Review Article

Diabetes Mellitus Long-Term Complications and Treatment Strategy

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ABSTRACT

Diabetes mellitus is growing more prevalent and a global public health emergency. The long-term effects of diabetes are the main focus of this review article. Some of these complications include the fact that coronary artery disease accounts for approximately 75% of diabetes-related deaths, that diabetic retinopathy, or damage to the eyes, can cause gradual vision loss and blindness, and that diabetic neuropathy, or damage to the kidneys, nerves, and eyes, is the main result of diabetes: small blood vessel damage. Long-term effects of diabetes include painful muscle weakening and atrophy from proximal diabetic neuropathy, as well as diabetic foot ulcers. The majority of these illnesses are associated with blood vessel injury.

Keywords: Diabetes mellitus, health emergency, diabetic retinopathy, diabetic neuropathy.

INTRODUCTION

Diabetes mellitus is a metabolic issue related to long-term symptoms, especially abnormalities in glucose metabolism. Special problems associated with diabetes include retinopathy, nephropathy, and neuropathy. Patients with many forms of diabetes, including insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetes, may have acute discomfort as a result of this issue with picture growth [1]. A nosological characteristic of non-insulin-dependent diabetic diabetes (NIDDM) is retinopathy. Sufficient hyperglycemia with retinopathy is the main diagnosis for NIDDM; medium hyperglycemia without retinopathy is defined as glucose intolerance. For retinal, nephropathy, and neuropathy, we discussed the clinical characteristics, risk factors, illness, diagnosis, and treatment strategies [2].

Diabetes type 1:

Type 1 diabetes (T1D) can be known before abnormal insulin secretion shows symptoms, and the disease's indications start to fade at least two years before a diagnosis is completed[3]. As the early response decreases, the final insulin response increases, which may indicate the presence of a compensatory mechanism. In the early stages after diagnosis, the amount of insulin gradually decreases. In the initial years after diagnosis, there is a biphasic decline in insulin secretion, with a decrease in the first year compared to the second. Following a diagnosis, the reduction in insulin levels may continue for years, until almost no insulin remains. Elevated blood sugar levels, even when they are within the normal range, are indicative of type 1 diabetes. As T1D develops, significant changes in blood sugar levels occur. In high-risk groups may be more predictable using metabolic signs such as blood sugar, which is unusual. Changes in glucose can be used in risk categorization to improve future prediction [4].

Diabetes type 2:

One important factor in the formation of type 2 diabetes (T2D) is insulin resistance [5]. How much insulin is generated and how much is needed to maintain normal glucose levels is determined by insulin sensitivity. The index evaluates the curvilinear relationship between secretion and insulin sensitivity. Additionally, those who have type 2 diabetes have a worse quality of life, making it difficult for them to make enough insulin to fight insulin resistance. Because of the severity of the insulin resistance, insulin accuracy is still much lower in overweight people with T2D, even if it is higher than in insulin-sensitive patients. Insulin production is slowed down or stops in response to glucose stimulation (Phase 1). Patients with T2D have higher pro-insulin-to-insulin levels.

Gestational diabetes:

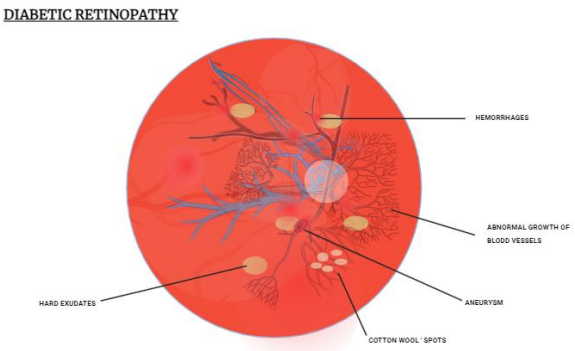
Pregnancy is related to hyperglycemia; it makes possible pregnancy, fetal death, and birth [6] [7]. This risk is independent of whether increased blood sugar is a kind of T2D detected before or during pregnancy. Children born to mothers who have gestational diabetes have a high risk of developing diabetes later in life [8]. An increased frequency of pregnancy-related issues, such as premature birth, large size for gestational age, macrosomia (birth weight greater than 4.5 kg), C-sections, and pre-eclampsia, often occur due to high blood sugar during pregnancy, resulting in larger babies. Gestational diabetes can be influenced by a wide range of risk factors, such as a sedentary lifestyle, exposure to environmental pollutants, obesity, polycystic ovarian syndrome, obesity, and advanced age in women [8]. According to earlier reports, the diagnosis of gestational diabetes is based on a set of criteria that include the evaluation of fasting glucose levels, glucose levels following a 75-g oral glucose load, and other indicators [9].

