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Long-Term Complications of Diabetes: A Comprehensive Review

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Annotation: Diabetes is a global epidemic, and its prevalence and thereby the financial burden are increasing at an unprecedented rate worldwide. A majority of the newly diagnosed diabetics in developing countries are unaware of the long-term complications of diabetes mellitus. One in two adults with diabetes is undiagnosed globally. After the diagnosis of diabetes mellitus, 10 to 15 years may pass before overt macrovascular complications take place. However, microvascular complications may already be present, even at the time of diagnosis, especially in type 2 diabetes patients. Therefore, it is crucial to be aware of the problems related to undiagnosed or inadequately treated long-term complications leading to high morbidity and mortality risk in these patients.

1. Introduction

Although the vascular complications of diabetes mellitus were identified years ago and are the principal cause of morbidity and mortality in the diabetic population, their exact etiopathogenesis is not clearly defined. Diabetes mellitus is a disease that runs along with metabolic disturbances in carbohydrate, fat, and protein. It promotes microvascular diseases before macrovascular issues show up. Various hormones provided by fat cells, including adiponectin, leptin, and resistin, may impact insulin sensitivity, the extent of the free fatty acid released from adipose tissue, inflammation, and blood pressure in people who are overweight or have type 2 diabetes. The expressions of adhesion particles and numerous inflammatory factors are raised in type 2 diabetes and obesity during conditions involving low-grade inflammation. Improved glycation is recognized in diabetics and in those with impaired glucose regulation as a contributory factor of long-term complications.

1.1. Overview of Diabetes Mellitus

Deprivation of metabolic energy in the individual cells of the human body results in a chronic disease condition known as diabetes mellitus. Diabetes, leading to vascular complications and involving many other organs, is common. At different levels, including genetics, molecular biology, and karyotypic studies, diabetes mellitus has been studied in detail. The two different subtypes of diabetes mellitus are Type 1 diabetes and Type 2 diabetes. Throughout the globe, diabetes is increasingly prevalent and is a primary cause of morbidity, mortality, and an enormous economic burden on health systems. Diabetes is quickly increasing and advancing in developing countries, with the majority of diabetics being brought to light by previously unsuspected cases. The lifestyle of individuals is a vitally important aspect that strongly establishes a person's survival and overall health. To suffer from diabetes or other lifestyle-related diseases, various factors may result in a permissive or premorbid state, leading to comprehensive quantifiable correlations. The aim is to review findings, interpretations, and suggestions on diabetes in a comprehensive approach, from statistics to the years' homeostatic adaptational changes and intense clinical complications. It deeply includes the etiopathogenesis, etiology, and epidemiology of diabetes. It will focus on whether diabetes is a commonly fatal condition of substantial metabolic power or a vascular disease of phenotypic expression with prominent features such as coronary artery disease, hyperlipidemia, hypertension, and many other interrelated conditions. It can be detected with microvascular and other end-organ conditions. Following is diabetes as it pertains to specific organs and systems. [1][2]

2. Pathophysiology of Diabetes Mellitus

Pathophysiology Diabetes Mellitus (DM) is a heterogeneous syndrome characterized by a disturbance of insulin secretion and/or insulin action with chronic hyperglycemia as a common endpoint. Type 1 diabetes mellitus (T1DM), also known as autoimmune diabetes, is characterized by absolute insulin deficiency resulting from the destruction of pancreatic β cells. This occurs in young individuals in response to exposure to high levels of blood glucose and lipids mediated through the CD8 cytotoxic T lymphocytes. Although relatively rare, its global incidence is increasing by 3–4% each year. Type 2 diabetes (T2DM) is a consequence of interaction between genetic and environmental factors, wherein there are abnormalities in signal transduction in pancreatic β cells, adipocytes, skeletal muscle, and liver, selective and gradual loss of β-cell function, and decreased tissue sensitivity to insulin. Ninety percent of the patients with diabetes have T2DM, and its prevalence is rapidly increasing around the world. Prediabetes or rapid increase in glycemia due to insulin resistance, and impairment and loss of additional β-cell function are proposed in these forms of diabetes. Clinically evident diabetic chronic hyperglycemia (fasting blood glucose level > 126 mg/dL) leads to injury of the heart, blood vessels, eyes, kidneys, nerves, and limbs, causing significant morbidity and/or mortality. Hyperglycemia in DM causes many complications in various organs, and the physiologic and pathophysiological processes are discussed in this topic. Abrogation of pathophysiological processes, such as oxidative stress, advanced glycation end products, inflammation, endoplasmic reticulum stress, protein and fat catabolism, that are involved in the development of diabetic complications is the basis for the treatment of diabetes. [3][4][5]

2.1. Type 1 Diabetes

Endocrinology and neurology, covering all these complications, necessitates the review of all the specific aspects of diabetes and their interactions.

