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Deep vein thrombosis of the lower limbs in intravenous drug users*

Zakrzepica żył głębokich u osób uzależnionych od dożylnych środków odurzających

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Summary

Background: Addiction to intravenously administered drugs has been a serious epidemiological problem for years. Among the related health complications, deep vein thrombosis (DVT) is one of the most important. This paper provides an illustrative presentation of DVT in intravenous drug users (IDUs), HIV-positive subjects among them.

Methods: We searched PubMed, Ovid Journals, Scopus, ScienceDirect, Cochrane Library, Google Scholar and references from articles obtained. The main terms used to identify appropriate studies of DVT in IDUs were 'intravenous drug users', 'substance-related disorders' and 'deep vein thrombosis'.

Results: No guidelines exist for DVT in intravenous drug users. As many as 47.6% of IDUs report having suffered from DVT. IDUs may constitute approx. 50% of patients under 40 years of age with DVT, this being promoted by multiple vein punctures, groin injections, lack of sterility, insoluble microparticles and other factors. The clinical appearance is more complex than in the general population, which also makes prognosis more difficult. HIV infection can worsen DVT. It often appears as proximal iliofemoral thrombosis, accompanied by local and general complications. Ultrasound with a compression test is an objective method of choice, but must often be complemented with computed tomography.
Antithrombotic therapy in IDUs needs to be applied individually. The optimal method is supervised therapy at addiction treatment services.

Conclusions: Individual and public preventive measures, among them locally prepared guidelines for DVT in IDUs, may be the most important processes capable of effectively reducing the morbidity of septic and non-septic DVT.

Key words: **injection drug use • substance-related disorders • deep vein thrombosis • phlebitis, HIV • therapy**

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Introduction

In the 1990s, the number of people addicted to drugs administered intravenously (intravenous drug users, IDUs) increased significantly. Despite a later decrease in that number, this kind of addiction remains a serious health and social problem [19].

The use of narcotic drugs administered in this way, beyond the addiction and psychological and sociological aspects, poses the risk of various pathological consequences. IDUs are hospitalized more often than those not addicted, and both the time spent in hospital and the costs of treatment are significantly higher [30,68].

IDUs suffering from DVT are very often excluded from clinical trials investigating venous thromboembolism because of addiction, mental alterations or ongoing infections. For the same reasons, no clinical presentation or guidelines for treatment of DVT have been presented, besides conclusions drawn from observations or case reports.

Considering the fact that the estimated number of IDUs in the world ranges from 11 to 21 million and that 4-47.6% of IDUs report having suffered from DVT, we may assume that there is still too little known about the occurrence of the disease in this group (especially in HIV-positive patients), as emphasized by other authors [14,49,50,63,67,74].

This paper provides an illustrative presentation of deep vein thrombosis in IDUs.

Epidemiological data on DVT in the IDU population

The scarce data on the morbidity and clinical presentation of DVT in this particular group of patients usually come from emergency rooms and internal disease wards of municipal hospitals.

Retrospective research in the United Kingdom has shown a rapid increase in the number of cases of cutaneous and vascular diseases in IDUs aged 15-44 occurring between 1997 and 2004. The greatest percentage increase, as high as 788%, was related to inflammation and thrombosis of the femoral vein. The occurrence of inflammation and thrombosis of other veins increased in the same period by 388% [34]. DVT was (after overdose and endocarditis) the third most common cause of hospitalization of IDUs in Johannesburg, affecting 12% of IDUs hospitalized [75].

In research conducted on IDUs who used the services of a medically supervised injection centre, a survey revealed that 29% had experienced problems and diseases related to injections throughout the history of their addiction. These problems were abscesses and skin infections (6%), vein thrombosis (4%), sepsis (2%) and bacterial endocarditis (1%) [63]. Surveys performed at supervised addiction therapy services revealed that 22% of addicts had experienced DVT [74].

In a similar Polish work, based on anonymous surveys involving IDUs at supervised addiction therapy facilities, 28.8% of 73 addicted patients had experienced at least one episode of venous thromboembolism, of whom 23.3% had suffered from DVT and 5.5% from pulmonary embolism [7].

Analysis of medical documentation from specialist drug services helped to determine that 20.8% of all IDUs injecting heroin and 41.2% of those administering the drug into the femoral veins had experienced DVT in the past [51].

In a retrospective study, DVT as a complication of intravenous administration of illicit drugs was the cause of hospitalization in 9.6% of patients with DVT [70]. Research conducted on female patients with objectively confirmed DVT revealed that IDUs constituted 21.4% of all cases [50]. Both papers indicate that approx. 50% of cases of DVT in patients under 40 years of age involved intravenous use of drugs as a risk factor [50,70].