Other types of diabetes:

A type of beta cell condition Diabetes mellitus in young people (MODY): This type of disease is only related to insufficient beta cell activity. It is naturally diagnosed early in life, usually before the age of 25, and is characterized by anomalies and a drop in insulin levels. One defective copy of the gene from a single parent can produce this disorder because it is inherited through an autosomal dominant component. Numerous genes, including glucokinase, hepatic transcription factor (HNF)-1, HNF-4, HNF-1α, IPF-1, and NeuroD1, are mutated in MODY [10].

DIABETIC RETINOPATHY:

Diabetic retinopathy has historically. most likely continued to contribute to the visual degradation of the US [11, 12]. The likelihood of developing retinopathy is closely tied to the extent and duration of blood sugar levels. After two decades of living with diabetes, all individuals diagnosed before age 30 show signs of retinopathy, with about half experiencing symptoms. While individuals over 30 have a risk of developing diabetes-onset retinopathy, this can sometimes be an indication of the disease. Among this demographic, those requiring insulin treatment are at a higher risk of developing retinopathy compared to those who do not need insulin. The prevalence of all types of retinopathies in patients is around 80% for those needing insulin and 20% for those not requiring insulin. The occurrence of retinopathy is 40% and 5%, respectively. Between 15 and 20 years after the onset of diabetes, the risk of macular oedema is between 10% and 15%, regardless of age or insulin dependence. Blindness can result from retinopathy, macular oedema, increased cataracts, and glaucoma[13, 14]. Preventing retinopathy is crucial to reducing the likelihood of blindness in individuals with diabetes, although this option remains inaccessible to patients at present [15]. If left untreated, the possibility of people with retinopathy is estimated to be at least 50%, with a high chance of becoming blind within five years[16, 17]. However, utilizing treatments developed over the past three years can significantly decrease the risk of blindness to below 5% [18].



TREATMENT:

Photocoagulation using laser

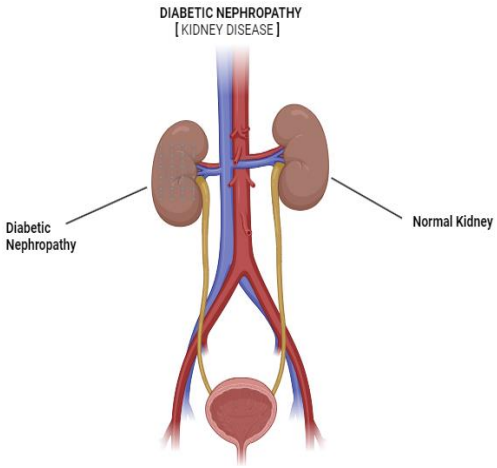
Diabetic macular edema and diabetic retinopathy can be treated with laser photocoagulation. The probable, randomized, controlled ETDR research, which involved 3711 patients in total and was published in 1991, is the basis for approvals affecting this type of treatment [19]. That is why the Mission for the Early Diagnosis of Diabetes-Related Eye Disease published national guidelines in Germany. Currently, lasers with a wavelength of 532 nm are made of dual-neodymium-frequency yttrium-aluminium-garnet [Nd-YAG] lasers. The treatment is performed by combining the laser with a separate light and contacting the lens placed on the cornea. If the cornea or lens is significantly opaque, due to treatment beam refraction and poor vision, Nd:YAG laser treatment may not be possible. In this case, an 810 nm diode laser can be used, or the cataract might be treated first a few days after cataract surgery[20], followed by laser treatment in a few days. Targeted laser coagulation of leaky microaneurysms and capillaries in the perifoveal region of the macula with a laser lesion size of 100 to 200 µm can be used to treat clinically severe diabetic macular edema.

Corticosteroids

Extensive research has been conducted on the use of injections in the eye for treating DME. There are three types of corticosteroids. Triamcinolone acetonide, dexamethasone, and fluocinolone acetonide [21]. Have been examined. It is noted that all such injections come with risks, including endophthalmitis, retinal tear or detachment, vitreous hemorrhage, elevated pressure (IOP), and cataracts.

