

<https://doi.org/10.35805/BSK2022IV024>

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Conflict of interest

The authors declare that they have no conflicts of interest

Keywords:

critical limb ischemia, peripheral artery diseases, diabetes mellitus, atherosclerosis, CLI, PAD, amputation

CRITICAL LIMB ISCHEMIA. LITERATURE REVIEW (PART 1)

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Abstract

Critical limb ischemia (CLI) is the final stage of peripheral arterial disease which may lead to the chronic restpain, loss of tissues and limbs. Despite the active development of new technologies, including endovascular and open surgical methods of treatment, and the development of various type of guidelines, CLI still remains an unresolved burden of vascular surgery around the world. In the first part of this review, we described the problem of PAD, in particular, critical lower limb ischemia and the role of diabetes mellitus in the progression of these pathologies. In addition, we tried to reveal the statistics of «small» and «large» amputations in different regions of the world, as well as their social and economic significance.

Аяқтардың критикалық ишемиясы. Әдебиет шолуы (1-Бөлім)

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Аңдатпа

Аяқтың критикалық ишемиясы перифериялық артерия ауруларының соңғы кезеңі болып табылады және қимылсыз созылмалы ауырсынуден, тіндерден және аяқтардан айырылу арқылы жүреді. Жаңа технологиялардың белсенді дамуына, соның ішінде эндоваскулярлық және ашық хирургиялық емдеу әдістеріне және әртүрлі нұсқаулардың дамуына қарамастан, аяқтың критикалық ишемиясы әлі күнге дейін бүкіл әлемде тамыр хирургиясының шешімін таппаған мәселесі болып қала береді. Осы шолудың бірінші бөлімінде біз төменгі аяқ ауруларының мәселелерін сипаттадық, атап айтқанда, төменгі аяқтың критикалық ишемиялары және осы патологиялардың дамуындағы қант диабетінің рөлі. Сонымен қатар, біз әлемнің әртүрлі аймақтарындағы «кіші» және «ірі» ампутиациялардың статистикасын, сондай-ақ олардың әлеуметтік және экономикалық маңыздылығын ашуға тырыстық.

Критическая ишемия нижних конечностей. Обзор литературы (часть 1)

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аяқтың критикалық ишемиясы, перифериялық артерия ауруы, қант диабеті, атеросклероз, ампутиация.

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Аннотация

Критическая ишемия нижней конечности (КИНК) является финальной стадией заболеваний периферических артерий и протекает с хроническими болями в покое, потерей ткани и конечности. Несмотря на активное развитие новых технологий, включающих эндоваскулярные и открытые хирургические методы лечения, и разработку различных методических рекомендаций, КИНК все еще остается нерешенным бременем сосудистой хирургии всего мира. В первой части данного обзора мы описали проблему заболеваний нижних конечностей, в частности, критической ишемии нижних конечностей и роль сахарного диабета в прогрессировании этих патологий. Кроме того, мы постарались раскрыть статистику «малых» и «больших» ампутаций в разных регионах мира, а также их социальную и экономическую значимость.

Конфликт интересов

Авторы заявляют об отсутствии конфликта интересов

Ключевые слова:

критическая ишемия нижних конечностей, заболевания периферических артерий, сахарный диабет, атеросклероз, КИНК, ЗПА, ампутация

Relevance

Critical lower limb ischemia (CLI) is the final stage of peripheral arterial diseases and occurs with chronic pain at rest, loss of tissue and limb. The most common causes of CLI are atherosclerosis and vascular complications of diabetes mellitus [1,2].

The role of diabetes mellitus

Diabetes mellitus (DM) is recognized worldwide as one of the most important noncommunicable diseases. The number of diabetic patients is constantly growing due to the increase in the size and age of

the population, the urbanization of the territory, the prevalence of obesity and a lifestyle [3].

The etiological classification of diabetes basically divides diabetes mellitus into two main types: type 1 and type 2, with type 2 diabetes accounting for the bulk (>85%) of the total prevalence of diabetes [4]. According to the latest estimates, there were 425 million people with diabetes in the world in 2017, and this is expected to rise to 629 million by 2045 (Figure 1) [4].

