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LETTER TO EDITOR

Diabetic foot.
How to achieve control goals?

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Abstract

Diabetic foot is a chronic complication that is observed in patients with type 1 and 2 diabetes, mainly related to suboptimal treatment in glycemic control, however, the risk factors that favor the clinical presentation depend on the mechanical, hygienic conditions of the foot, and the decrease in the sensitivity of the foot, which added to the poor control of blood pressure, cholesterol levels and other fats favor an ischemic environment conducive to infection, inadequate healing, which in many patients will end in osteomyelitis and amputation of the foot. affected limb.

Numerous workshops aimed at the prevention and treatment of diabetic foot, recommend skin care, changes in footwear and mainly in education so that the patient recognizes the early signs of these complications, the classic treatment for glycemic control is with insulin in its various treatment modalities and there is no solid evidence to suggest that any scheme is superior to another. This review establishes the need for a comprehensive treatment where the goals of glycemic control, hypertensive control, cholesterol levels and ideal weight are the pillars to improve the comprehensive clinical status of the patient in conjunction with the general recommendations for diabetic foot care.

Keywords: Diabetic foot, Glycemic interventions, Cardiovascular complications

Introduction

The World Health Organization WHO defines the diabetic Foot as "a group of syndromes in which neuropathy, ischemia and infection lead to tissue disruption, resulting in morbidity and possible infection".[1] In Mexico, despite the wide dissemination of preventive measures and foot care, foot complications are frequent in people living with diabetes. According to results from the last two national health surveys 2012 and 2016, the prevalence of ulcers increased from 7.2% to 9.1% and the number of amputations increased from 2% to 5.5%. Among the most frequent causes of amputation is osteomyelitis, a frequent complication of infected ulcers occurring in up to 66% of all those with uncontrolled disease.[2]

This complication, in addition to being the result of poor glycemic control, is accompanied by underlying neuropathy, peripheral vascular disease or poor foot care, neuropathic ulcers are associated with a 5-year mortality of 45% and 47% after amputation. According to the International Consensus on the Diabetic Foot, a diabetic foot ulcer is defined as a wound below the ankle in a patient with diabetes, regardless of its duration, ulcers are usually found in areas of the foot that undergo repetitive trauma due to bony malformations which are the effect of intrinsic and extrinsic pressures.[2]

Since 2019, the International Working Group on Diabetic Foot Disease IWGDF has been outlining the main principles for the prevention and maintenance of diabetic foot disease, including the prevention of foot ulcers in people with diabetes, changes in ulcer site burden, diagnosis, prognosis and maintenance of peripheral arterial disease with ulceration and diabetes, diagnosis and treatment of infection in people with diabetes, interventions to improve healing of foot ulcers in people with diabetes.

This chapter focuses exclusively on explaining the pathophysiological phenomena that cause ulcers, general guidelines for ulcer staging and recommendations for metabolic control[16-20] the entirety of this text with the introduction to your chapter.

Pathophysiological phenomena associated with diabetic foot disease.

Multiple factors contribute to ulcer formation (neuropathy, vascular insufficiency, altered response to infection), oxidative/nitrosamine stress, alterations in the inflammatory response, impaired cutaneous microcirculation and extracellular matrix dysfunction have emerged as critical mediators.[3]

Oxidative stress such as nitrative stress are important in the development of diabetic complications including neuropathy and foot ulceration,[3] hyperglycemia increases vascular superoxide production, inactivating nitric oxide (NO) and contributing to vascular dysfunction. In addition, ON plays an important role in wound repair by promoting angiogenesis, migration, and proliferation of fibroblasts, epithelial cells, endothelial cells and keratinocytes.[3]

The accumulation of advanced glycation end products (AGEs) and progressive atrophy of skin connective tissue have also been implicated in the pathogenesis of diabetic complications, including impaired wound healing.[3,4]

