

Thromboangiitis obliterans episode: autoimmune flare-up or reinfection?

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Background: The possible role of infectious pathogens in the development of thromboangiitis obliterans (TAO) was considered soon after the disease was first described. However, it is not yet known whether infectious pathogens induce thrombotic vasculitis or if they cause a type of autoimmune disease. To investigate whether TAO relapses are more likely due to reinfection or autoimmune flare, the serum levels of toll-like receptor (sTLR) 4, sTLR2, C-reactive protein (CRP), and neopterin were evaluated in TAO patients during both the acute and quiescent phases of the disease as well as in a gender-, age-, and smoking habit-matched control group.

Methods: Following a cross-sectional study design, 28 patients in the acute phase of TAO and 23 patients in the quiescent phase participated in this study. In addition, 31 matched controls were enrolled.

Results: Toll-like receptor (TLR) 4 was significantly higher in patients in the acute phase of the disease than in patients in the quiescent phase ($P=0.012$). Also, TLR4 was significantly higher in the patients with CRP $>7 \mu\text{m}/\text{mL}$ than in the patients with lower CRP ($P=0.031$). Notably, TLR4 in the patients in the quiescent phase of TAO was significantly lower than in the controls ($P=0.006$). No significant difference in the level of TLR2 was found among the groups ($P>0.05$). Neopterin was significantly higher in the acute phase of TAO in comparison to the quiescent phase ($P=0.003$) and the controls ($P=0.005$).

Conclusion: These findings indicate that the trigger of TAO might be Gram-negative bacteria, which can be hidden or immunologically suppressed in the quiescent phase of TAO, leading to a lower level of TLR4 accompanying the normal level of neopterin. However, relapses might develop according to toxic or hypoxic cell injuries. Hence, TLR4 shedding will increase, and therefore, sTLR4 could become closer to the level demonstrated in the controls.

Keywords: thromboangiitis obliterans, Buerger's disease, TLR2, TLR4, neopterin, CRP, peripheral arterial diseases, vasculitis, innate immunity, infection

Introduction

Thromboangiitis obliterans (TAO), or Buerger's disease, is an episodic, non-atherosclerotic segmental inflammatory and occlusive vascular disease that affects small- and medium-sized vessels of the extremities.¹ The intervals between flare-up episodes of TAO ranged from 6 months to 12 years.² Such episodes typically occur following changes in smoking habit, lifestyle, or mental stress.^{3,4} Currently, TAO is most prevalent in the Middle East, Southeast Asia, the Far East, and Eastern Europe.¹ The etiology of TAO remains unknown.¹ Although there is a close relationship between TAO and smoking, smoking explains neither the low prevalence of TAO among smokers nor its geographical distribution.⁴ The possible role of infectious pathogens in the development

of TAO has been considered since the disease was first described.⁴ However, it is not yet known whether infectious pathogens induce thrombotic vasculitis or if they cause a type of autoimmune or autoinflammatory disease.⁵ The two main challenging pathogens, according to recent studies, are *Porphyromonas gingivalis*, which is a commensal oral bacteria^{6,7} (in which case autoinflammatory diseases would be more likely), and *Rickettsias*,^{8–11} which might either induce the disease itself or induce autoimmune immunity because of its close structural similarity with human mitochondria.¹²

However, without considering which of these pathogens might be responsible for the development of TAO, the clues that point to the role of infectious pathogens in TAO suggest Gram-negative pathogens.^{5,6,8,9} Owing to the fact that innate immunity only recognizes the pathogen's category and not its precise species,¹³ studying the innate immunity of TAO patients might clarify whether TAO is an autoinflammatory disease, an autoimmune disease, or an infectious disease.

Toll-like receptor (TLR) 4 is a transmembrane protein that mainly mediates the innate immune response against the lipopolysaccharide (LPS) of Gram-negative bacteria. TLR2 is usually responsible for Gram-positive bacterial recognition, although Gram-negative bacteria can also activate the TLR2 signaling pathway.^{14,15} While TLR4 and TLR2 are transmembrane proteins, they are also normally detectable in serum due to the shedding of the cell surface receptor and the normal regulatory function of the cells.¹⁶ It has been demonstrated that the LPS of Gram-negative bacteria will downregulate the gene expression of TLR4 and, consequently, deplete TLR4.¹⁷ However, hypoxic or toxic cell injury will increase TLR4 shedding.¹⁸

The aim of this study was to evaluate the serum levels of TLR4 (sTLR4) and TLR2 (sTLR2) in TAO patients in comparison with controls. Also, to investigate whether TAO relapses are more likely due to reinfection or autoimmune reaction, sTLR4, sTLR2, high-sensitivity C-reactive protein (hsCRP), and neopterin, which assists adaptive immunity in eliminating intracellular pathogens,¹⁹ were compared between patients in the acute and quiescent phases of TAO.