In one emergency room, IDUs constituted 58.8% of patients with objectively confirmed DVT [11].

Retrospective research on a Chinese population of patients with DVT has shown that 13.3% of cases were IDUs and that intravenous use of drugs was one of the main DVT risk factors in patients under 45 years of age [44].

Patients with DVT associated with the use of intravenous drugs are young or middle-aged, usually under 40 years of

age, whereas in the general population the highest morbidity occurs in patients aged over 60 [73]. These people actively use intravenous drugs, usually heroin, with this being administered mostly into the femoral vein. Average time from beginning the use of intravenous drugs to the appearance of DVT is approx. 6.5 to 10 years [45,64]. DVT occurs mostly in men addicted to intravenous drugs, which probably results from an addict profile similar in relation to sex [19]. The ratio of males to females, according to various authors, is 11.5:1, 7:1 or 2.8:1 [14,44,52], whereas in the general population this proportion varies accordingly from 1:1 to 1.6:1. Geographical and cultural factors have also impact on the results [4,73].

Risk factors and aetiopathogenesis of deep vein thrombosis in IDUs

The most common intravenous drugs are heroin, cocaine, amphetamine and opioids other than heroin [9,55]. The direct effect of these drugs on the coagulation system is not well known, nor is the role of various psychoactive substances as potentially independent DVT risk factors. Most studies of the effect of drugs on the vascular system and haemostasis focus on stimulating agents, mainly cocaine and its impact on the arterial system.

Opioid addiction per se is not a risk factor for DVT, although intravenous injection of these substances is an independent risk factor [12,48]. Heroin induces an increase in the density of alpha-2-adrenergic receptors in platelets, which intensifies adrenaline-dependent platelet aggregation [28]. In people addicted to opioids, a lowered antithrombin activity has been detected [9]. Antonowa et al. detected higher blood viscosity caused by increased aggregation of red blood cells and platelets and their deformability in individuals addicted to opioids [2]. Opioids may induce the concentration of fibrinogen and the aggregation of leukocytes to rise in people actively using these narcotics [27].

Data regarding the effect of cocaine on haemostasis are based on studies of its pathological influence on the arterial system, but there are no data on its pathogenetic impact on the coagulation system in veins. Moreover, some discrepancies exist between the *in vitro* and *in vivo* assays. Cocaine induces platelet activation through the release of the content of alpha granules and increases binding of fibrinogen to platelets, intensifies platelet aggregation and potentiates thromboxane synthesis [39,58,72]. Reversible deficiency of endogenous anticoagulants, antithrombin and protein C has been detected in patients with arterial thrombosis related to the use of cocaine [10]. Nasal application of cocaine induces increased activity of plasminogen activator inhibitor-1 (PAI-1) [53]. Intravenous introduction of a 0.4 mg/kg dose of cocaine causes a rise in the concentration of von Willebrand factor, haemoglobin, haematocrit and the number of red blood cells [35]. The authors conclude that these changes, by altering the viscosity of blood and augmenting the concentration of von Willebrand factor without compensational changes in endogenous fibrinolysis, may enhance adhesion and platelet aggregation and consequently lead to thrombosis. Amphetamine intensifies the release of 5-hydroxytryptamine (5-HT) from platelet granules [7]. As for the plasma coagulation mechanisms, it has been shown that amphetamine induces endothelial expression of the tissue factor and disables the *tissue factor pathway inhibitor* (TFPI) [29].

IDUs represent many risk factors associated with DVT development, the most important of which are vein lesions caused by multiple vein punctures and no sterility thereof, the type of substances injected, injection of insoluble particles of drugs and pills, irritation of vein walls by adulterants resulting in vein hardening, infection and inflammation [65]. In order to evaluate the effectiveness and safety of the filters used by IDUs, Scott et al. performed a simulated preparation of drugs in pills for intravenous application using techniques and equipment used by addicts. The size of the insoluble drug particles, depending on the type of substance, ranged from 2 to 50 microns, and some of the particles were derived from other sources, specifically kettle, cup, water, spoon, filter (cigarette filter, cotton bud), injection set and a non-sterile environment, including sloughed off epidermis of the person preparing the drug for intravenous use [65].

When IDUs are no longer able to inject into the upper limbs owing to vein damage, they use the femoral vein in the groin area or other lower limb veins, even though such a location constitutes a serious DVT risk factor. Sometimes IDUs commence punctures in the lower limbs in order to conceal injection sites [46,63].