AGEs accumulate in the wounds of patients with diabetes and interact with their receptor (RAGE), leading to the expression of proinflammatory molecules includingendothelin-1, tumor necrosis factor-alpha (TNF-a) and matrix metalloproteinases (MMPs), the latter of which are responsible for connective tissue degradation.[3] Oxidative stress produced in blood vessels increases diacylglycerol and protein kinase C, thus contributing to vascular dysfunction, disease of the skin microvasculature and thus generating alterations in skinperfusion.[3] Extracellular matrix (ECM) production and remodeling is a fundamental process in wound healing. Following injury, tissue repair and closure relies on a dynamic interaction between ECM and local/circulating cells.[5] This interaction leads to the rapid onset of a temporary inflammatory response, fibroblast and keratinocyte proliferation, angiogenesis and ultimately results in permanent functional healing. Chronic wounds lack a functional ECM, and this condition impedes the normal healing process.[6]

The cells of diabetic patients are also abnormal,[6] for example, fibroblasts produce less collagen and proangiogenic factors such as vascular endothelial growth factor, this added to the lack of surface receptors for fibronectin binding prevents their proper migration to the affected site and delayed wound healing,[6] Furthermore, the absence of a functional ECM in chronic wounds limits the migration and proliferation of keratinocytes into the wound necessary for successful re-epithelialization and of endothelial cells in the capillaries essential for neoangiogenesis.[6]

Hyperglycemia, dyslipidemia, insulin resistance and oxidative stress can lead to cell damage, endothelial dysfunction and various diabetes-associated complications through several pathways.[7]

Glycoxidation and lipoxidation of vascular wall structural proteins may facilitate atherogenesis through the effect on vascular wall characteristics and the interaction of inflammatory cytokines. This atherogenesis of the microvasculature supplying peripheral nerves contributes to neuropathy.[7]

Diabetic neuropathy is among the most common long-term complications in people living with DM and can present with various clinical manifestations (sensory, autonomic and motor components), it is estimated that at the time of diagnosis of DM, 20% of patients already have the disease, and the remainder will develop the complication around 8-12 years after diagnosis.[8]

Neuropathy leads to foot deformity or limited joint mobility, resulting in abnormal foot pressure and subsequent callus formation over the pressure points. Callus further increases local pressure and when combined with undetected repetitive injury leads to local tissue injury, inflammation, tissue death (necrosis) and finallyulceration.[9,11] The presence of plantar callus is a consequence of peripheral sympathetic dysfunction in the neuropathic foot, and is strongly associated with the risk ofulceration.[11] On the other hand, musculoskeletal changes lead to common foot deformities such as claw toes, hammer toes, equines, changes in the arch of the foot, Charcot foot, stiffness of the plantar aponeurosis, stiffness of the muscles of the foot and lower extremities, etc. Primary changes in musculoskeletal structures could be attributed to changes in joint structure and function, such as decreased range of motion andstrength.[1] Once a diagnosis of diabetic foot, with or without ulceration, has been established, the patient needs to have a staging of the damage and the risk of new ulcers. Metabolic control refers to periodic reviews of metabolic parameters such as blood glucose, glycosylated hemoglobin (HbA1c), cholesterol, triglycerides, blood pressure; and criteria for the patient's lifestyle. The criteria for adequate metabolic control in diabetic patients, according to the ADA are: basal blood glucose <110 mg/dl, postprandial blood glucose 130-180 mg/dl, HbA1c less than or equal to 7%, systolic/diastolic blood pressure <130/<80, total cholesterol <185 mg/dl, HDL-cholesterol >40 mg/dl, LDL-cholesterol <100 mg/dl, triglycerides<150 mg/dl, no smoking and aerobic physical exercise at least 150 minutes/week.[21-22] Blood glucose monitoring is an essential part of DM management. Analysis of capillary glucose and HbA1c levels allows assessment of the state of metabolic control of patients with DM and diabetic foot, self-monitoring of capillary glucose with pre- and postprandial measurements, or the results obtained by measuring interstitial glucose with continuous subcutaneous glucose measurement devices, allow identification of glycemic descontrol, glycaemic variability, identification of asymptomatic hypoglycemia; These results provide the information necessary to make targeted metabolic adjustments, long before the HbA1c result, which is still considered the integrated index of long-term glycaemia (3-4 months). This is why it is so imperative that the medical team caring for patients with diabetic foot not only consider HbA1c as the "gold standard" or the only test for metabolic control of diabeticpatients.[23,24]