Materials and methods

From February 2016 through August 2017, patients who had been clinically diagnosed with TAO, according to Shionoya's criteria (including disease onset under the age of 50, history of tobacco use, infrapopliteal arterial occlusion, either upper limb involvement or phlebitis migrans, and absence of atherosclerotic risk factors other than smoking)²⁰ with imaging confirmation were enrolled in the study. All patients and

controls signed a written informed consent form. The study was approved by the Ethics Committee for Clinical Research of the Mashhad University of Medical Sciences (no 941335).

Patients who experienced pain at rest, painful ischemic ulcers, gangrene, or progressive claudication were included in a study group designated as being in the acute phase of TAO. The quiescent phase group comprised patients with a prior history of hospital admissions who were called and invited to participate in the study after undergoing a physical exam. Both groups of patients were matched by age and smoking habit, according to the influence of age and smoking on the serum levels of neopterin, TLR2, and TLR4. Additionally, controls were included who were matched according to age, gender, and smoking habit.

sTLR2 and sTLR4 were evaluated by the ELISA method (ZellBio GmbH, Ulm, Germany). The serum level of neopterin was evaluated using the GenWay ELISA kit (GenWay Biotech Inc, San Diego, CA, USA) with the normal range being 0–10 nmol/L. Also, hsCRP was determined using the Monobind Kit (Monobind Inc, Lake Forest, CA, USA) according to its instructions, with the normal range being 0–3 µg/mL. SPSS version 11.5 (SPSS Inc, Chicago, IL, USA) was used for analysis of the patient data. The descriptive data are presented as mean ± standard error. According to the distribution of the data, ANOVA, *t*-tests, and Mann–Whitney and Kruskal–Wallis tests were used.

Results

A total of 94 serum samples from 51 patients who had been clinically diagnosed with TAO and 31 healthy, matched controls were selected for the current study. Of the 51 TAO patients, 28 were in the acute phase of the disease, while 23 patients were in the quiescent phase. Seven of the TAO patients had a history of more than one hospital admission as a result of disease flare-ups. In addition, seven patients underwent below-knee amputation either before or during the study. Of the seven TAO patients who underwent below-knee amputation, three were in the quiescent phase with amputation background and four were in the acute phase of the disease. All patients and controls were Caucasian men and current smokers at the time of blood sampling. The chief symptoms among the TAO patients in the acute phase were burning pain at rest (32.1%), toe or limb gangrene with rest pain (35.7%), chronic ulcer with pain (28.6%), and progressive claudication (3.6%).

The mean ages of the patients in the acute phase group, the quiescent phase group, and the control group were 40.6±1.1, 43±1.8, and 40.3±0.5 years, respectively. No significant difference was observed relative to age among

the studied groups ($P=0.34$). The mean number of cigarettes smoked per day in the acute phase group was 17.7 ± 1.2 vs 18.9 ± 3.3 in the quiescent phase group and 18.8 ± 0.79 in the control group. No significant difference in terms of cigarette consumption was found among the studied groups ($P=0.85$).

The mean level of sTLR4 in the acute phase patients was 3.3 ± 0.59 ng/mL, while in the quiescent phase group it was 1.98 ± 0.18 ng/mL, and in the control group it was 4.55 ± 0.87 ng/mL. Interestingly, sTLR4 in the acute phase group was significantly higher than in the patients in the quiescent phase of the disease ($P=0.012$). However, notably, the level of sTLR4 in the quiescent phase group was significantly lower than in the controls ($P=0.006$). Nonetheless, no correlation was demonstrated between the sTLR4 level in the acute phase group and the controls ($P=0.96$). The mean levels of sTLR2 in the acute phase group, the quiescent phase group, and the healthy controls were 7.6 ± 1.89 , 4.22 ± 0.94 , and 7.2 ± 1.98 ng/mL, respectively. However, no significant difference between the levels of sTLR2 was found ($P>0.05$).