In the period of narcotic stupor, the main risk factor for thrombosis and/or the development of chronic vein pathologies is immobilization, lack of muscle activity and, as a consequence, blood stasis. Multiple injections generate simultaneous injuries to subcutaneous tissue, muscles, nerves and vessels. Patients tend to limit the mobility of the talocrural joint because of pain. All of these circumstances, appearing in various configurations, lead to the impairment of the calf and foot muscle pump, which is an important pathogenetic factor associated with chronic venous diseases [55].

Salmon et al. list among the most significant risk factors for non-viral injecting-related injuries and diseases in IDUs the following: female sex, use of other drugs in addition to heroin, overdose and/or the offering of sexual services. Other factors are frequency and time of injection, use of shared needles and syringes during group injections and treatment sessions [63]. Some patients at supervised addiction therapy centres still perform drug injections. To conceal this fact, they do not use the services of a syringe and needle exchange [24]. Moreover, multi-dependent IDUs may be dissatisfied with methadone substitution treatment, hence the use of other drugs. One of the papers reports IDUs with DVT and pathological lesions in the groin area, 90% of whom were undergoing

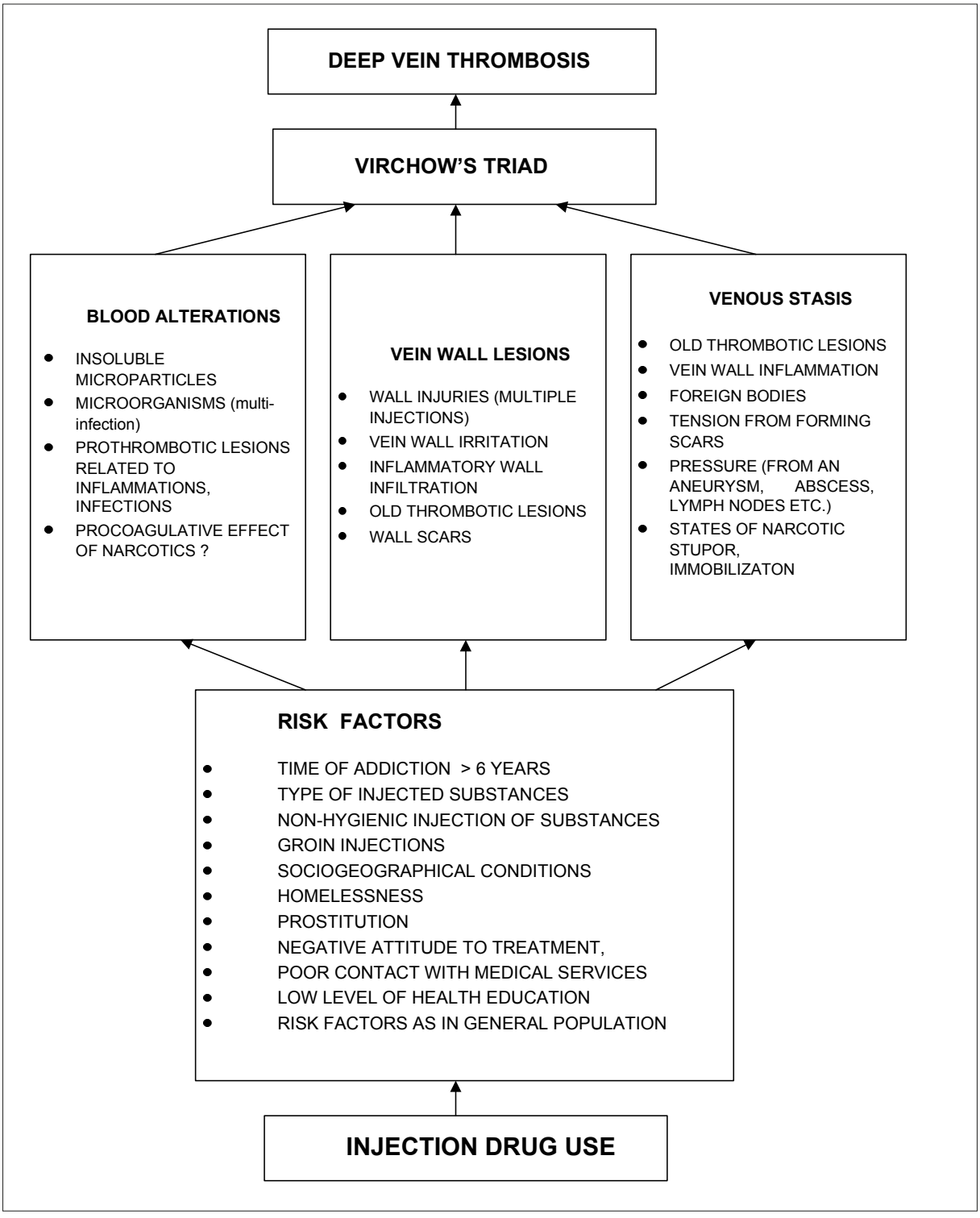

Fig. 1. Ethiopathogenesis of deep vein thrombosis in IDUs

substitution therapy at the time [64]. Intravenous use of drugs is responsible for a growing number of HIV infections, particularly in those parts of the world in which the phenomenon of addiction is the greatest problem. The percentage of IDUs infected with HIV exceeds 40% in some countries [69]. HIV infection is considered a risk factor for venous thromboembolism, and it is estimated that people who are HIV-positive bear a risk of DVT 2-10 times higher than the general population [38]. The correlation between HIV infection and increased predisposition to venous thromboembolism is still unclear. HIV infection, a low number of CD4 T cells, co-existing

infections (cytomegalovirus, *Pneumocystis jiroveci*) and antiretroviral treatment may be responsible for numerous aetiopathological mechanisms, such as endothelium activation and the presence of an increased number of circulating procoagulant microparticles, and for high expression of tissue factor (TF), which initiates coagulation processes through the extrinsic pathway. What is more, the role of deficiency or reduction in activity of endogenous anticoagulants is raised. Increased concentration of tissue plasminogen activator (tPA), its inhibitor PAI-1 and soluble thrombomodulin were also reported in those patients [38].

