

Complications of Diabetes and Diabetic Foot

Subjects: [Peripheral Vascular Disease](#)

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Globally, a leg is amputated approximately every 30 seconds, with an estimated 85 percent of these amputations being attributed to complications arising from diabetic foot ulcers (DFU), as stated by the American Diabetes Association. Peripheral arterial disease (PAD) is a risk factor resulting in DFU and can, either independently or in conjunction with diabetes, lead to recurring, slow-healing ulcers and amputations.

mesenchymal stromal cells

MSC

diabetic foot

foot ulcer

charcot foot

amputation

1. The Global Burden of Diabetes Mellitus

Diabetes mellitus is a chronic metabolic disease characterized by elevated levels of blood glucose (hyperglycemia). Persistent hyperglycemia can lead to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. The number of people with diabetes in the world rose from 108 million in 1980 to 422 million in 2014. Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries as shown in **Table 1**. The 2023 global burden of Diabetes Mellitus is significant, with about 537 million people worldwide having diabetes ^{[1][2]}.

Table 1. Prevalence of Diabetes Mellitus (DM) in 2021 and projected prevalence for 2030 and 2045 ^[2]. In USD millions.

	2021	2030	2045	Increase (%)
Global	537	643	783	46
Europe	61	67	69	13
North-America & Caribbean	51	57	63	24
Western Pacific	206	238	260	27
South & Central America	32	40	49	50
Africa	24	33	55	134
Middle East & North Africa	73	95	136	87

	2021	2030	2045	Increase (%)	
South East Asia	90	113	152	68	in lower- main non-

communicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases or diabetes) between the ages of 30 and 70 decreased by 22%. Many people with diabetes develop problems with their feet from nerve damage and poor blood flow. This can cause foot ulcers and may lead to amputation. This research deals with innovative treatments for this unmet medical need: ulcers and amputation of the diabetic foot.

Types of Diabetes

- Type 1 diabetes (previously known as insulin-dependent, juvenile or childhood-onset) is characterized by deficient insulin production and requires daily administration of insulin. Prevalence of type 1 Diabetes Mellitus in 2017 was approximately 9 million people; the majority of them live in high-income countries.
- Type 2 diabetes may be due either by insufficient insulin production by the beta cells of the pancreatic islets or by defective action in peripheral tissues (muscle, liver) also called insulin resistance. Combination of both leads to high levels of blood sugar if not treated. Factors that contribute to developing type 2 diabetes include being overweight, not getting enough exercise, and genetics [3].
- Gestational diabetes, in which there is dysregulated glucose levels is at an increased risk of complications during pregnancy and at delivery. These women and possibly their children are also at increased risk of type 2 diabetes in the future.
- Monogenic diabetes, directly linked to the mutation of a gene related with the pancreatic beta cell physiology.

2. Economic Burden of Diabetes

Direct costs of diabetes represent approximately 10% of the budget of developed countries [2][4]. The 10 countries or territories with the highest total health expenditure due to diabetes (20–79 years) in 2021 (in USD billion) are shown in **Table 2**. The projected increase in the global burden of diabetes highlights the need for effective interventions to prevent and manage diabetes and their complications. For example, healthcare costs from patients with peripheral artery disease (PAD) and diabetes have an estimated cost of more than 80 billion USD in the US [5].

Table 2. Direct Cost of Diabetes Mellitus [2].

Country	Cost (in USD Billion)
United States of America	379.5
China	165.3
Brazil	42.9
Germany	41.3

Country	Cost (in USD Billion)
Japan	35.6
United Kingdom	23.4
France	22.7
Mexico	19.9
Spain	15.5
Italy	14.7

Diabetes can cause a range of complications that affect various parts of the body (**Figure 1**). In fact, although Acute Metabolic complications are more related with type 1 diabetes, the rest are present in both in type 1 and type 2 diabetes. Both the economic cost and death risk depend on complications. Chronic complications may be classified as: microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (infarction, stroke, peripheral artery disease). Complications are heterogeneous, but unfortunately, it has not been fully characterized the ethnic, genetic and lifestyle linked to specific complications, hospitalizations, and mortality among diabetic patients and contribute significantly to the high costs of diabetes care (**Table 2**).