Treatment of DM

Diet and physical activity

Overweight and obesity are the most important modifiable risk factors for DM and diabetic foot disease, as well as other cardiovascular complications (CVD). Indeed, it is well known that abdominal adiposity induces insulin resistance and, consequently, a constant increase in the need for insulin secretion. This condition represents a stressful state that can lead, over time, to decreased β-cell function with impaired blood glucose control. For every 5% increase in body weight there is an increase in blood pressure 3-4 mm/hg and a significant increase in cholesterol and triglycerides. In addition, excessive body weight is associated with an increase in many of the mechanical factors affecting foot dynamics (Charcot deformity), increased pressure foot and hemodynamic changes due to fluid distribution (increased oedema and protein extravasation due to peripheral venous insufficiency).[17]

Therefore, in overweight or obese individuals with T2DM, evidence-based recommendations suggest that weight loss is the first step in management, because improving insulin resistance and β-cell function can improve glucose metabolism, and reduce all other CV risk factors related to overweight/obesity.[17] Diet is recognized as one of the cornerstones in the treatment of DM, with the main objectives being not only the improvement of blood glucose control and other metabolic (CV) risk factors.[18,19] but also the reduction of CVD, which accounts for about 70% of total mortality in these patients.[20]

Furthermore, given that diet and its components may act on CV risk reduction through different mechanisms, having pleiotropic effects, a healthy diet may be especially important in patients characterized by the aggregation of multiple risk factors (overweight/obesity, poor glycemic control, dyslipidemia and high blood pressure).[17]

The ADA recommends individualized medical nutrition therapy, preferably provided by a registered dietitian, for all people with T2DM.[21] The food groups include macronutrients and micronutrients. As there is no single ideal dietary distribution of calories between carbohydrate, fat and protein for people with DM; macronutrient distribution should be individualized taking into account total calories and metabolic goals. Reducing fat intake (saturated fat, trans fat, cholesterol) in diabetic patients aims to reduce the risk of cardiovascular disease by lowering plasma cholesterol and low-density lipoprotein (LDL)at the discharge sites on the sole of the cholesterol levels.[22] The ADA guidelines find that a variety of dietary patterns are acceptable for the management of diabetes, including the DASH diet, Mediterranean diet and culturally diverse regionalized dietary programmes as long as they are based

on fibred-rich vegetables.

Physical activity is essential in the treatment of DM, yet most patients do not maintain regular physical activity. Previous studies have established that regular physical activity improves blood glucose control and may prevent DM. The benefits of physical activity in the prevention and treatment of DM are achieved through acute or chronic improvement of insulin resistance. This benefit has been demonstrated for both aerobic and resistance exercise. Regular exercise, in addition to improving glycemic control, has been shown to reduce cardiovascular risk factors, contribute to weight loss and increase the patient's sense of well-being.[23]

In patients at risk or diagnosed with diabetic foot disease, exercise improves sarcopenia and makes specific improvements in the complex skeletal muscle deficits that develop with chronic hyperglycemia. However, when exercise is weight-bearing it may increase the cumulative stress on plantar tissue, which in turn may increase the risk of skin lesions. Based on two clinical trials in which patients at risk for foot ulceration participated in a training programmed that increased their weight-bearing activity, it did not result in an increase in the number of lesions compared to the non-weight-bearing group, Therefore, it is suggested that people at low to moderate risk for ulceration be advised to use appropriate footwear, off-loading insoles and continuous foot surveillance. In patients at high risk, a walking programmed at a tolerance of 1000steps per day, with slight weekly increments of a maximum of 10% per week, is suggested, the quality of evidence to support this information is low.

