower than that in healthy individuals (P=0.000001). In PAD-DM2+ patients, this parameter was insignificantly higher than that in the PAD-DM2− subgroup.

Table 3 sVEGFR-1/VEGF-A ratio and sVEGFR-2/VEGF-A ratio in the study group (PAD) and control group

Group	sVEGFR-1/VEGF-A	sVEGFR-2/VEGF-A
PAD (*n*=46)		
(a) DM2+ (*n*=15)	2.9±2.1	242.5±266.9
(b) DM2− (*n*=31)	2.7±3.1	174.7±151.4
(c) Control (*n*=30)	10.0±7.5	965.3±523.8
P-value	(a) vs. (c): **0.0002**	(a) vs. (c): **0.000 006**
	(b) vs. (c): **0.00001**	(b) vs. (c): **0.000001**
	(a) vs. (b): 1	(a) vs. (b): 1

Date are expressed as mean±standard deviation (SD). The difference is considered to be significant at *P*-value of <0.05 (in bold)

4 Discussion

The study revealed that PAD-DM2+ and PAD-DM2− patients had significantly higher concentrations of VEGF-A than healthy individuals (4- and 5-fold, respectively). The subgroup of PAD-DM2+ revealed slightly higher sVEGFR-1 levels and the subgroup of PAD-DM2− revealed slightly lower sVEGFR-1 levels when compared with the control group. In both subgroups, there were significantly lower sVEGFR-2 concentrations than those of healthy subjects.

The literature does not provide a uniform interpretation of angiogenesis parameters obtained in *in vitro* testing, animal models, or diabetic blood testing.

In the study conducted by Hochberg *et al.* (2001), blood samples were collected from PAD patients with coexisting diabetes or without diabetes, considering the classification based on critical limb ischemia (CLI) or chronic ischemia. In non-diabetic patients, no significant difference was observed in hypoxia-induced expression of VEGF, produced by monocytes, depending on the existence of CLI. Notably, patients with diabetes and coexisting CLI demonstrated significantly higher levels of VEGF produced by monocytes when compared with patients with diabetes but without CLI. The role of monocytes in angiogenesis and stimulation of their chemotaxis with VEGF in diabetic patients was also emphasized by Waltenberger *et al.* (2000) who determined VEGF levels in diabetic patients and healthy subjects, achieving significantly higher plasma concentrations of VEGF in patients with diabetes.

An animal model conducted by Hazarika *et al.* (2007) provided interesting results. A mouse with induced diabetes diet and artificially (surgically) induced lower limb ischemia had significantly higher baseline VEGF levels (before ischemia) in comparison with the control group. Then, after inducing ischemia, on the third day an insignificant VEGF increase was observed in mice with diabetes in comparison with non-diabetic mice, whereas on the tenth day an insignificant decrease in VEGF levels was noted in mice with diabetes as opposed to the non-diabetic group with ischemia. The authors claimed that this could suggest certain "depleting" compensation mechanisms—comprising the essence of angiogenesis and collateral circulation. Our study revealed slightly lower VEGF concentrations in the subgroup of PAD-DM2+, compared with PAD-DM2− patients with chronic ischemia.

Attempts to explain complex angiogenesis processes in patients with diabetes were made by Chung *et al.* (2006) who performed internal mammary artery biopsy in 32 diabetic patients and 32 non-diabetic patients and, apart from the levels of VEGF, they determined angiostatin and metalloproteinases (MMP-2 and MMP-9). They found significantly lower VEGF expression in patients suffering from type 2 diabetes in comparison with the control group and emphasized the involvement of other above-mentioned factors in angiogenesis. Libra *et al.* (2006) analyzed the impact of genetic polymorphism on interleukin-6 (IL-6) which affects VEGF secretion. Specific IL-6 genotypes were identified in individuals with type 2 diabetes coexistent with PAD, which induced higher VEGF levels in diabetic patients with PAD.