A. ACUTE METABOLIC COMPLICATIONS

- Ketoacidosis
- Hyperglycaemia hyperosmolar state
- Lactic acidosis
- Hypocalcemia

B. CHRONIC COMPLICATIONS

- Ketoacidosis
- Hyperglycaemia hyperosmolar state
- Lactic acidosis
- Hypocalcemia

C. OTHERS

- Arteriosclerosis
- Cataracts and Glaucoma
- Intergumentary damage
- Reproductive damage
- Psychological damage; Depression

B1. MICROVASCULAR

- Nephropathy
- Retinopathy
- Neuropathy

B2. MACROVASCULAR

- Peripheral Arterial Disease
- Myocardial Infarction
- Stroke

CTLI

[Foot damage]

**Wound
Infections**

Figure 1. Complications of Diabetes Mellitus. CTLI: Chronic Life Threatening Limb Ischemia (No-Option Chronic Limb Ischemia).

Some of the chronic complications of diabetes include nerve damage (diabetic neuropathy), chronic kidney disease (diabetic nephropathy), eye problems (diabetic retinopathy), foot problems, heart attack, stroke, skin problems, digestive problems, sexual dysfunction, oral and dental problems, etc. These complications can be serious and can

lead to amputation, blindness, heart disease, and kidney failure if left untreated. However, with proper management of blood glucose and conventional treatments, many of these complications can be prevented or delayed. This research deals with innovative therapies to treat some of these complications related with PAD, critical limb ischemia (CLI), ulcers and amputations, in fact an unmet medical need.

About 20% of people with diabetes will develop PAD which remains to be a serious public health problem. Estimated prevalence of PAD in 2019 was 113,443,017 people with an annual incidence of 10,504,092 [6] and 11% of people with PAD may end with Chronic Life Threatening Limb Ischemia (CTLI).

Figure 2 summarizes the prevalence and distribution of patients with CTLI (chronic threatening limb ischemia, and CLI with no option of revascularization). Although these figures mostly depend on differences in prevention, evolution and ethnicity. Since there is an estimation of 537 million people with diabetes [2] the risk of CTLI may reach a prevalence of approximately 2.95 million people all over the world (diabetes has a 20% risk of PAD, PAD a 11% risk of CLI and 25% CLI are considered non revascularizable or CTLI).