In patients with established ulcer, rest of the limb is suggested as an important measure to promote healing, seated or lying down exercises of various muscles as a whole is a good recommendation, allow a caloric expenditure, reduce peripheral insulin resistance and prevent sarcopenia of other body areas and performed without weight on the foot allow better blood flow. A good practice recommendation is to suggest performing the exercise under adult supervision to avoid falls and to confirm that the foot injury is not more serious.

Pharmacological treatments available

The physiology and treatment of the patient with diabetes and the diabetic foot are complex and require a multitude of interventions for successful disease management. Diabetes education and patient and caregiver involvement are fundamental to management. Because chronic hyperglycemia is considered the most important factor in the development of microvascular complications, patients do best if they can control their diet (carbohydrate and overall calorie restriction), engage in regular physical activity (more than 150 minutes per week) and maintain tight glycemic control.[24] Intensive glucose control reduced the risk of amputation by 36% in type 2 diabetes (relative risk [RR] 0.64, 95% CI 0.43 to 0.95; 6960 participants in eight trials).[25] In addition, there was an 11% relative risk reduction (RR 0.89, 95% CI 0.83 to 0.95; 25,760 participants in four trials) and a 1% to 2% absolute risk reduction in composite microvascular outcomes in favor of intensive glycaemic control for all included trials.[25] Several meta-analyses have shown that the incidence of hypoglycemia (low blood glucose) increased during intensive glycemic control, making it a significant adverse outcome.[24,25] It should be noted that the beneficial effects on microvascular complications from the use of intensive glycemic control took more than five years to appear, and the benefits were less pronounced for people with advanced type 2 diabetes compared with people with new-onset type 2 diabetes.[24,25] Despite this, data on retinopathy (retinal disease) suggest that people with advanced stages of type 2 diabetes may also benefit from intensive blood glucose control.[25-27]

Most guidelines recommend a glycemic control target of 7% or less for glycated hemoglobin HbA1c. Ideally, glucose levels should be maintained between 90 and 130 mg/dl, postprandial glucose below 180 mg/dl. Revised guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend individualization, with HbA1c targets being more stringent (6.5% or less) or less stringent (8% or less) as appropriate for individuals (ADA 2012; Cheung 2009; Inzucchi 2012). There is marked variation in the definition of intensive glycemic control between guidelines and trials (Hemmingsen 2011a). For the purposes of this review, we included trials in which an intervention was delivered with the aim of achieving better glycemic control compared to a conventional control group.

Comprehensive metabolic control, identification of peripheral arterial disease and assessment of global cardiovascular risk is essential in this group of patients to set goals for lipid and systemic blood pressure control.

All guidelines for recommendations and follow-up of patients with type 1 and 2 diabetes recommend insulin as the cornerstone of intensive treatment. We conducted an advanced search of the medical literature, using the keywords, diabetic foot, comparative trials with basal insulin, superiority, efficacy and safety to demonstrate the real benefit of a specific basal insulin; E. Fernando et al. in 2016 conducted a systematic search of intensive glycemic control. We considered for inclusion published, unpublished and ongoing randomized controlled trials (RCTs) that investigated the effects of intensive glycemic control on the outcome of active foot ulcers in patients with diabetes. Non-

-randomized and quasi-randomized trials were excluded. To be included, the trial had to have:

1) attempted to maintain or control blood glucose levels and measured changes in markers of glycemic control (HbA1c or fasting, random, mean, home capillary or urine glucose), and

2) documented the effect of these interventions on active foot ulcer outcomes.[26]

Glycemic interventions included subcutaneous insulin administration, continuous insulin infusion, oral anti-diabetic agents, lifestyle interventions or a combination of these interventions. The definition of the intervention (intensive) group was that it should have a lower glycemic target than the comparison (conventional) group. Within the results of the systematic review, only one trial was identified that met the inclusion criteria, but this trial did not have any results, so it was not possible to conduct the planned subgroup and sensitivity analyses due to lack of data. Two ongoing trials were identified that may provide data for analyses in a later version of this review. The completion date of these trials is currently unknown.