The mean serum levels of neopterin in patients in the acute phase, the quiescent phase, and the matched controls were 13.1 ± 0.8 , 8.2 ± 0.6 , and 8.9 ± 0.3 nmol/L, respectively. The neopterin level was significantly higher in the patients in the acute phase of the disease in comparison with the patients in the quiescent phase ($P=0.003$) and the controls ($P=0.005$).

Moreover, 73.1% of patients were positive for C-reactive protein (CRP) and 26.9% were negative. The mean serum level of hsCRP was 16.6 ± 2.5 μ g/mL in positive subjects and 1.77 ± 0.29 μ g/mL in hsCRP-negative patients. The mean level of hsCRP in the quiescent and active phase of the disease was 5.76 ± 3.62 and 14.08 ± 3.2 μ g/mL, respectively. However, no significant difference was found between the hsCRP levels in the active and quiescent phases of TAO ($P=0.29$).

Table 1 shows an overview of the summarized data on sTLR4, sTLR2, hsCRP, and neopterin for TAO patients in the acute and quiescent phase of the disease and the control group.

The mean sTLR4 in hsCRP-positive subjects was 2.05 ± 0.3 ng/mL, while in the hsCRP-negative patients it was 2.97 ± 1.1 ng/mL, without any statistically significant difference between them ($P=0.95$). Additionally, the mean level of TLR2 in hsCRP-positive subjects was 3.8 ± 0.68 ng/mL, and in hsCRP-negative patients it was 8 ± 4.7 ng/mL ($P=0.57$).

According to several studies,^{21–23} the hsCRP cutoff value for differentiating infections from autoimmune disease flare-up has been considered $>5–7$ μ g/mL. Hence, the mean sTLR4 and sTLR2 were evaluated and compared in patients with positive and negative hsCRP according to the revised cutoff point of 7 μ m/mL. The mean sTLR4 in the revised

Table 1 Overview of the summarized data on sTLR4, sTLR2, hsCRP, and neopterin for TAO patients in the acute and quiescent phase of the disease and the control group

	TAO acute phase	TAO quiescent phase	Controls
Number of subjects	28	23	31
Number of patients with history of major amputation	4	3	
sTLR4 (mean \pm SE), ng/mL	3.3 ± 0.59 $P=0.012^*$	1.98 ± 0.18	4.55 ± 0.87
sTLR2 (mean \pm SE), ng/mL	7.6 ± 1.89 $P=0.26$	4.22 ± 0.94	7.2 ± 1.98
Neopterin (mean \pm SE), nmol/L	13.1 ± 0.8 $P=0.003^*$	8.2 ± 0.6	8.9 ± 0.3
hsCRP (mean \pm SE), μ g/mL	14.08 ± 3.2	5.76 ± 3.62	

Notes: * P -value <0.05 .

Abbreviations: sTLR, serum level of toll-like receptor; hsCRP, high-sensitivity C-reactive protein; TAO, thromboangiitis obliterans; SE, standard error of mean.

positive hsCRP patients was 2.79 ± 0.6 ng/mL, and in the hsCRP-negative patients it was 1.68 ± 0.18 ng/mL ($P=0.031$). The mean level of TLR2 in positive adjusted hsCRP subjects was 6.6 ± 2.6 ng/mL, while in the hsCRP-negative patients it was 2.8 ± 0.3 ng/mL ($P=0.08$) (Table 2).

Discussion

The role of infectious pathogens in the development of TAO was first hypothesized by Leo Buerger in 1908, who reported that the thrombosis of the patients he studied looked like syphilis thrombosis, although he did not detect *treponema pallidum* in their tissue specimens.²⁴ While the relationship between smoking and TAO was noted and emphasized by other angiologists, in 1924, Buerger concluded that smoking might be a predisposing factor for – but not the main etiology of – TAO development.²⁵ However, studies that investigated pathogens inside the vascular tissue of TAO patients were rare, possibly owing to a lack of facilities and scientific methods for conducting molecular tests.