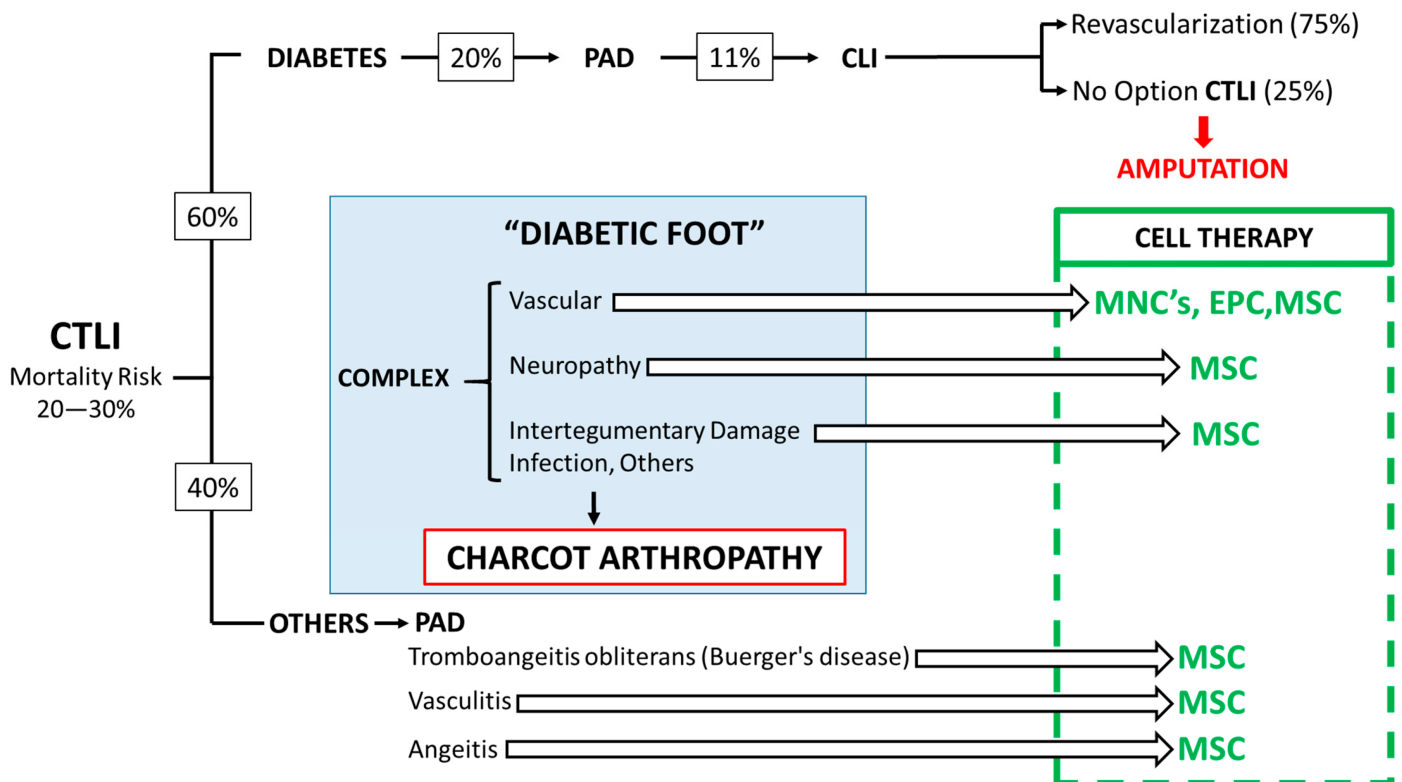


Figure 2. Prevalence and distribution of patients with CTLI. Proposed ATMP treatment depending on the complex nature of the diabetic foot. MNC: Mononuclear Cells, EPC: Endothelial Progenitor Cells, MSC: Mesenchymal Stromal Cells.

Since a high percentage of PAD patients develop CLI and 25% of CLI has no option for Revascularization (chronic threatening limb ischemia, CTLI), the risk for ulcers, amputation and mortality increases substantially. Furthermore, the mortality risk associated with CTLI ranges between 20% and 30%. Then, there is an obvious need to develop novel therapeutic strategies focused in ameliorate limb perfusion and neuropathy together with a decrease in the

concomitant inflammatory process. Ulcer healing will be a consequence. However, when Charcot arthropathy and infections appears researchers can only expect a limited response. Although researchers do not have yet an advanced therapy medicinal product (ATMP) approved by regulatory agencies (FDA, EMA, etc.) to treat CTLI and prevent amputation, the amount of results in pilot, Phase I and Phase II studies strongly suggest that a proper segmentation of CTLI patients and the selection of worth primary and secondary endpoints in the Phase III trials will help to establish the profile for Cell Therapy of CTLI. The right side of the **Figure 2** summarizes the ATMP cell therapy options.

1.3.1. The Diabetic Foot

Diabetic foot a complex complication in which PAD, neuropathy, arteriosclerosis and intertegumentary damage are related, with a “personal mix” that differs from one to another patient. Diabetes is a significant risk factor for developing CTLI due to PAD. Patients with diabetes concomitant to CLI represent a sub-group at particular risk. CLI appears when a severe obstruction of the arteries markedly reduces blood flow to the extremities and progress to the point of severe pain and even skin ulcers or sores. Unfortunately, vessels affected in diabetic patients are distal, small diameter and profusely distributed making nonviable surgical revascularization. Furthermore, diabetes is associated with decreased limb survival in patients with CLI.

Figure 3 also depicts the concomitant process and tentative biomarkers. A decrease in endothelial progenitor cells (EPC) with reduction on oxygen availability (as measured by transcutaneous oxygen pressure-TcPO₂) and ischemic pain is accompanied by an increase in inflammation and the appearance of ulcers.