DIABETIC NEPHROPATHY:

Diabetic kidney disease (DKD) is a chronic microvascular problem that is sometimes severe and arises from lesions in the renal tubuli and glomeruli. Simultaneously, the illness is commonly linked to other atherosclerotic methods that mimic macrovascular morbidity in people without diabetes. These processes tend to arise earlier in diabetes, particularly in young adults, and have an impact on both the patient and the community. According to previous epidemiological research, eventually, DN affects 25% to 40% of people with type 1 diabetes (T1D) and 5% to 40% of people with type 2 diabetes (T2D) [22]. Furthermore, microalbuminuria (MA) is seen in 20% to 30% of individuals with type 1 diabetes after an average of five to ten years with diabetes. However, 20% of individuals may develop type 2 diabetes at the time of diagnosis, twenty to thirty years after type 1 diabetes first appears [23 24], According to reports, the prevalence of end-stage renal disease (ESRD) ranges from 4 to 17%. 2-4 As a result, early DN screening should start when a patient has diabetes[25]. Although nonalbuminuric diabetic nephropathy (NADN) is a less well-studied condition, Thorn et al. recently revealed that 2% of T1D patients had NADN, which was frequently linked to cardiovascular morbidity [26].



TREATMENT:

Consideration of the condition is the basis for diabetic nephropathy prevention and treatment plans. A history should be taken as part of the evaluation process for trauma patients in order to determine the risk factors for maternal hypertension, cardiovascular disease, and mortality. Measuring glycated hemoglobin is essential to assessing the glycemic control index [27]. In 100 million people, microalbuminuria is a sign of glomerular pathology (dilated mesangial matrix, for example) and a precursor to overt nephropathy and heart failure [28]. Treatment plans designed specifically for these high-risk individuals may stop or decrease the development of overt nephropathy. In patients with NIOOM, microalbuminuria is linked to a greater cardiovascular death rate than expected due to nephropathy [29].

Control of glucose

Initially, the major objective of treatment should be glucose control, but if there is already proteinuria (>500 mg/24 hours), this control is helpful only for macrovascular disease and not for renal disease. Insulin pump therapy or many daily injections are needed to reach blood sugar levels close to normal, which is better than one or two injections per day3] [30]. Two clinical studies evaluated the effect of early glycemic control on 100M using intent-to-treat analysis. Glycemic control kept normal buminuria or increased microalbuminuria [31, 32] and in one study [33], but not in another, it decreased hypertension [34]. Also, improvements in glycemic control brought GFR, RPF, and kidney size back to normal after only three weeks of therapy [33]. Still, the efficacy of severe glucose management in preventing diabetic nephropathy or end-stage renal disease is still unidentified due to a lack of long-term probable data. Direct inhibition of AGEP creation may provide extra therapeutic changes if glycemic control, which provides long-term safety against diabetic nephropathy or end-stage renal disease [35], partially prevents AGEP buildup. A helpful, probable trial was planned to begin in the winter of 1992–1993 to assess the efficacy of aminoguanidine, an AGEP inhibitor, in delaying the progression of diabetic retinopathy and nephropathy.

GESTATIONAL DIABETES:

This condition also predisposes women to metabolic diseases, including hypertension, dyslipidemia, and heart disease. Fetal respiratory distress syndrome, preterm birth, hypoglycemia, hyperbilirubinemia, macrosomia, and death are some of the common fetal and neonatal complications in GD pregnancies. Macrosomia is very common, where there's more than 4500 grams of fetus; this has been thought to be due to fetal hyperinsulinism caused by maternal hyperglycemia [36]. This could result in a number of problems, like abdominal pain and difficulty in delivery, resulting in emergency surgery. Additionally, these children have a prolonged risk for obesity, glucose intolerance, diabetes, high blood pressure, and heart disease because their mothers had GDM. AcGD is associated with both short-term and long-term issues for the mother and her offspring. Hypertension, eclampsia, and infections such as urinary tract infections are examples of short-term maternal issues. However, in the case of obese people, this can lead to type 2 diabetes, which may last a lifetime [37]. Saucedo et al. (2015) state that kids whose mothers have GD are connected to Barker's theory that the fluctuating conditions of the womb lead to long-term illness among newborns. One possibility is through epigenetic remodeling. Histone acetylation and methylation are affected by the rapidly altering fetal epigenome through metabolic and inflammatory changes in the intrauterine environment, which is very plastic and can be modified early in pregnancy. As an example, there are some modifying changes in DNA that do not involve alterations at the nucleotide sequence level but rather may be transmitted. This is due to the fact that when a mother suffers from type 2 diabetes, compared to when it is the father, this increases the chances of one child contracting diabetes [38] Recently,'metabolic memory' has evolved based on animal data and epidemiologic observation, which explains how maternal diabetes can cause metabolic syndrome among infants. Plagemann et al. examine the effects of hyperinsulinism on the fetal mothers of gestational diabetic rats' hypothalamus [39]. They showed abnormal development in different hypothalamic nuclei, including the paraventricular, ventromedial, and arcuate hypothalamic nuclei. It is important to keep in mind that this was not an observational study, and more research is needed. Rat pups born to mothers with gestational diabetes (GD) have been shown to be overweight and hyperinsulinemic. These rats, born to GD mothers, were overweight, hyperinsulinemic, and showed disturbances in different hypothalamic nucleus development, which could modify their feeding behaviors and metabolism [40] In a 3-year period, children with diabetes mothers gained more weight per m2 when they were 10–13 years old, as indicated by their greater BMI growth velocity. Thus, it is evident that there is a high correlation between maternal GD and offspring obesity, as well as other metabolic problems.