A retrospective observation showed that approx. 30% of patients diagnosed with AIDS suffer from venous thromboembolism and that the risk of occurrence of the latter is increased by a low immune status [62]. The presence of antiphospholipid antibodies has been detected in the course of AIDS. The frequency with which venous thromboembolism occurs in HIV-positive patients has not been determined. A report based on data from surveys completed by Polish IDUs at supervised addiction therapy facilities revealed that among HIV-positive drug addicts 28.1% had suffered from DVT in the lower limbs and 12.5% had experienced a pulmonary embolism, whereas among HIV-negative patients those values were 19.5% and 0% respectively. The authors consider HIV infection to be one of the risk factors associated with venous thromboembolism, and regard vein punctures in the lower limbs as the most important risk factor, this being present in all cases of venous thromboembolism in the IDUs examined [14].

Development of the disease is also supported by the IDUs' negative attitude towards healthcare and treatment. They explain their not reporting to a doctor as being due to a lack of money for the visit, lack of transportation, absence, their having forgotten or excessive pain. A common reason is a past negative experience of inappropriate behaviour by medical services towards addicts [24,30]. Patients themselves do not pay attention to early symptoms of chronic venous insufficiency until such problems as lesions or pain occur. Symptoms in the lower limbs are often disregarded due to other co-existing diseases, such as HIV/AIDS or viral hepatitis [54].

Level of education on possible thromboembolic risk from the use of intravenous drugs is of great significance in the spreading of venous diseases in this group. In a group of patients addicted to opioids, and participating in methadone or buprenorphine substitution programmes at detoxification facilities, a lack of basic knowledge on DVT risk was reported. As many as 22% had experienced DVT and 76% were aware of this complication in other patients. The most correct data were obtained from those patients who had recently suffered from DVT. Among the participants, 59% knew that DVT may be fatal, and 50% stated that DVT may lead to limb amputation [74].

As in the general population, other risk factors may occur in these patients, such as cancer, pregnancy, obesity, age, surgery, traumas, heart diseases, congenital or acquired thrombophilia, etc. [1,26,55]. However, no data on the occurrence of the above factors in IDUs diagnosed with deep vein thrombosis are available.

Dwyer lists a number of protective factors against injuries and diseases related to the use of intravenous narcotics, these being higher education, residence in a large city, hand washing, use of sterile water, preparation of the drug using acid and use of pulverized agents [18].

Although no studies have been performed to estimate haemostasis in IDUs with DVT, we may infer that the above-mentioned risk factors initiate or promote the chain of pathogenetic changes leading through Virchow's triad to the induction of the coagulation process, which is presented in broad outline in Figure 1. McColl proposes a potential pathomechanism of DVT in IDUs: repeated vein injury as a result of puncture and irritation of the vein wall leading to damage to the vascular endothelium and a local release of tissue factor. Co-existing infections, common in this population of patients, cause increased