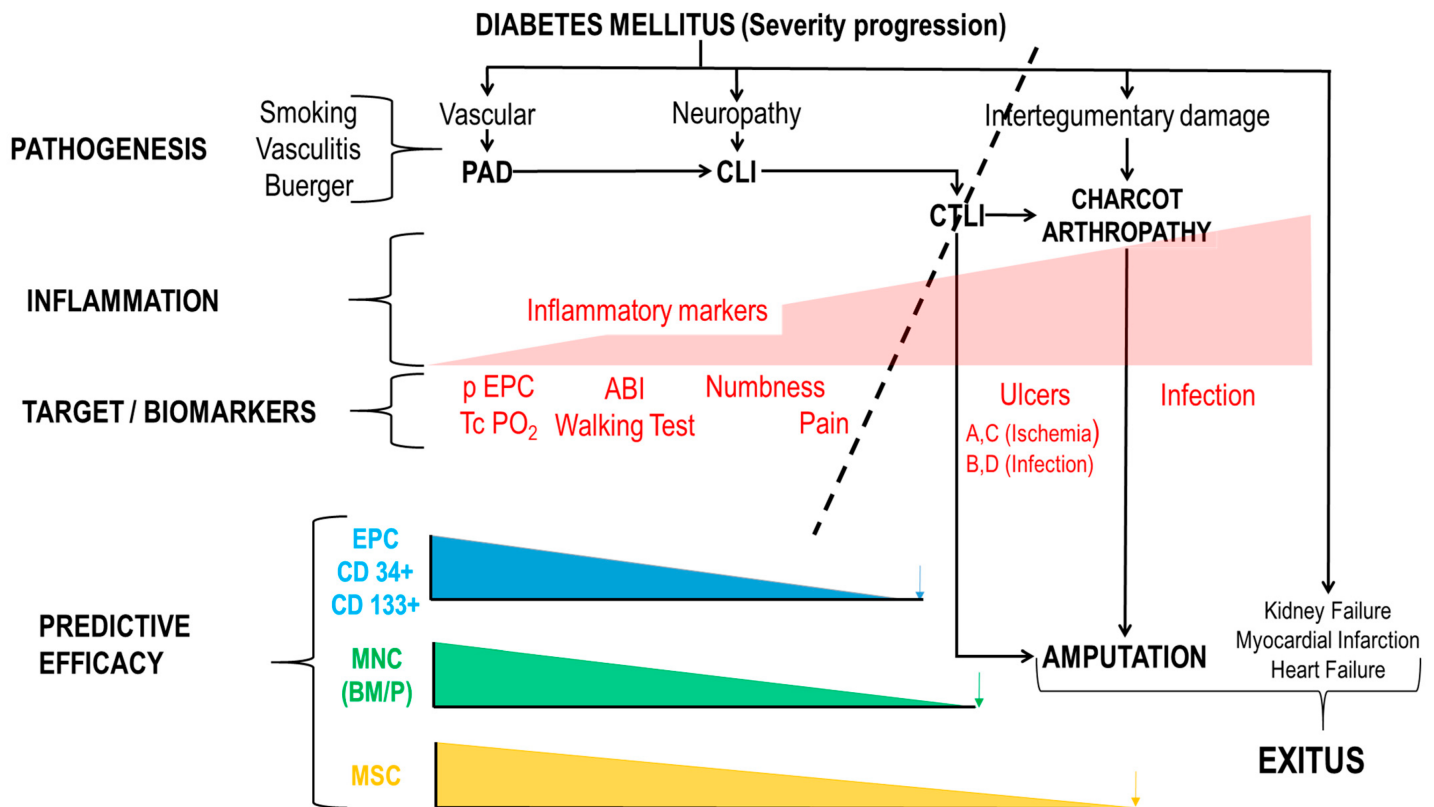


Figure 3. Pathogenesis, target biomarkers and predictive efficacy of AMTPs. PAD: Peripheral Artery Disease. CLI: Critical Limb Ischemia. CTLI: Chronic Life-threatening Limb Ischemia. ABI: Ankle Brachial Index. EPC; Endothelial Progenitor Cells. ABCD; University of Texas Staging System for Diabetic Foot Ulcers. Blue, Green and Orange arrows mean that at that point, outcome is amputation.

CLI characterized by ischemic rest pain, ulcers, or gangrene is the end-stage of PAD, usually associated with a significant risk of affected limb loss and a high risk for cardiovascular events. No-option CLI or CTLI [7][8][9], is an independent risk factor for major amputation in diabetic patients. The annual incidence is approximately 500–1000 new cases per million in industrialized countries [7][10][11]. Then, there are between 0.6 million and 1.36 million people with CTLI per year. According to the World Bank 17% of the world population live in industrialized countries. To note that by 2030, China, Thailand, Mexico and Turkey will join the developed countries, then it is expected that it will be 50% of the world population by 2050. Tobacco, diabetes and age are independent risk factors. Critical threatening limb ischemia grasps for different pathologies: such as Buerger disease, thromboangiitis obliterans and others, but diabetes is in the origin of more than 60% of CTLI. In conclusion, healthcare systems are facing a costly high prevalence threatening situation.

Diabetes is the leading nontraumatic cause of lower limb amputations [12][13]. As a result, neuropathy injuries in their feet and ankles are more frequent and more severe than people without diabetes. Wounds and skin infections heal poorly in persons with diabetes. Endovascular intervention and bypass surgery are the current treatment options [11][14][15][16][17]. However, approximately 20–30% of CLI patients are not eligible for revascularization, or this procedure has failed.

1.3.2. The Complex Nature of the Diabetic Foot

Atherosclerosis in distal arteries in combination with diabetic neuropathy can lead to CLI (**Figure 1**). The distal nature of the arterial narrowing in CLI is less amenable to revascularization. CLI is the advanced stage of PAD, which results from a progressive thickening of an artery's lining (caused by atherosclerosis) and narrowing of the vessel, which reduces blood flow to the limbs. Patients with diabetes are more likely than other patients to have distal disease that is less amenable to bypass grafting. Limb salvage after bypass is better for insulin and non-insulin diabetics, compared to the endovascular approach.