Blann *et al.* (2002) assessed the expression of angiogenic factors in plasma of patients with type 2 diabetes, and revealed significantly higher VEGF concentrations in diabetic patients comparable with healthy subjects. Similarly higher VEGF concentrations in plasma of patients with PAD irrespective of diabetes (non-)coexistence were reported by Botti *et al.* (2012). Yet Zakareia (2012) observed much higher plasma VEGF levels in subjects with diabetes and PAD. In the study on patients with the DFS, Drela *et al.* (2014) reported significantly higher VEGF-A concentrations in patients with type 2 diabetes. Ruszkowska-Ciastek *et al.* (2014) observed non-significant differences in the serum concentrations of VEGF-A between the patients with well-controlled diabetes and the control group. Orrico *et al.* (2010) carried out a study involving 33 subjects with CLI, identifying a subgroup of 22 type 2 diabetic patients. Notably, they revealed higher VEGF levels in plasma of all patients with CLI compared with the control group, whereas no differences were observed between the subgroups of diabetic and non-diabetic patients. The study of 70 subjects suffering from diabetes coexistent with PAD carried out by Bleda *et al.* (2012) revealed higher plasma VEGF levels in individuals with CLI compared with patients with chronic ischemia.

Based on the studies outlined above, patients with PAD and coexisting type 2 diabetes have higher VEGF-A levels. Undeniably, the crucial factor affecting high concentrations of VEGF-A, regardless of the presence of type 2 diabetes in patients with PAD, is hypoxia caused by stenosis or obstruction of "large and medium" caliber arteries due to the presence of atherosclerotic plaques. The achieved findings suggest that the coexistence of type 2 diabetes may inhibit angiogenesis, which is reflected by lower VEGF-A levels than that in arterial disease alone, as demonstrated in this study. This may be connected with the currently adopted view that hyperglycemia has a considerable impact on functional and structural damage to vascular endothelial cells—the so called microangiopathic complications (Duh and Aiello, 1999). Moreover, it is postulated that the stock of EPCs, responsible for vessel repair mechanisms, runs down much more in patients with diabetes than in patients with arterial disease, while hyperglycemia,

observed in patients with diabetes, can damage chemotaxis and migration of EPCs (Fadini *et al.*, 2005; Orrico *et al.*, 2010). Therefore, not only VEGF therapy but also administration of mononuclear cells is included in the treatment of CLI (Skóra *et al.*, 2013). To evaluate the role of VEGF in the angiogenic process in PAD and diabetes, the contribution of such factors as angiopoietin-1 and angiopoietin-2 should also be taken into consideration (Lim *et al.*, 2005). sVEGFR-1 is a recognized angiogenesis inhibitor. Soluble receptor (sVEGFR-1) and stationary VEGFR-1 anchored in endothelial cell membrane comprise a significant mechanism that inhibits VEGF circulating in the blood, and are referred to as decoy receptors (Meyer *et al.*, 2006). Their role is to catch VEGF-A ensuring a significant decrease in its bioavailability to VEGFR-2 on the surface of endothelial cells, reduce stimulation of cell signaling pathways, and therefore decrease biological function of VEGF. Our study showed slightly higher mean concentrations of sVEGFR-1 in the subgroup of patients with PAD and coexisting type 2 diabetes in comparison with the control group. Hazarika *et al.* (2007) conducted a study on an animal model to test sVEGFR-1 concentrations. Initial marking of sVEGFR-1 (before inducing ischemia) in the blood of mice with diabetes revealed significantly lower values comparable with non-diabetic mice. Then, on the third and tenth days following ischemia induction, sVEGFR-1 levels grew in the diabetic group and were higher than those in the non-diabetic subgroup.

Although this study did not reveal significantly different sVEGFR-1 levels in both subgroups of patients suffering from PAD, the inhibition capacity of VEGF decreased noticably in comparison with healthy individuals, from a 10-fold sVEGFR-1 predominance to ca. 3-fold in sick subjects. In this study we noted lower mean values of sVEGFR-2 in both subgroups of PAD-DM2+ and PAD-DM2− compared with the control group. Moreover, slightly higher sVEGFR-2 levels were observed in the subgroup with PAD and diabetes comparable with the non-diabetic subgroup with PAD. Similar results (versus the control group), i.e. decreased mean concentrations of sVEGFR-2 in patients with DFS, were achieved by Drela *et al.* (2014). No significant differences in the serum concentration of (s)VEGFR1 or (s)VEGFR-2

were observed by Ruszkowska-Ciastek *et al.* (2014) between the subjects with diabetes and the control group.