Early screening in pregnancy:

There are several high-risk populations for whom national guideline bodies recommend screenings as presented [41, 42, 43, 44]. However, the HbA1c, random plasma glucose, fasting plasma glucose, and the 75-g 2-hour oral glucose tolerance test (OGTT) are among the tests that are advised for early screening for pre-existing diabetes mellitus, even if there isn't yet a gold standard for this [45, 46, 47]. According to the World Health Organization's (WHO) analytical criteria for diabetes mellitus (DM) outside of pregnancy, which contain fasting glucose levels of 7 mmol/l, 2-hour oral glucose tolerance test results of 75 g, random glucose levels of >11.1 mmol/l, or HbA1c levels of >48 mmol/mol, these results should be categorized as "diabetes in pregnancy" and suitable care should be started.

Later screening in pregnancy:

An OGTT is used between 24 and 28 weeks of gestation to screen for GDM later in pregnancy. The IADPSG, WHO, and national guideline committees support a "one-step" two-hour, 75-gram OGTT [41, 42, 43, 44]. In the US and Canada, other "two-step" screening methods that involve a glucose challenge test and an OGTT for individuals who receive a positive result are also advised as an alternative [American Diabetes Association (ADA)] or as the preferred [American College of Obstetricians and Gynecologists (ACOG), Diabetes Canada] [45, 46, 47]. While many organizations (IADPSG, ADA, ACOG, Diabetes Canada) support universal screening in the third trimester, the Scottish Intercollegiate Guidelines Network (SIGN), a division of the National Institute for Health and Care Excellence, recommends restricting screening to women who have clinical risk factors for GDM[41, 42, 43, 44 45, 46, 47].

Current management:

Many women follow stringent regimens that involve insulin injections in the hopes of preventing pregnancy-related problems. The goal of this is to lower blood glucose levels in order to enhance the health of mothers and their newborns. In certain situations, insulin therapy was used in conjunction with home blood glucose monitoring and food control as therapies. Exercise is now reviewed by Cochrane as a less intrusive and alternative strategy [48] A different Cochrane review evaluated dietary counseling's impact on preventing GDM [49]. In order to diagnose defects and prevent macrosomia and stillbirth, this frequently leads to greater obstetric surveillance, such as more frequent prenatal clinic visits and ultrasound scans. In addition, the women who must have these examinations find it even more bothersome than receiving standard prenatal care. Further, when a person who thought she was healthy is told she has gestational diabetes, worry may ensue [50].

TREATMENT:

The management of GDM is aimed at reducing hyperglycemia and minimizing the risk of adverse pregnancy results. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) [51] was one of the first studies that showed medical intervention could alter feto-maternal morbidity. It was discovered that dietary advice and blood glucose monitoring on top of insulin therapy if needed resulted in a 67% reduction in the primary composite result comprised of infant death, shoulder dystocia, bone fracture, and nerve palsy when compared to usual care. Also, average birth weight reduced as well as rates of macrosomia decreased. Similar findings were made by Maternal-Fetal Medicine Unit Network's randomized trial conducted among 958 women with "mild" GDM (i.e., normal fasting glucose levels on OGTT). Such a program had similar outcome reductions on these clinical measures, such as macrosomia, cesarean section, shoulder dystocia, and preeclampsia, compared to standard care [52]. This should be carried out through a multidisciplinary approach involving both diabetes services and obstetricians. Education regarding lifestyle modification and capillary blood glucose monitoring ought to be given by diabetic specialist nurses and dieticians. It is recommended that diabetic patients monitor their fasting as well as their 1- or 2-hour postprandial capillary blood glucose concentration [7, 53, 54, 55]

Metformin:

The primary study that measured metformin use in pregnancy was a unit of 118 patients with type 2 diabetes, or GDM [56]. The study population's metformin, glyburide, and insulin levels were assessed by the authors. Many doctors refused to prescribe metformin in addition to insulin until the first randomized controlled trial (n = 751) comparing metformin and insulin [57] could be finished because of the greater perinatal mortality associated with metformin during the third trimester (11.6 versus 1.3% with insulin, p<0.02). According to this research, there was no difference between the primary composite outcomes (neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute APGAR <7, and preterm delivery [<37 weeks]) for the two groups: metformin versus insulin[58]. There were fewer hypoglycemic episodes with metformin compared to other drugs (3.3 vs. 8.1% with insulin, p<0.008). Sixty-four percent needed additional administration of insulin before delivery [59].