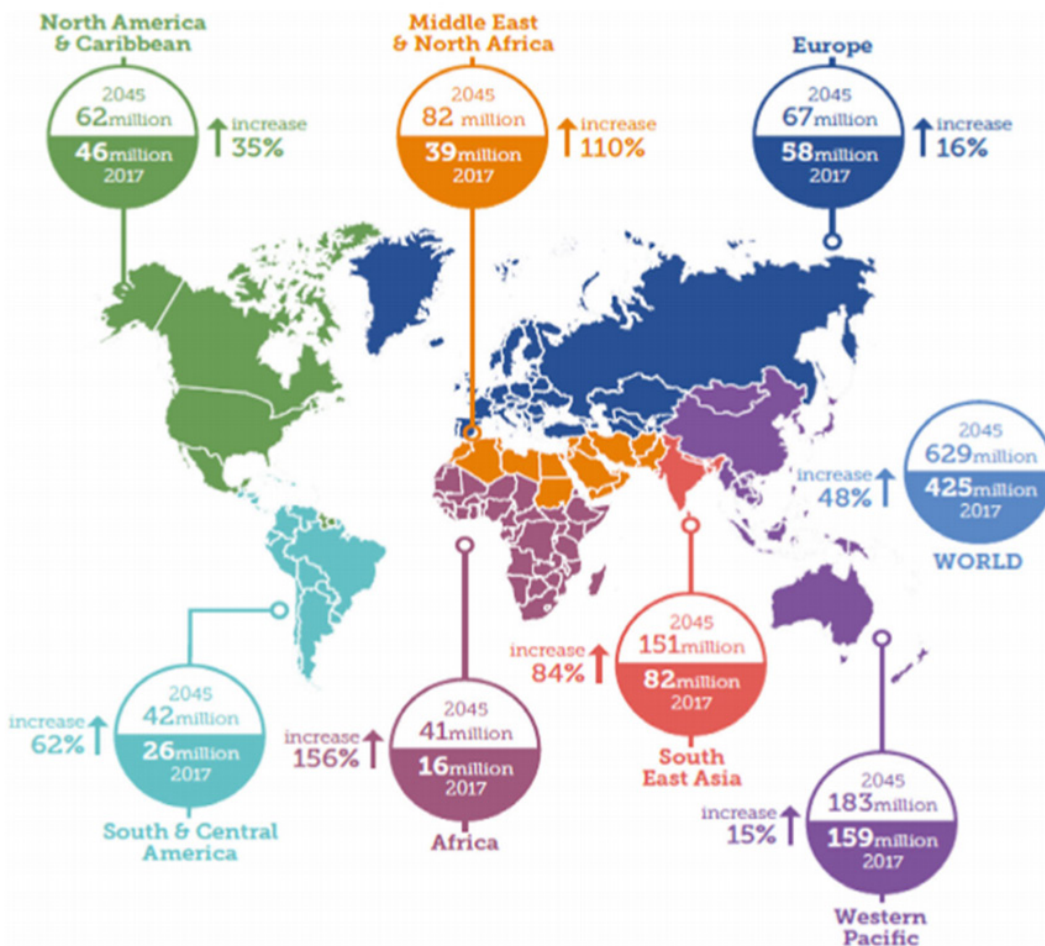


Figure 1.

Forecast of the incidence of DM by region (comparison of 2017 and 2045) [4]

Source: International Diabetes Federation. IDF diabetes Atlas. 8th edn. 2017

Determining the epidemiology of the comorbidity of diabetes and PAD faces the same challenges as measuring disease prevalence in PAD alone. Although the diagnosis of diabetes mellitus is well described, there is a wide variation in the severity and symptoms of PAD [5]. Thus, many patients may remain “asymptomatic”, making the true prevalence of comorbid PAD and diabetes mellitus difficult to ascertain. According to the best estimates, diabetes mellitus increases the prevalence of PAD by 2-4 times [6].