By consensus it is established that insinuation should be performed with safe basal insulins, with low risk of hypoglycemia, less variability throughout the day and a safe predictability, insulin glargine U300 and degludec, are insulins with a basal profile of 24 hr or more that meet the above requirements, should start with 0.1- 0.2Ui/kg/day and titrate individually until target fasting glucose levels are reached (average of 0.5Ui/kg/day) and consider the use of ultra-rapid acting insulins (lispro, aspart, glulisine) for control of postprandial blood glucose excursions, initially at the main meal and later adding applications at breakfast and/or dinner.

If the patient has evidence of insulin resistance and renal function is adequate, metformin should be continued and thiazolidines should be avoided because of the risk of lower limb oedema.

There are no safety and efficacy studies on the use of di-peptidyl peptidase 4 (DPP4) inhibitors and Glucagon like peptide (aGLP-1) analogues. There are no clinical trials specifically conducted in patients with diabetic foot, clinical experience and study results of these drugs have not demonstrated increased amputation outcomes or foot complications in patients with diabetes and diabetic foot that were included in various studies. An added benefit to metabolic control (1% reduction in Hba1c) is the weight reduction observed in patients under treatment with aGLP1, which allows for a reduction in the burden on the affected limb.

Moreover, it has been shown that they may have a positive impact on reducing the underlying atherosclerosis in cardiovascular disease, although the mechanisms linking hyperglycemia and accelerated atherosclerosis have not been fully explained but appear to be mediated by vascular inflammation, endothelial dysfunction and oxidative stress.[27]

A clinical trial demonstrated that exenatide stimulates nitric oxide production in endothelial cells inducing vasodilation even in the presence of elevated blood glucose or lipid levels; similarly, in vivo studies in animal models treated with liraglutide have demonstrated an improvement in endothelial function given by anincrease in endothelial nitric oxide synthase expression and a decrease in type 1 intercellular adhesion molecules.[49] The evidence accumulated throughout the different clinical trials approving GLP-1 receptor analogue drugs for the treatment of diabetes mellitus and their post hoc analysis allows establishing a broad benefit of this class of drugs in the progression of cardiovascular diseases associated or not with diabetes mellitus.[28]

The iSGLT2s are a class of antidiabetics that block renal tubular reabsorption of glucose with distinct multisystem metabolic and hemodynamic benefits. In recent years, three iSGLT2s have been approved in Mexico: canagliflozin, dapagliflozin and empagliflozin.

In addition to urinary glucose excretion, which has a direct impact on lowering glycosylated hemoglobin (HbA1c), weight and fasting blood glucose, iSGLT2, due to osmotic diuresis, may also provide a further reduction in blood pressure. Data from clinical trials suggest that iSGLT2s produce an average weight loss of approximately 2 to 3 kg in patients with DM2, regardless of background treatment (monotherapy, as adjunctive therapy to other oral agents, and insulin).[29,30] ISGL2s are indicated in patients in whom intensive glucose control is indicated, metformin and an iSGLT2 can be considered as initial treatment, in those at high CV risk or CVD or renal disease, as their effects are complementary and go beyond glucose control,

specifically for their benefits on CV risk, blood pressure reduction, cardio- renal protection and weight loss. There is agreement that iSGLT2 is a good option for reducing glucose variability, as its mechanism of action independent of insulin- mediated glucose lowering reduces excursions throughout the day, including fasting and postprandial glycaemia, with a pharmacological profile of low risk for hypoglycemia. iSGLT2 can be used in patients with insulin resistance when the patient is intolerant to metformin, as glucose lowering by a non-insulin-dependent mechanism improves insulin secretion

capacity by eliminating the phenomenon of glucotoxicity and, indirectly, improves insulin resistance. This mechanism, together with weight reduction, decreases insulin resistance. Amputation is a very rare adverse effect (≥ 1/1,000 to < 1/100 events per 1,000 patient-years). The incidence of lower limb amputations is very low in trials and observational studies relative to the number of patients exposed to iSGLT2. However, it seems prudent to perform regular foot examinations and to avoid iSGLT2 in patients with previous amputation or active foot ulceration.