DIABETIC FOOT PROBLEMS:

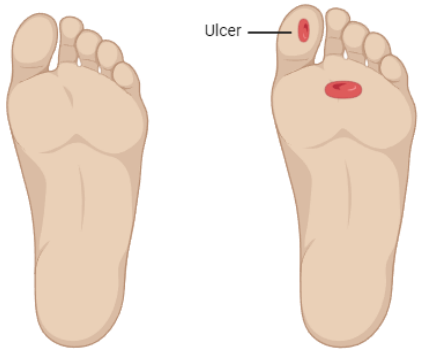
Hospitalization of diabetics is mainly due to foot disorders such as gangrene, ulcers, and infection. Foot ulceration is one of the main causes of hospitalizations among an estimated 15–20% of the approximately 16 million diabetes cases in America.

Unfortunately, many patients with diabetes will have to have parts of their feet or legs amputated because they are severely infected or peripherally ischemic. Ulceration and amputation are often associated with neuropathy. It costs billions in direct medical expenditure, lengthy hospitalization, and disability episodes [60]. The hallmark lesion of a diabetic foot is a malperforan ulcer, which

therefore becomes one of the greatest risk factors for amputation. About 85% of all lower-extremity amputations that occur in people with diabetes are preceded by foot ulcers. Among diabetic patients, the main reason for hospitalization is because diabetic foot complications are a major health burden. The risk of developing a foot ulcer in the lifetime of a patient with diabetes mellitus is up to 25 percent, as an active foot ulcer is present in 2–3 percent of these patients. Obviously, the last stages of foot ulcers' complications and their seriousness contribute significantly to morbidity and decreased quality of life [61]. In that vein, it is estimated that 84% of non-traumatic lower limb amputations involve an ulcer, offering a chance for early therapy. However, peripheral vascular diseases underneath pose a complicating factor, hence most diabetic foot ulcers don't cause any symptoms, especially in the early stages. At this juncture, tissue loss becomes more noticeable with time, making chronic non-healing foot ulcers frequently occur at the most advanced stages.

Etiology:

A minor trauma appears to be the source of most foot ulcers when sensory neuropathy is present. This recognized yet basic observation by McNeely et al. [62] most effectively describes the important trio of peripheral sensory neuropathy, deformity, and trauma among people who have diabetic foot ulcers. All three of these risk variables are present in 65% of diabetic foot ulcer cases. Calluses, edema, and peripheral vascular dysfunction have also been recognized as causes associated with diabetes-related foot ulcers.



TREATMENT:

Three fundamental problems need to be fixed in order to treat diabetic foot ulcers: debridement, unloading, and infection management.

Debridement:

Debridement is the process of eliminating all dead tissue, callus surrounding the incision, and foreign objects up to live tissue. Proper wound description can reduce the risk of infection and lessen peri-wound pressure, which can obstruct normal wound contraction and healing. It is advised to rinse the wound with saline or a cleanser after debridement before treating it [63]. Dressings are meant to prevent tissue drying, increase liquid absorption, and provide contamination protection. Growth factors, hydrogels, foams, calcium alginates, absorbent polymers, and skin substitutes are just a few of the many dressings available on the market. Because becaplermin contains chain platelet-derived growth factor, it has been shown in double-blind placebo-controlled trials to improve entire wound healing. It can be used in situations where ulcers do not respond to regular dressings [64]. In the case of an abscess, a cut must be made through which any abscessed material can be excised from it while the incision is being carried out. Many limbs have been saved by prompt incision and drainage methods; nevertheless, many limbs have been lost due to the neglect of these therapies. There is a considerable risk of morbidity and death when antibiotics are only used to treat a major, deep-seated abscess. This also causes a delay in the proper course of therapy.