Table 1. Clinical presentation of DVT in the subpopulation of IDUs

Location
Often bilateral [40,50,57,64]
More often right-sided [31,57,70]
Most often DVT in the femoral vein and the iliac vein [40,45,64]
Local symptoms
Groin pain
Skin redness
Higher skin temperature
Limb cyanosis
Swelling of the groin/limb
Groin haematoma
Skin necrosis of the groin, thigh, abdomen [20,24,40]
General symptoms
Septic state
Fever
Dyspnea
Cough
Chest pain
Other symptoms related to addiction [20,24,31,59]

Table 2. Clinical presentation of DVT in the subpopulation of IDUs – co-existing diseases

Skin fistula in the groin with leakage, haemorrhage [18,64]
Skin necrosis at injection sites [24]
Groin abscesses, abscesses at other injection sites [18,20,22,41,50,60]
Necrotizing fasciitis of the groin, thigh and abdominal region [18,20,24,52]
Skin and subcutaneous tissue inflammations [18,40,41,45,50,60,64]
Skin and subcutaneous tissue scarring [18,64]
Foreign bodies in soft tissues [60]
Enlargement of groin lymph nodes [60,64]
Septic phlebitis of deep and superficial veins [18,20,31,45]
Postthrombotic syndrome and chronic vein insufficiency [24,45,55]
Venous pseudoaneurysms [60]
Arterial injuries, pseudoaneurysms, infected pseudoaneurysms, arteriovenous fistulas, limb ischemia [20,40,52,60,64]
Osteomyelitis 18,24,60,73]
Sepsis [18,31,45]
Pulmonary embolism [14,41]
Septic pulmonary embolism, lung abscesses [20,60]
Infective endocarditis caused by multi-infection [18,20,24,60]
Anaerobe infection diseases – tetanus, botulism and others [6,24]
HBV, HCV infections [24,45]
HIV infection [14,24,64,69]

concentration of such factors as fibrinogen, factor VIII and von Willebrand factor, creating conditions favourable to the development of DVT [50].

Clinical presentation of DVT among IDUs

The clinical presentation of DVT among IDUs is highly variable (see Table 1). It may be assumed that the medical staff taking care of such patients will meet, besides the clinical presentation of the main disease, also addiction symptoms, consequences of the toxic effects of the drugs, psychiatric symptoms and problems of a sociological nature: hygiene problems, a negative attitude towards health care and/or therapy, homelessness, prostitution, lack of insurance, etc. [30].

DVT most often affects the lower limbs, and ilio*femoral* deep vein *thrombosis* is the most common in IDUs. It may also appear in the upper limbs and neck. In a retrospective study of a series of DVT cases, thrombosis in the upper limbs caused by intravenous injection of narcotics represented 42% of all diagnosed cases of thrombosis in this location and 8.5% of all thromboses in the upper and lower limbs [43].

The occurrence of bilateral thrombosis is estimated at 6.8-37%, although thrombosis in the other limb can be asymptomatic [40,50,57,64]. In three reports, thrombosis in IDUs occurred more often on the right side, in contrast to the general population [31,57,70]. Other diseases commonly co-exist with DVT in these patients (Table 2). Injuries to the arteries lead to their damage and the development of pseudoaneurysms and arteriovenous fistulas, often complicated by haemorrhages. Limb ischaemia may be a cause for amputation. Osteomyelitis is another example of local complications related to infection. Septic pulmonary embolism, bacteraemia and infective endocarditis caused by multiple infection may be general complications of non-sterile vein punctures and septic DVT. As such, the clinical presentation and course of the disease usually differ from those of DVT in the general population. Pain, skin redness, cyanosis with accompanying fever and an often grave septic condition are clinical symptoms of DVT in IDUs. Infections are usually caused by Gram-positive bacteria, mostly *Staphylococcus aureus*. Some difficult to cure cases of infection with methicillin-resistant *Staphylococcus aureus* (MRSA) in IDUs have been presented, as well as local and general infections with mixed bacterial flora, including anaerobes [3,5,20,24,25,45,47,59]. Descriptions of mycotic pseudoaneurysms in IDUs are also not uncommon [60].

Diagnostics of DVT in IDUs

Physical examination in the case of DVT is characterized by low sensitivity and specificity [26]. The most typical symptoms of the disease are swelling, cyanosis of the limb, increased tissue tonus and, in IDUs, overlapping local and general infections with impaired lymphatic drainage [64]. This combination of symptoms in IDUs makes diagnosis of DVT probable [20]. Diagnostics based on the clinical presentation in these cases seems easier than in the general population [11,64]. No false positives among IDUs reporting to emergency departments with suspected DVT have been described. Studies using colour duplex ultrasound of veins in IDUs with pathological symptoms in the groin area and an addiction of approx. 10 years in duration revealed occlusive or partially occlusive DVT in all patients [64]. By using the Wells Score for DVT Probability, examination of D-dimers and ultrasound in the emergency department, it was determined that the diagnosis in all IDUs reporting with suspected DVT was confirmed by objective methods. In a group not using intravenous narcotics, and with the same diagnostic model, the correct positive diagnosis was made in only 42.1% of cases [11].