The pathogenesis of CLI is complex and involves atherosclerosis, peripheral arterial disease, and other vascular risk factors (**Figure 3**).

1.3.3. Arthropathy of Charcot

Charcot arthropathy (CA), also known as Charcot foot and Charcot neuroarthropathy, affects the bones, joints, and soft tissues in the feet and ankles, caused by an inability to sense injuries, which can result in significant deformities. Diabetes is the main risk factor of CA, but not the only one. Leprosy, syphilis, poliomyelitis, chronic alcoholism, or syringomyelia among other conditions, may also end with CA. It occurs most commonly in patients who have peripheral neuropathy, or loss of sensation, in the foot and ankle, which can be caused by diabetes.

CA results in progressive destruction of bone and soft tissues at weight bearing joints. The neurovascular theory suggests that CA is caused by a combination of vascular and neuropathic factors. The earliest signs of Charcot are mild pain and discomfort, swelling of the foot, redness and warmth that may be confused with and infections and which can occur without an obvious injury.

Hyperglycemia, decreased blood supply and neuropathy that impairs sensation in the feet and makes it difficult to heal wounds, together with pressure and inability to sense injuries ends with minor undetected lesions, deformities and ulcers. Non-surgical conservative treatments (Immobilization, protective footwear, activity changes) are used in the first phases however surgical treatment are necessary with the progression of the disease including debridement of ulcers, exostectomy, deformity corrections, arthrodesis and amputation for severe cases.

One of the key issues is diabetic wounds, particularly leg ulcers and diabetic ulcers. Diabetes slows the healing process by affecting each stage of wound healing, including homeostasis, inflammation, proliferation, and remodeling. This has a long-term detrimental impact on morbidity and mortality as well as quality of life. Diabetic wounds display a long-lasting inflammatory phase together with a delay in the development of mature granulation tissue and a decrease in the tensile strength of the wound. This could be as a result of the ischemia-causing vascular damage [18][19]. In severe cases of CA, it may not be possible to save part or all of the foot resulting in minor or major amputations.

Prevention of CA and new treatments for this unmet medical need, such as new ATMPs, to avoid amputation are needed. Given the complexity of Diabetic Foot, the results of cell therapy published so far are difficult to compare.

1.3.4. Treatment of Critical Ischemia of the Limb

Conventional Medical Care

Percutaneous transluminal angioplasty (PTA) has become the first line treatment. However, despite the high success rate of PTA, clinical restenosis still represents a huge problem, reaching around 70% at 1-year follow-up [20][21], even more, since in the obstructive pattern is more distal and disperse is quite difficult to succeed with PTA then is considered as no-option CTLI [22][23]. No-option CTLI drives to non-healing ulcers, failure of surgical approaches with a high risk of major amputation, and mortality [24].

Advanced Therapies: Clinical Trials with ATMP to Treat the Diabetic Foot

In 2001, the EMA (European Medicines Agency) defined Advanced Therapy Medicinal Products (ATMPs)/Advanced Therapies as medicines for human use including Somatic Cell Therapy, Gene Therapy, Tissue Engineering and Combined Advanced Therapies. The legal definitions of Cellular and Gene Therapies can be found in Directive 2001/83/EC amended by Directive Commission 2008/12/EC. Definitions of Tissue Engineering and Combined Advanced Therapies can be found in Regulation (EC) No 1394/2007 [25]. Shown in **Figure 2** and **Figure 3** are the tentative ATMPs that have been use so far and the expected effects bases in their mechanism of action.

Photodynamic Therapies

Typically, the conventional approach for managing diabetic foot ulcers (DFU) involves several key steps, including debridement (cleaning and removal of dead tissue), enhancing blood circulation, maintaining a moist wound environment, and effectively controlling infections ^[26]. Nevertheless, traditional topical treatments for DFU are expensive and often demonstrate limited effectiveness, especially when faced with multidrug-resistant bacteria, therefore photodynamic therapy (PDT) could stand as a promising approach for addressing infections in the treatment and recovery of DFU. This method entails the application of light-sensitive compounds on the affected area, followed by exposure to either laser (light amplification by stimulated emission of radiation) or LED (light emitting diode) light. When combined with tissue oxygen, this process triggers the generation of reactive oxygen species, leading to a potent local cytotoxic effect that effectively contests the infection in the affected area ^[27].

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