Offloading:

Patients who completely remove all weight from the affected foot using a wheelchair or crutches are most suited to allow a foot ulcer to heal. Wounds treated with them tend to heal between 73% and 100% in all cases; however, while TCCs are an excellent option for treating wounds, their use is fraught with difficulties and time-consuming [65]. In one study, Armstrong et al. constructed an "instant TCC" by covering a detachable cast walker with a cohesive bandage or plaster of Paris, and they were able to obtain comparable healing rates. For patients who are obese, blind, morbid, noncompliant, or have deep or draining ulcers, TCCs should not be used. Also, new ulcers may arise if the application of total contact casts is inappropriate, for example, in deep, open wounds. Removable cast walkers are often preferred by providers because they lack certain disadvantages exhibited by TCCs [66]. Its detachable nature allows for early infection detection, dressing changes, and daily wound checks; however, the greatest disadvantage of this footwear is that studies show that patients only wear it about thirty percent (30%) whilst walking to and from the doctor's office (usually) [66].

Infection Control:

Polymicrobial pathogens often cause diabetic foot infections that are life-threatening. Among the most common pathogens are enterobacteriaceae, pseudomonas aeruginosa, enterococci, β hemolytic streptococci, and methicillin-resistant Staphylococcus aureus. Anaerobic organisms such as bacteroides, peptococcus, and peptostreptococcus are rarely the only pathogens in mixed infections with aerobes [67]. Gram-positive and gram-negative aerobic and anaerobic bacteria should be covered by the antibiotics used to treat severe or potentially life-threatening illnesses. Such wounds require hospital admission for the purpose of administering intravenous antibiotic therapy [68, 69]. Outpatient treatment options for mild to severe infections resulting in localized cellulitis include moxifloxacin,

clindamycin, amoxicillin with clavulanate potassium, and oral cephalexin. Following the taking of initial cultures, the course of treatment should be started; it may alter based on subsequent results [70].

CONCLUSION

Diabetes mellitus, diabetic retinopathy, diabetic nephropathy, gestational diabetes, diabetic foot ulcers, and their long-term impacts and treatments were all discussed in this review paper. If diabetes is not treated in sufficient time, serious complications such as heart disease, nerve damage, and blindness may result. Diabetes is controllable with suitable medicine and a healthy lifestyle.

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REFERENCES

1. Kaul K, Tarr JM, Ahmad SI, Kohner EM, Chibber R. Introduction to diabetes mellitus. Adv Exp Med Biol. 2012;771:1-11.

2. Blair M. Diabetes Mellitus Review. Urol Nurs. 2016;36(1):27-36.

3. Katsarou A, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, et al. Type 1 diabetes mellitus. Nat Rev Dis Primers. 2017;3:17016.

4. Gregory JM, Moore DJ, Simmons JH. Type 1 diabetes mellitus. Pediatr Rev. 2013;34(5):203-15.

5. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, et al. Type 2 diabetes mellitus. Nat Rev Dis Primers. 2015;1:15019.

6. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. Oman Med J. 2012;27(4):269-73.

7. Buchanan TA, Xiang AH. Gestational diabetes mellitus. J Clin Invest. 2005;115(3):485-91.

8. Kjos SL, Buchanan TA. Gestational diabetes mellitus. N Engl J Med. 1999;341(23):1749-56.

9. Jovanovic L, Pettitt DJ. Gestational diabetes mellitus. Jama. 2001;286(20):2516-8.

10. Antar SA, Ashour NA, Sharaky M, Khattab M, Ashour NA, Zaid RT, et al. Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. Biomed Pharmacother. 2023;168:115734.

11. Ferris FL, 3rd, Davis MD, Aiello LM. Treatment of diabetic retinopathy. N Engl J Med. 1999;341(9):667-78.

12. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, et al. Diabetic retinopathy. Diabetes Care. 2003;26 Suppl 1:S99-s102.

13. Zhang X, Saaddine JB, Chou CF, Cotch MF, Cheng YJ, Geiss LS, et al. Prevalence of diabetic retinopathy in the United States, 2005-2008. Jama. 2010;304(6):649-56.

14. Engerman RL. Pathogenesis of diabetic retinopathy. Diabetes. 1989;38(10):1203-6.

15. Aiello LM. Perspectives on diabetic retinopathy. Am J Ophthalmol. 2003;136(1):122-35.

16. Wang W, Lo ACY. Diabetic Retinopathy: Pathophysiology and Treatments. Int J Mol Sci. 2018;19(6):50-56.

17. Gardner TW, Antonetti DA, Barber AJ, LaNoue KF, Levison SW. Diabetic retinopathy: more than meets the eye. Surv Ophthalmol. 2002;47 Suppl 2:S253-62.

18. Porta M, Bandello F. Diabetic retinopathyA clinical update. Diabetologia. 2002;45(12):1617-34.

19. Evans JR, Michelessi M, Virgili G. Laser photocoagulation for proliferative diabetic retinopathy. Cochrane Database Syst Rev. 2014;2014(11):Cd011234.