Determination of D-dimer concentration is one of the sensitive tests (96.8%), although not very specific for the diagnosis of DVT (35.2%) [56]. A positive test result has low positive predictive value, and its negative predictive value is very high [37,42,61]. In patients with a septic form

of DVT caused by intravenous injections, a high concentration of D-dimers may be a result of an inflammatory or septic condition.

Ultrasound with a compression technique in transverse projection of the vessels is a suitable tool for the assessment of patients presenting with symptoms suggestive of lower extremity DVT. The examination in longitudinal projection is used to estimate the extension and location of the front of the thrombus and flow conditions. An enlarged vein insusceptible to pressure with a thickened, irregular wall and a more or less echogenic structure in its lumen is a typical ultrasound image of DVT [60,64,78]. Ultrasound allows co-existing pathological conditions to be revealed in the surrounding tissues: pseudoaneurysms, arteriovenous fistulas, abscesses, enlarged lymph nodes, haematomas and foreign bodies, e.g. a needle [60,64]. On the other hand, these lesions, as well as tissue scarring and acoustic shadow generated in a puncture site, may render the examination technically difficult, while significant swelling may force the examiners to use a low frequency sector transducer [64,70]. The same authors point to the following ultrasound DVT changes in IDUs visiting a doctor due to any problem with the groin: an occlusive or partially occlusive thrombus, a thickening of the vein wall, a narrow vein lumen, a hypoechogenic "halo" around vessels, thrombosis limited to the femoral vein in the area of a puncture, "waterfall-like" branches of the collateral veins upon obstruction of the femoral vein and thrombus characteristics demonstrating a chronic nature [64]. Ultrasonography can identify previously unrecognised femoral vein damage in those IDUs who inject drugs into the groin, and personalized feedback of ultrasound findings may enhance the patient's awareness of groin injecting risk [67]. The sensitivity and specificity of ultrasound in patients with symptomatic proximal DVT in the general population are 95% and 98% respectively [26].

Phlebography is generally not indicated, and it could be difficult to perform due to the inaccessibility of superficial veins [23,60].

Another imaging examination is contrast-enhanced computed tomography (CT), which allows, in the case of septic DVT especially, viewing of abscesses situated near a vein, particularly in locations inaccessible to ultrasound, e.g. the pelvis minor [20]. Also indicated in the diagnosis of septic forms of DVT is performance of echocardiography and chest X-ray to exclude endocarditis or septic pulmonary embolism. In the latter case, spiral CT of the lungs is also performed [20,44]. When septic osteomyelitis or arthritis is suspected (in IDUs, the latter is mostly in the pubic symphysis, hip or sacroiliac joints), it may be necessary to perform bone scintigraphy or CT [48]. Indicated in patients with a septic form of DVT is blood examination with assessment of white blood cells and CRP, as well as microbiological assays: blood cultures and smears from injection sites and purulent lesions. Serological tests for infections with HBV, HCV and HIV also need to be made [45].

Treatment of DVT in IDUs

Treatment of DVT in this population of patients is often difficult for various reasons. IDUs are treated mainly in emergency departments, which suggests poor contact with medical services until a critical moment in the course of the disease is reached. Homelessness, lack of cooperation, poor access to veins and continued use of narcotics are the main factors limiting the potential for application of proper therapy [34,45].

IDUs with diagnosed DVT are hospitalized more often than non-addicted patients (45% vs. 25%), and the average time to discharge is two days longer. More frequent hospitalization is explained variously by: a severe proximal form of DVT with extensive swelling, insufficiently controlled pain, a chaotic patient lifestyle making further tests and treatment difficult, social problems (homelessness), cognitive disorders and a lack of financial means for transport to examination and treatment centres [11]. On the other hand, there are cases of IDUs leaving the hospital before therapy begins. In various reports the percentage of IDUs diagnosed with DVT who were discharged from hospital on request was 17.6%, 20.7% and 34% [41,50,57].

The need for an individual approach to each of these patients is emphasized – one without prejudice, as this type of approach allows appropriate therapy [11]. Judging patients is to be avoided, and a cooperative attitude is preferred [30]. Studies by Carroll show that older medical staff are characterized by more positive relations with addicts [8].