The CANVAS study[31] showed an incidence of amputation of 0.6 events per 1,000 patient-years in the canagliflozin group vs. 0.3 in the placebo group, although the CREDENCE study subsequently found no increased risk of amputation in the canagliflozin-treated vs. placebo-treated group, with rates of 12.3 vs. 11.2 per 1,000 patient-years in the canagliflozin group and placebo group, respectively (HR: 1.11; 95% CI: 0.79 to 1.56). The FDA withdrew the black box warning regarding the risk of amputations with canagliflozin because of new evidence from controlled, real-life clinical studies, where this risk was not increased over placebo.[32]

Observe 4D23, a real-life study of more than 700,000 patients with DM 2 treated with different antidiabetics, compared the effects of treatments on HF hospitalization and incidence of below-knee lower limb amputations. The comparison was made with canagliflozin (150,000 patients) versus the other iSGLT2 and other antidiabetics, adjusting for *propensity score*, and no increased risk of amputation was observed with canagliflozin versus the other therapies. The results were similar in patients with and without established CVD.[33] In the same vein, a recent meta-analysis of five iSGLT2 studies assessing amputation risk has concluded that iSGLT2 use was not associated with a significant increase in amputation risk compared to controls.[33,34]

Conclusion

The World Health Organization defines the diabetic foot as "a group of syndromes in which neuropathy, ischemia and infection lead to tissue disruption, resulting in morbidity and possible infection". This complication, in addition to being the result of poor glycemic control, is accompanied by underlying neuropathy, peripheral vascular disease or poor foot care, neuropathic ulcers are associated with a 5-year mortality of 45% and 47% after amputation. Diabetes education and patient and caregiver involvement are critical in the management of hyperglycemia.

Because chronic hyperglycemia is considered the most important factor for the development of microvascular complications, consensus has established that inzulinisation should be performed with safe basal insulins, with low risk of hypoglycemia, lower variability throughout the day and safe predictability, the usefulness of oral hypoglycemic agents will depend on the individual characteristics of each patient, achieving goals of strict control of lipids, blood pressure and weight control as an integral treatment is fundamental.

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Conflicts of Interest

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References

1. Gutierrez JP, Rivera Dommarco J, Shamah Levy T, et al. Encuesta Nacional de Salud y Nutrición 2012. National Results. Cuernavaca, Mexico: National Institute of Public Health (MX), 2012.
2. Oliver TI, Mutluoglu M. Diabetic Foot Ulcer. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.
3. Singer AJ, Tassiopoulos, Kirsner RS. Evaluation and Management of Lower- Extremity Ulcers. *N Engl J Med*. 2018; 378(3):302–303.
4. Ahmad J. The diabetic foot. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2016;10:48-60.
5. Wear Magi H, Lee J, Conejero A. Use of topical RAGE in diabetic wounds increased neovascularization and granular tissue formation. *Ann Plas Surg*. 2004;52:512-522.
6. Tracy LE, Minasian RA, Caterson EJ. Extracellular matrix and dermal fibroblast function in the healing wound. *Adv Wound Care*. 2016;5(3):119-136.
7. Syafril S. Pathophysiology of diabetic foot ulcer. *IOP Conf. Ser: Earth Environ Sci.* 2018;12161:1-6.
8. Hazari A, Maiya AG. Clinical Biomechanics and its Implications on Diabetic Foot. 1st Ed. India: Springer; 2018.
9. Alavi A, Sibbald RG, Mayer D, et al. Diabetic foot ulcers, part I. Pathophysiology and prevention. *J Am Acad Dermatol*. 2014; 7(1):1.e1-1.e18.