20. Chew EY, Ferris FL, 3rd, Csaky KG, Murphy RP, Agrón E, Thompson DJ, et al. The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the early treatment diabetic retinopathy follow-up study. Ophthalmology. 2003;110(9):1683-9.

21. Chawan-Saad J, Wu M, Wu A, Wu L. Corticosteroids for Diabetic Macular Edema. Taiwan J Ophthalmol. 2019;9(4):233-42.

22. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care. 2005;28(1):164-76.

23. Papadopoulou-Marketou N, Chrousos GP, Kanaka-Gantenbein C. Diabetic nephropathy in type 1 diabetes: a review of early natural history, pathogenesis, and diagnosis. Diabetes Metab Res Rev. 2017;33(2):18-25.

24. Papadopoulou-Marketou N, Chrousos GP, Kanaka-Gantenbein C. Diabetic nephropathy in type 1 diabetes: a review of early natural history, pathogenesis, and diagnosis. Diabetes/metabolism research and reviews. 2017;33(2):e2841.

25. Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010;21(4):556-63.

26. Cooper ME. Pathogenesis, prevention, and treatment of diabetic nephropathy. Lancet. 1998;352(9123):213-9.

27. Adler S, Nast C, Artishevsky A. Diabetic nephropathy: pathogenesis and treatment. Annu Rev Med. 1993;44:303-15.

28. Fineberg D, Jandeleit-Dahm KA, Cooper ME. Diabetic nephropathy: diagnosis and treatment. Nat Rev Endocrinol. 2013;9(12):713-23.

29. Lim A. Diabetic nephropathy - complications and treatment. Int J Nephrol Renovasc Dis. 2014;7:361-81.

30. Robinson TW, Freedman BI. Assessing glycemic control in diabetic patients with severe nephropathy. J Ren Nutr. 2013;23(3):199-202.

31. Fioretto P, Bruseghin M, Berto I, Gallina P, Manzato E, Mussap M. Renal protection in diabetes: role of glycemic control. J Am Soc Nephrol. 2006;17(4 Suppl 2):S86-9.

32. Strowig S, Raskin P. Glycemic control and diabetic complications. Diabetes Care. 1992;15(9):1126-40.

33. Thorn LM, Forsblom C, Fagerudd J, Thomas MC, Pettersson-Fernholm K, Saraheimo M, et al. Metabolic syndrome in type 1 diabetes: association with diabetic nephropathy and glycemic control (the FinnDiane study). Diabetes Care. 2005;28(8):2019-24.

34. Park TS. How much glycemic control is needed to prevent progression of diabetic nephropathy? J Diabetes Investig. 2012;3(5):411-2.

35. Ellis D, Avner ED, Transue D, Yunis EJ, Drash AL, Becker DJ. Diabetic nephropathy in adolescence: appearance during improved glycemic control. Pediatrics. 1983;71(5):824-9.

36. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The Pathophysiology of Gestational Diabetes Mellitus. Int J Mol Sci. 2018;19(11).

37. Gestational diabetes mellitus. Diabetes Care. 2004;27 Suppl 1:S88-90.

38. Chiefari E, Arcidiacono B, Foti D, Brunetti A. Gestational diabetes mellitus: an updated overview. J Endocrinol Invest. 2017;40(9):899-909.

39. Landon MB, Gabbe SG. Gestational diabetes mellitus. Obstet Gynecol. 2011;118(6):1379-93.

40. Sweeting A, Wong J, Murphy HR, Ross GP. A Clinical Update on Gestational Diabetes Mellitus. Endocr Rev. 2022;43(5):763-93.

41. Johns EC, Denison FC, Norman JE, Reynolds RM. Gestational Diabetes Mellitus: Mechanisms, Treatment, and Complications. Trends Endocrinol Metab. 2018;29(11):743-54.

42. Harper LM, Jauk V, Longo S, Biggio JR, Szychowski JM, Tita AT. Early gestational diabetes screening in obese women: a randomized controlled trial. Am J Obstet Gynecol. 2020;222(5):495.e1-.e8.

43. Hong WY, Biggio JR, Tita A, Harper LM. Impact of Early Screening for Gestational Diabetes on Perinatal Outcomes in High-Risk Women. Am J Perinatol. 2016;33(8):758-64.

44. Pezeshki B, Chiti H, Arasteh P, Mazloomzadeh S. Early screening of gestational diabetes mellitus using hemoglobin A1C: Revising current screening guidelines. Caspian J Intern Med. 2019;10(1):16-24.