The problem of treatment procedures and follow-up of these patients is still unresolved, as there are no standards regarding DVT in IDUs. Therapeutic options are low molecular weight heparin (LMWH) or antithrombotic treatment using vitamin K antagonists (VKA) taken orally. The use of the latter poses a higher risk of haemorrhagic complications and drug interactions, but also requires regularity and proper monitoring, which in this particular group may be difficult to obtain. Cases of self-therapy using illegally purchased warfarin have been described [16]. Furthermore, there have been reports of vitamin K deficiency among IDUs, which may increase the risk of complications in the course of such treatment [15]. Expert opinions indicate the need to avoid therapies based on coumarin derivatives [17,45]. In HIV carriers treated with protease inhibitors or *non-nucleoside reverse-transcriptase inhibitors* there is a risk of interactions leading to inhibition or induction of metabolism of VKA [33,71,77].

Used in appropriate doses, LMWH provides effective antithrombotic treatment without the need for monitoring, although the intended duration of the therapy may not be reached for various reasons, and the risk of haemorrhage is high in this cohort. The patient has to be informed that LMWH treatment should be continued for 12 weeks. An accurate estimation of the level of compliance with the indications for treatment with LMWH under ambulatory

conditions is difficult, and in one study the therapy lasted a length of time ranging from 2 to 12 weeks (an average of 6.5 weeks) [45]. Lawson et al. report that in the post-hospitalization period it is very difficult to obtain the appropriate duration of treatment. In one hospital, the average therapy length was 16 days. The authors conclude that a pragmatic approach to antithrombotic treatment in IDUs is a supervised use of LMWH for 6 weeks [41]. Poor compliance with the indications in the case of warfarin treatment and a lack of therapeutic efficiency expressed in an unsatisfactory INR (international normalized ratio) value are the other issues. In a small group of patients, only 20% completed a 6-month cycle of warfarin therapy. Far higher compliance was presented by patients treated with LMWH [57]. If a high risk of serious haemorrhagic complications exists during antithrombotic treatment, inserting a filter into the inferior vena cava has to be considered [45]. As in the general population, compression therapy should be prescribed, including graduated compression stockings [55]. It seems that in prescribing treatment to this group of patients the balance between the risks and the benefits has to be considered. It may be that shortening the total therapy time in IDUs is advisable, but only with a strict regime in the acute phase and maintenance of a sense of increased risk of complications and relapse of the disease. Patients should be directed to those addiction therapy centres where, besides methadone/buprenorphine administration, a supervised thrombosis treatment might be conducted using LMWH [17,41]. No data on the use of the novel oral *antithrombotic drugs* in IDUs diagnosed with deep vein thrombosis are available. At present, the standards governing DVT therapy are those for the general population [1]; thus all of the above-mentioned threats and limitations have to be considered in antithrombotic treatment in IDUs (authors' note). There is a need for guidelines relating to DVT therapy in these patients, and they should be developed locally [11].

Pain management in these patients may be a serious problem. If a patient is addicted to opioids, use of non-opioid analgesics such as non-steroid antiinflammatory drugs is indicated. In the case of very strong pain sensations, it may be necessary to administer them as short-acting opiates and in higher doses due to opioid tolerance. Methadone therapy needs to be introduced or continued [30].

Given that in septic DVT, sometimes requiring intensive care, the most common pathogenic microorganism is *Staphylococcus aureus*, the initial period requires empirical antibiotic therapy using intravenously administered penicillin resistant to beta-lactamase or benzylpenicillin with flucloxacillin [20,31,59]. In the following period, the results of cultures and antibiograms should be taken as a guide. Other commonly utilized antibiotics are aminoglycosides, cephalothin, ceftriaxone, vancomycin, ticarcillin, imipenem, metronidazole, etc. [21]. Depending on how advanced the septic condition is, intravenous antibiotic therapy may last up to 1 month [20]. The length of time may depend on the clinical condition of the patient and CRP concentration, since at one of the facilities intravenous antibiotic therapy was continued until the normalization of CRP level (from 2 to 6 weeks) [31]. A review and an analysis of a series of septic DVT cases, both relating to intravenous use of heparin and antibiotics, concluded that heparin should be introduced as early as possible in such cases [21]. Patients suffering from a septic form of DVT belong to a group at high risk of infective endocarditis [45]. Conservative therapy is usually sufficient against septic phlebitis in IDUs, and surgical treatment is rarely required [20,31].

Purulent lesions at injection sites, most commonly the groin, should first undergo surgical intervention and drainage [45,52]. Suppurative superficial phlebitis not responding to conservative therapy should be resected. In the case of co-existing arterial complications, patients may require intervention in the form of vascular surgery: resection, ligature or cleansing of a pseudoaneurysm, single or triple ligature of arteries, or selective or non-selective reconstructive procedures. All such surgical interventions should be carried out under the protection of broad-spectrum antibiotics [13].