As shown in Table 3, the figures of sVEGFR-1/VEGF-A ratio in both subgroups of patients with PAD and in the control group indicated that the inhibition capacity expressed by the value of the above ratio is lower in patients with PAD than in healthy individuals despite significantly higher VEGF-A levels, which indicates the role of receptor type 1 in this process. Available studies do not provide information to assess the concentrations of formed sVEGFR-1–VEGF-A complexes. However, it should be noted that relatively low angiogenic inhibition capacity in both subgroups with PAD vs. the control group is the result of sVEGFR-1 being used up in the binding processes of VEGF-A when the levels of VEGF-A were high. Therefore, sVEGFR-1/VEGF-A ratio well illustrates decreased bioavailability of VEGF-A in patients with lower limb ischemia.

There are no studies on the evaluation of mutual proportions of VEGF-A and sVEGFR-1 levels or VEGF-A and sVEGFR-2 levels in patients suffering from PAD and coexisting diabetes. VEGF-A/sVEGFR-1 index was assessed in patients with pancreatic cancer and acute myeloid leukemia with regard to the severity of the disease and prognosis (Aref *et al.*, 2005; Chang *et al.*, 2008). This parameter could be used in practice to assess the degree of severity of PAD, which is the subject of the current research (Rość *et al.*, 2014). The studies by Toi *et al.* (2002) involving patients with breast cancer and the studies by Yamaguchi *et al.* (2007) concerning individuals suffering from colorectal carcinoma, were focused on analyzing the sVEGFR-1/VEGF ratio in terms of clinical parameters and prognosis of cancer. This study showed stronger angiogenic inhibition capacity demonstrated by the ratio of concentrations (sVEGFR-1/VEGF-A and sVEGFR-2/VEGF-A) in the control group in comparison with PAD subgroups. Yet the subgroup of patients with PAD and coexisting diabetes revealed a tendency towards higher anti-angiogenic potential comparable with non-diabetic patients with PAD, better illustrated by sVEGFR-2/VEGF-A ratio than by sVEGFR-1/VEGF-A ratio. This may have clinical significance and suggest increased but impaired angiogenesis in diabetic individuals, which

may explain, for example, impaired healing in the DFS. Nevertheless, this certainly needs to be confirmed by large-scale studies of patients with PAD and diabetes. This study should be treated as preliminary because there were insufficient numbers of patients in the study groups and the subgroup of non-diabetic patients with PAD was twice the size of the subgroup of type 2 diabetic subjects with PAD.

5 Conclusions

The coexistence of type 2 diabetes and PAD is demonstrated by a tendency to lower plasma levels of proangiogenic factor (VEGF-A) and higher levels of angiogenesis inhibitors (sVEGFR-1 and sVEGFR-2) at the same time. Regardless of the coexistence of type 2 diabetes, hypoxia appears to be a crucial factor stimulating the processes of angiogenesis in PAD patients comparable with healthy individuals, whereas hyperglycemia may have a negative (inhibitive) impact on angiogenesis in lower limbs.

Compliance with ethics guidelines

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中文概要

题　目：2 型糖尿病对外周动脉疾病患者血浆内的血管内皮生长因子及其可溶性受体浓度的影响

目　的：研究 2 型糖尿病对外周动脉疾病患者血浆内的血管内皮生长因子（VEGF-A）及其水溶性受体（sVEGFR-1 和 sVEGFR-2）浓度的影响。

创新点：首次研究了 2 型糖尿病对外周动脉疾病患者血浆内 sVEGFR-1 和 sVEGFR-2 浓度的影响。

方　法：选取 46 个外周动脉疾病患者，根据有无 2 型糖尿病分为糖尿病组（15 例）和无糖尿病组（31 例），另选 30 个健康志愿者为正常对照组。采用酶联免疫吸附法（ELISA）检测他们血浆中 VEGF-A 及 sVEGFR-1 和 sVEGFR-2 的浓度，然后通过对比各组浓度研究 2 型糖尿病的影响。

结　论：与正常对照组相比，外周动脉疾病患者具有较高的 VEGF-A 浓度（2 型糖尿病组 *P*=0.000007，非糖尿病组 *P*=0.0000001）以及较低的 sVEGFR-2 浓度（2 型糖尿病组 *P*=0.02，非糖尿病组 *P*=0.00001）。同时，2 型糖尿病组比非糖尿病组具有较低的 VEGF-A 浓度及较高的 sVEGFR-1 和 sVEGFR-2 浓度。研究结果表明：无论 2 型糖尿病是否共存，缺氧是导致血管生成的一个关键的刺激因素；同时，高血糖状态对下肢的血管生成有抑制作用。

关键词：血管生成；外周动脉疾病；可溶性受体；2 型糖尿病；血管内皮生长因子