Type 2 diabetes leads to a 2-fold increase in the risk of cardiovascular disease, 10-fold increase in blindness, and 20-fold increase in limb amputation [7].

Diabetic foot ulcers are described as a full-thickness skin defect below the ankle that heals slowly or does not heal. Among 1000 patients with ulcers (one year study and follow-up), median healing time for toe was 147 days (95% CI 135–159 days), 188 days for midfoot (95% CI 158–218 days), and 237 days for heel ulcers (95% CI 205–269 days) with healing success at 1 year of 79% for plantar and 73% for non-plantar ulcers [8].

In a systematic review of Jupiter D.C. et al described that a certain cohort of individuals with diabetic foot ulcers, older age, peripheral neuropathy, male sex, long duration of diabetes and poor glycemic control are associated with a high risk of mortality [9].

The growing burden of diabetes mellitus around the world every year is one of the main priorities of public health, requiring overwhelming efforts for patients and their caregivers, health systems and society as a whole.

Morbidity and mortality

Peripheral arterial disease (PAD) is associated with a reduced quality of life and an increased risk of cardiovascular disease. Data on the incidence of PAD in the population vary depending on the age category of the examined and methods for diagnosing arterial blood flow disorders. Despite its wide prevalence, the

situation with PAD remains generally insufficiently resolved and underestimated [10].

It is estimated that more than 200 million people worldwide have PAD with a range of symptoms, a significant proportion of which occurs in the elderly (>20% of people over 80) [11]. Almost 40 million people with PAD live in Europe [12].

Patients with diabetes mellitus and PAD most often have the so-called “distal form”, where damage to the popliteal or tibial arteries occurs with wall calcification compared to non-diabetic patients [13]. The consequences of the progression of diabetes mellitus and peripheral arterial disease are critical ischemia of the lower extremities and the so-called diabetic foot syndrome.

Critical lower limb ischemia (CLI) occurs with chronic pain at rest, loss of tissue and limb. The most common causes of CLI are atherosclerosis and vascular complications of diabetes mellitus. In addition, severe atherosclerotic lesions of the arteries of the popliteal segment and below are often observed in patients with both diabetes and CLI [14].

There is a close relationship between diabetes mellitus and CLI [15]. The annual incidence of CLI is 100 cases per 100,000, and mortality reaches more than 20% in the first 6 months after diagnosis [16]. In a separate population of PAD patients with CLI, the estimated prevalence of diabetes mellitus ranged from 27% to 76% [17].

Most patients with CLI are in the final stages of their lives. A meta-analysis of studies of patients with CLI describes mortality from 10 to 54.3 patients with diabetes [18]. Mortality rates show the severity of the disease over time. Thus, the 5-year mortality associated with CLI without amputation ranges from 55% to 65% (Table 1) [19]. For example, this exceeds the 5-year mortality from breast cancer in women (10%), colon cancer (35%) and myeloma (50%) [20].

Table 1.
Comparison of 5-Year mortality rates across diseases

Disease	5-year mortality rate
Critical limb-threatening ischemia (without amputation)	55-65%
Female breast cancer	10%
Bladder cancer	23%
Colon cancer	35%
Myeloma	50%
Lung and bronchus cancer	82%
Pancreatic cancer	92%

Among patients who underwent a “major” amputation for CLI (below or above the knee), mortality at 1 year was 40.4% in a recent US Medicare study; This is 10% higher than in patients diagnosed with CLI who did not undergo amputation, where the annual mortality rate was 30% [21].

Treatment of critical lower limb ischemia in patients with diabetes mellitus remains an urgent problem. The treatment of this category of patients presents

certain difficulties, which are most often associated with multilevel and distal lesions of the arteries of the lower extremities, the presence of severe concomitant pathology.

Amputation statistics

Every year, more than 1 million lower limb amputations are performed in the world for diabetes mellitus, more than 600 thousand patients lose their sight, and approximately 500 thousand patients

develop renal failure [22]. More than 50% of all non-traumatic amputations occur in patients with diabetes mellitus [23].