During the 1980s, when immunochemistry techniques were being refined, Bartolo et al detected antibodies against *Rickettsias* in the serum of TAO patients in two different study sets.^{8,9} This work failed to draw significant attention. More recently, the footprint of *Rickettsias* has been detected using more precise tests, such as microimmunofluorescence and tissue PCR tests.^{10,11}

In addition, Iwai et al demonstrated the presence of patients' oral bacteria, *P. gingivalis*, in the thrombosis of their occluded arteries using tissue PCR.⁶ In another study in 2016 involving intravenous administration to beagles of

Table 2 Mean sTLR4 and sTLR2 in patients with positive and negative hsCRP according to two cutoff values

	TAO hsCRP >3 $\mu\text{m}/\text{mL}$	TAO hsCRP \leq 3 $\mu\text{m}/\text{mL}$	TAO hsCRP >7 $\mu\text{m}/\text{mL}$	TAO hsCRP \leq 7 $\mu\text{m}/\text{mL}$
sTLR4 (mean \pm SE), ng/mL	2.05 \pm 0.3 P=0.95	2.97 \pm 1.1	2.79 \pm 0.6 P=0.031*	1.68 \pm 0.18
sTLR2 (mean \pm SE), ng/mL	3.8 \pm 0.68 P=0.57	8 \pm 4.7	6.6 \pm 2.6 P=0.08	2.8 \pm 0.3

Note: *P-value<0.05.

Abbreviations: sTLR, serum level of toll-like receptor; hsCRP, high-sensitivity C-reactive protein; TAO, thromboangiitis obliterans; SE, standard error of mean.

the bacteria responsible for periodontitis, Chen et al demonstrated that this bacteria might have direct effects on platelet activation and, consequently, increase the risk of thrombosis.⁷

Given this information, if we consider infectious pathogens as a possible trigger for the development of TAO, we must identify the underlying mechanism to determine appropriate treatment.

Although TLRs are the main components of innate immunity, their potential role in the pathogenesis of autoimmune and autoinflammatory diseases has also been noted. For instance, it has been demonstrated that TLR4 plays a role in the induction of T helper 17, which is known as a key player in the development of autoimmune diseases.^{26,27} In a recent study, a significantly high expression of TLR2 and a significantly low expression of TLR4 on the monocytes' surface – but not in the serum levels – of patients with systemic lupus erythematosus (SLE) were demonstrated. However, no association was found between TLR2 and TLR4 expression and SLE activity.²⁸

As previously mentioned, neopterin is a biomarker of cellular immunity, being produced by human monocytes/macrophages and endothelial cells upon stimulation with interferon gamma, which is the key cytokine in cellular adaptive immunity.¹⁹ Evidence also points to an increase in the production of neopterin during acute Gram-negative bacterial infections, although the enhanced neopterin production is not specific to a particular infectious disease but only indicates that an immunological process is ongoing.^{29–32} An elevated concentration of neopterin in rheumatoid arthritis and SLE during disease activity has also been demonstrated,^{33,34} although its underlying mechanism is not well understood.

CRP is an inflammatory biomarker that is synthesized by the liver following IL-6 regulation. A high serum level of CRP has been reported in both infections and autoimmune diseases, such as SLE. However, as mentioned previously, several studies have been conducted on serum levels of CRP with the aim of differentiating bacterial infection from disease

flare-ups in patients with autoimmune diseases, and the best cutoff value of hsCRP for this purpose has been reported as 5–7 $\mu\text{g}/\text{mL}$.^{21–23,35}

The results of the current study demonstrated that neopterin and TLR4 were significantly increased in TAO patients in the acute phase of the disease in comparison with the TAO patients in the quiescent phase. Notably, in this study, sTLR4 was significantly higher in patients with hsCRP >7 $\mu\text{g}/\text{mL}$ in comparison to the patients with hsCRP <7 $\mu\text{g}/\text{mL}$. However, sTLR4 was significantly lower in patients in the quiescent phase of TAO in comparison with the controls. These findings indicate that the trigger of TAO might be intracellular Gram-negative bacteria, which can be hidden or immunologically suppressed in the quiescent phase of the disease, leading to a lower level of TLR4 accompanying the normal level of neopterin. However, relapses might develop according to a cell injury trigger. This trigger might be a toxic trigger following the smoking of an unprocessed or low-quality cigarette, a hypoxic trigger due to cold-induced vasoconstriction, or the presence of an infectious pathogen. Following cell injury, TLR4 shedding will increase, and therefore, sTLR4 could become closer to the level demonstrated in controls.

Conclusion

The data of the current study do not support the claim that TAO relapses are due to reinfection, but they do support the important role of infectious pathogens in TAO development. Further studies on the possible infectious trigger behind TAO development are highly recommended to achieve improved disease management.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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