45. Kattini R, Hummelen R, Kelly L. Early Gestational Diabetes Mellitus Screening With Glycated Hemoglobin: A Systematic Review. J Obstet Gynaecol Can. 2020;42(11):1379-84.

46. Neelakandan R, Sethu PS. Early universal screening for gestational diabetes mellitus. J Clin Diagn Res. 2014;8(4):Oc12-4.

47. Bhattacharya S, Nagendra L, Krishnamurthy A, Lakhani OJ, Kapoor N, Kalra B, et al. Early Gestational Diabetes Mellitus: Diagnostic Strategies and Clinical Implications. Med Sci (Basel). 2021;9(4).

48. Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. Cochrane Database Syst Rev. 2009;2009(3):Cd003395.

49. Martis R, Crowther CA, Shepherd E, Alsweiler J, Downie MR, Brown J. Treatments for women with gestational diabetes mellitus: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev. 2018;8(8):Cd012327.

50. Lapolla A, Dalfrà MG, Fedele D. Management of gestational diabetes mellitus. Diabetes Metab Syndr Obes. 2009;2:73-82.

51. Meltzer SJ. Treatment of gestational diabetes. BMJ. 2010;340:c1708.

52. Agarwal MM, Punnose J. Recent advances in the treatment of gestational diabetes. Expert Opin Investig Drugs. 2004;13(9):1103-11.

53. Chatzakis C, Cavoretto P, Sotiriadis A. Gestational Diabetes Mellitus Pharmacological Prevention and Treatment. Curr Pharm Des. 2021;27(36):3833-40.

54. Moholdt T, Hayman M, Shorakae S, Brown WJ, Harrison CL. The Role of Lifestyle Intervention in the Prevention and Treatment of Gestational Diabetes. Semin Reprod Med. 2020;38(6):398-406.

55. Retnakaran R, Ye C, Hanley AJ, Connelly PW, Sermer M, Zinman B. Treatment of Gestational Diabetes Mellitus and Maternal Risk of Diabetes After Pregnancy. Diabetes Care. 2023;46(3):587-92.

56. Kitwitee P, Limwattananon S, Limwattananon C, Waleekachonlert O, Ratanachotpanich T, Phimphilai M, et al. Metformin for the treatment of gestational diabetes: An updated meta-analysis. Diabetes Res Clin Pract. 2015;109(3):521-32.

57. Goh JE, Sadler L, Rowan J. Metformin for gestational diabetes in routine clinical practice. Diabet Med. 2011;28(9):1082-7.

58. Niromanesh S, Alavi A, Sharbaf FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. Diabetes Res Clin Pract. 2012;98(3):422-9.

59. Zhao LP, Sheng XY, Zhou S, Yang T, Ma LY, Zhou Y, et al. Metformin versus insulin for gestational diabetes mellitus: a meta-analysis. Br J Clin Pharmacol. 2015;80(5):1224-34.

60. Ahmad J. The diabetic foot. Diabetes Metab Syndr. 2016;10(1):48-60.

61. Slovenkai MP. Foot problems in diabetes. Med Clin North Am. 1998;82(4):949-71.

62. Rosyid FN. Etiology, pathophysiology, diagnosis and management of diabetics' foot ulcer. International Journal of Research in Medical Sciences. 2017;5(10):4206-13.

63. Dayya D, O'Neill OJ, Huedo-Medina TB, Habib N, Moore J, Iyer K. Debridement of Diabetic Foot Ulcers. Adv Wound Care (New Rochelle). 2022;11(12):666-86.

64. Sohrabi S, Russell D. Diabetic foot and foot debridement technique. Surgery (Oxford). 2017;35(9):500-4.

65. Bus SA. Priorities in offloading the diabetic foot. Diabetes Metab Res Rev. 2012;28 Suppl 1:54-9.

66. de Oliveira AL, Moore Z. Treatment of the diabetic foot by offloading: a systematic review. J Wound Care. 2015;24(12):560, 2-70.

67. Hurlow JJ, Humphreys GJ, Bowling FL, McBain AJ. Diabetic foot infection: A critical complication. Int Wound J. 2018;15(5):814-21.

68. Cigna E, Fino P, Onesti MG, Amorosi V, Scuderi N. Diabetic foot infection treatment and care. Int Wound J. 2016;13(2):238-42.

69. Pitocco D, Spanu T, Di Leo M, Vitiello R, Rizzi A, Tartaglione L, et al. Diabetic foot infections: a comprehensive overview. Eur Rev Med Pharmacol Sci. 2019;23(2 Suppl):26-37.

70. Peters EJ, Lipsky BA. Diagnosis and management of infection in the diabetic foot. Med Clin North Am. 2013;97(5):911-46.