Thus, in a systematic review by Moxey P.W. et al that rates of major amputations varied significantly (from 3.6 to 68.4 per 100,000 per year) around the world, likely due to differences in ethnicity, social deprivation, and, in particular, the prevalence of DM [24]. According to another systematic review by Narres M. Et al, including 19 publications, the risk of lower limb amputation in people with diabetes ranged from 7.4 to 41.3 per 100,000 [25].

Diabetes mellitus and PAD independently have a high risk of amputation [26]. Every year, more than 1 million lower limb amputations are performed in the world for diabetes mellitus, more than 600 thousand patients lose their sight, and approximately 500 thousand patients develop renal failure [22].

According to Vamos et al. and Trautner et al. people with diabetes have a 40 times greater risk of LEA compared to the general population, and approximately half of all people undergoing non-traumatic amputations are diagnosed with diabetes mellitus [27,28].

In the United States in 2015, about 504,000 people (out of a total population of 295.5 million) were living after a “major” amputation due to PAD, and this figure was predicted to more than double by 2050

[29]. According to a study of about 100,000 «major» lower limb amputations in the United States, more than half were associated with diabetes mellitus and PAD [30,31]. Other studies have shown that between 25% and 90% of amputations in study populations are associated with diabetes mellitus. [32].

In Germany, the absolute number of amputations was 57,637 in 2014, of which 13,048 were major amputations. The number of minor amputations increased from 35,513 in 2014. The number of amputations per 100,000 inhabitants was 43.9 in 2014, an increase of 25.4% [33].

It is worth noting that this range of relative risks of amputation exceeds that of people with diabetes and mortality from coronary heart disease by 3.5 (among women) and by 2.1 (among men). A significant reduction in the incidence of lower limb amputation has been shown in specific risk groups after the establishment of specialized clinics for the treatment of diabetic foot [34.].

In Kazakhstan, data on the number of amputations was taken from the National Patient Database (Electronic Register of Inpatients), where patients were classified according to ICD-10, as well as amputations according to the ICD-9 code (Table 2). Based on these data, the absolute number of lower limb amputations was 16,073, which corresponds to 87.9 per 100,000 population.

Type of amputation	Number Rate	per 100000 population
ABOVE THE KNEE AMPUTATION	597	3,26
AMPUTATION OF THE ANKLE JOINT	404	2,21
AMPUTATION OF LOWER LIMB, NOT OTHERWISE SPECIFIED	2602	14,2
TOE AMPUTATION	8094	44,3
FOOT AMPUTATION	3797	20,8
Total	16073	87,9

Table 2.
Types of amputation
of patients in Kazakhstan
for 2020

Social and economic importance

Amputation for diabetes mellitus and PAD represents a huge burden for patients, families and communities. At the patient level, of those who undergo amputations as a result of diabetes mellitus or PAD, >55% are permanently disabled thereafter. A similar number, especially those who undergo above-the-knee amputations, never return to ambulatory status [31].

In healthcare systems, patients with comorbid DM and PAD place a significant burden on the healthcare system. So, for example, according to some estimates, according to the Medicare insurance program in the United States, in just one year, the cost of patients with PAD exceeded \$84 billion [35,36]. Among those with PAD and DM who require intervention, they are the most expensive, with an average annual Medicare cost of ≈\$120,000 per patient compared to \$70,000 for non-diabetics per year of treatment [37]. The intensification of treatment inevitably leads to an increase in the

cost of treatment, however, it is clear that investing in effective methods of treating type 2 diabetes will slow down the occurrence of more costly complications. Thus, the earlier insulin therapy is started, the greater the cost-effectiveness.

Conclusion

Solving the problem of critical ischemia requires not only the development of technology, but also complex timely diagnosis and treatment, which makes the problem one of the priorities of public health. Peripheral arterial disease in diabetic patients is much more aggressive, with early involvement of large vessels coupled with distal symmetrical neuropathy. The need for high amputation in diabetics occurs 5-10 times more often compared to non-diabetics. The growing burden of diabetes mellitus around the world every year is one of the main priorities of public health, requiring overwhelming efforts for patients and their caregivers, health systems and society as a whole.

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