10. Sdobler HF, Faist V. Maillard reaction products: uptake, metabolic transit and selected parameters of biopotency and safety. *Forum Nutr.* 2003;56: 353-355.
11. Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. *Diabetes Metab Res Rev*. 2004;20:S90-95.
12. Islam S. Microbial profile of diabetic foot infections in Trinidad and Tobago. *Primary Care Diabetes*. 2013;7:303-308.
13. Abbas Z, Lutale J, Game F, et al. Comparison of four systems of classification of diabetic foot ulcers in Tanzania. *Diabetic Medicine*. 2008;25(2):134-137.
14. Chuan F, Tang K, Jiang P, et al. Reliability and validity of the perfusion, extent, depth, infection and sensation (PEDIS) classification system and score in patients with diabetic foot ulcer. *PloS one*. 2015;10(4):e0124739.
15. Ince P, Abbas ZG, Lutale JK, et al. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. *Diabetes care*. 2008;31(5):964-967.
16. Lavery LA, Armstrong DG, Murdoch DP. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. *Clinical infectious diseases*. 2007;44(4):562-565.
17. Monteiro Soares M, Boyko EJ, Jeffcoate W, et al. Diabetic foot ulcer classifications: A critical review. *Diabetes Metab Res Rev*. 2020;36:e3272.
18. Mendoza Martínez P, Almeda Valdés P, Janka Zires M, et al. Clinical and microbiological characteristics of patients with diabetic foot. *Med Int Mex*. 2021;37(2):196-211.
19. Monteiro Soares M, Russell D, Boyko EJ. International Working Group on the Diabetic Foot (IWGDF). Guidelines on the classification of diabetic foot ulcers (IWGDF 2019). *Diabetes Metab Res Rev*. 2020;36 Suppl 1:e3273.
20. Lindström J, Peltonen M, Eriksson JG, et al. High-fibre, low-fat diet predicts long-term weight loss and decreased type 2 diabetes risk: the Finnish Diabetes Prevention Study. *Diabetologia*. 2006;49(5):912-920.
21. Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes*. 1999;48(5):937-942.
22. Nieto Martínez R. Physical activity in the prevention and treatment of diabetes. *Venezuelan journal of endocrinology and metabolism*. 2010;8(2):40-45.
23. Umpierre D, Ribeiro PAB, Kramer CK, et al. Physical Activity Advice Only or Structured Exercise Training and Association With HbA1c Levels in Type 2 Diabetes: A Systematic Review and Meta-analysis. *JAMA*. 2011;305(17):1790-1799.
24. Mattila TK, De Boer A. Influence of intensive versus conventional glucose control on microvascular and macrovascular complications in type 1 and 2 diabetes mellitus. *Drugs.* 2010;70(17):2229-2245.
25. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ*. 2011;343:d6898.
26. Fernando ME, Seneviratne RM, Tan YM, et al. Intensive versus conventional glycaemic control for treating diabetic foot ulcers. *Cochrane Database of Systematic Reviews.* 2016;1.
27. Shah MS, Brownlee M. Molecular and cellular mechanisms of cardiovascular disorders in diabetes. *Circulation Research.* 118:1808-1829.
28. Gaspari T, Liu H Bin, Welungoda I, et al. A GLP-1 receptor agonist liraglutide inhibits endothelial cell dysfunction and vascular adhesion molecule expression in an ApoE- /- mouse model. *Diabetes and Vascular Disease Research*. 2011;8:117-124.
29. Miranda Fernández Santos C, Egocheaga Cabello MI. Guía práctica de uso de los iSGLT2 en diabetes mellitus tipo 2. *Spanish Society of General and Family Physicians*; 2020.
30. Brown E, Wilding JPH, Barber TM, et al. Weight loss variability with SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes mellitus and obesity: Mechanistic possibilities. *Obesity Reviews*. 2019;20:816-828.
31. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644-657.
32. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295-2306.
33. Ryan PB, Buse JB, Schuemie MJ, et al. Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: A real-world meta-analysis of 4 observational databases (OBSERVE-4D). *Diabetes ObesMetab*. 2018;20(11):2585-2597.
34. Miyashita S, Kuno T, Takagi H, et al. Risk of amputation associated with sodium-glucose co-transporter 2 inhibitors: A meta- analysis of five randomized controlled trials. *Diabetes Res Clin Pract*. 2020;163:108136.