Prevention of DVT in IDUs

Education of addicted patients and facilitation of access to appropriate medical care are important elements in prevention of vein complications [17,30]. A system of education for active IDUs could be introduced at supervised injection centres or supervised substitution therapy clinics. Each physician meeting an IDU patient should provide advice on limiting damage to health, breaking the addiction, avoiding intravenous drug administration or, if the latter seems impossible, safe injection methods [30]. The range of knowledge aimed at harm reduction covers information on medical complications of intravenous use of narcotics, indications for safe and hygienic injection methods, proper drug filtering, application of single-use equipment, hand washing, skin sterilization with alcohol and vein puncture techniques. It is important to develop harm reduction services and distribute single-use equipment, washing and sterilizing agents and filters [18,22,30,74].

Prognosis

It is difficult to estimate the prognosis in this group of patients. There are few data regarding the history of DVT in IDUs over time [44,70]. Long-term monitoring of complications and recurrence of the disease is practically impossible, as emphasized by some authors. Some observations may relate only to information registered in databases storing personal data, which may allow the fact of treatment at medical facilities and patient survival to be established [11]. The prognosis probably depends on many factors: clinical presentation, acute DVT treatment, co-existing diseases, compliance, addiction-related behaviour and many others (authors' note).

The recurrence of thrombosis within the first 6 months of an episode is observed more often in IDU patients than in

the general population and affects 31.6% of patients [70]. In the general population, a relapse of DVT in the same time-frame affects 8.6% - 9.1% - 10.1% of patients, and is thus three times as rare [32,56,70].

In the general population, a DVT episode increases the risk of developing chronic vein disorders by as much as 25.7 times [66]. Chronic symptoms of post-thrombotic syndrome in the follow-up period have been reported in 8 out of 20 IDUs with DVT [45]. Yegane et al. describe persistent swelling in the follow-up period in 25% of IDUs with DVT and a co-existing pseudoaneurysm of the femoral artery, subsequent to resection of the aneurysm, ligature and removal of necrotic tissues [76]. What is more, there are no data on the development of chronic vein disorders after a DVT episode in IDUs. However, it is known that such disorders occur in 88% of IDUs, far more often than in the general population [54].

The literature available suggests that pulmonary embolism has been reported more rarely than in the general population. In some studies no cases of pulmonary embolism were reported with confirmed DVT [45,50,64], while in others the incidence of the former is estimated at 5.5-13% of addicted patients with diagnosed DVT [14,41]. In the general population, 40 to 50% of patients with symptomatic proximal DVT without symptoms of PE have ventilation–perfusion lung scan findings associated with embolism [36]. Septic DVT may be complicated by sepsis, septic pulmonary embolism or bacterial endocarditis, all of which are life-threatening conditions. Infective endocarditis is estimated to occur in 4-10% of IDUs (without evaluation of its relation with DVT) [59,68]. No epidemiological data are available on the above complications in IDUs with vein thrombosis. The prognosis in such cases depends on the course of the given disease.

Co-existing DVT and artery injuries increase the risk of limb amputation, either because of critical ischaemia or because of ischaemic complications which follow reconstructive surgery or artery ligature due to infected pseudoaneurysm [18,76]. In the optimal scenario for such cases, patients present chronic ischaemia at various stages of peripheral artery disease [76].

Conclusions

Despite the limitations of this review, there emerges from it a highly complex problem of deep vein thrombosis related to intravenous injections of illegal drugs. The complexity of the problem relates both to its clinical symptoms and to diagnostics, treatment and observation in the follow-up period. The low number of original papers, the varying patient groups (often small), varying examination methods and varying assessment criteria, and, finally, the sociogeographical variation all make for an inability to compare these studies. Intravenous administration of drugs is not considered a risk factor for DVT, and there are no guidelines covering diagnostics and therapy in these cases. Deep vein thrombosis in IDUs requires an individual medical approach in each case, owing to the variety of symptoms. Behind the symptoms which the patient reports to the physician, there may be other, far more serious diseases. Diagnostics should therefore be expanded to all objective methods for the assessment of local and general conditions. Therapy based on common standards should be modified according to patient health (including HIV infection), addiction-related behaviour, drug interactions and cooperation with medical staff. Introduction and popularization of preventive measures among IDUs and for IDUs may be the most important process capable of effectively reducing the morbidity of septic and non-septic deep vein thrombosis, as well as other diseases related to the injection of drugs.

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