Type 1 diabetes Type 1 diabetes (T1D) is caused by a progressive destruction of the pancreatic insulin-producing beta cells by the immune system, so that without insulin supplementation, hyperglycemia will occur and cause severe symptoms and possibly diabetic ketoacidosis, ultimately leading to death if not treated with insulin. There is also destruction of the alpha cells, inducing loss of glucagon, massive interstitial edema in the skin, and a T-cell mediated progressive vasculopathy throughout the body. The diagnosis is usually made by the clinical symptoms of

polydipsia (thirst), polyuria (excessive urination), and weight loss combined with hyperglycemia, although not all the classical symptoms are necessarily present. An HbA1c of ≥ 48 mmol/mol (6.5%) also diagnoses diabetes, but it is advisable to confirm with a fasting plasma glucose (FPG) ≥ 7.0 mmol/L or 2 hours post 75g oral glucose load (OGTT) of ≥ 11.1 mmol/L. Otherwise, mandatory testing for diabetes includes testing for gestational diabetes in pregnancy and testing for additional conditions that require insulin treatments. Random non-fasting glucose gives immediate diagnosis if ≥ 11.1 mmol/L with classical hyperglycemia symptoms. T1D is often mistaken for type 2 diabetes or other gestational diabetes when thirst and urination are mild. A well-delimited phenotypic and pathophysiological distinction must be clearly defined within these classifications for their correct approach.

Pathophysiology T1D occurs when environmental, mainly viral, triggers combine with genetic factors to develop recruiting antibodies to the beta cells, so that by the time of diagnosis, 10-50% of the cells have been destroyed. The trigger is primary infection with usually a common virus, after which antibodies may be seen early on blood tests. There is worldwide variation in the incidence of type 1 diabetes, with eightfold differences being recorded. Insulin is the basis of treatment once diagnosed. Unrelieved hyperglycemia leads to further beta-cell destruction by the auto-reactive immune cells that are then activated by the release of auto-antigens from the damaged beta cells. Insulin-deficient diabetes, when diagnosed, affects 5-20 children per 100,000. Treatment aims to restore the blood glucose to as normal a range as possible (4.0 - 7.8 mmol/L) where weight loss ceases and fatigue, hyperglycemia, polyuria, and polydipsia come under control. Other than early and accurate detection of diabetes complications to prevent end-organ damage, for example, kidney and nerve damage, glycated hemoglobin is an area that has the most importance for international consensus. Continuous glucose monitoring is the newest aid in patient education, as hypo- and hyperglycemia can be demonstrated with facts. Using different modalities of insulin treatment, with or without dedicated insulin pumps, parents and patient education in the increasing rate of diabetes is mandatory. The paradigm of treatment has now changed to a more comprehensive awareness of the importance of diabetic control in diabetes parameters, e.g., HbA1c in all diabetes patients based on national and international guidelines. [6][7][8]

2.2. Type 2 Diabetes

Type 2 diabetes syndrome, also referred to as maturity-onset diabetes, primarily results from insulin resistance at the level of the skeletal muscles as well as the liver. In addition to insulin resistance, genetic predisposition is characterized by beta-cell dysregulation. In the past few decades, there has been a paradigm shift involving advances in gene technology and molecular biology that expanded knowledge of disease biology. Clinical medicine has, in response, placed these two disorders into a category of genetically defined diabetes. At-risk individuals and first-degree relatives have indeed been tested before the disease even occurs; how frequently this proactive approach has proved to be affordable as well as acceptable to patients.

Approximately 95% of diabetes mellitus type 2 cases are type 2 diabetes resulting from insulin resistance and some form of pancreatic beta-cell failure. The continued insulin resistance and decreased insulin output progression to hyperglycemia (and its consequences) is modified by lifestyle and pharmacologic intervention. Increased physical inactivity and obesity are strong risk factors for type 2 diabetes. Indeed, there is an age-related decrease in the function of the pancreas when cells are partially resistant to insulin. By the time that diabetes is diagnosed, about 50% of pancreatic cells are not functioning normally. For long-term health practitioners, this means that diabetes is already present when the disease is detected. Although this is a serious condition, individuals can stay healthy for many years if their glucose levels are kept close to average when they have type 2 diabetes. These latter findings are not new, resulting from a project. [9][10][11]

3. Macrovascular Complications

Cardiovascular disorders constitute the predominant macrovascular complications in diabetes. The two- to threefold risk of subsequent cardiovascular events in diabetes patients implies a powerful

association between the two conditions. Manifestations of atherosclerosis, chiefly of the coronary and cerebral arteries, are responsible for the majority of the excess mortality seen in diabetes. Hyperglycemia has a direct effect on the arterial wall over and above the indirect acceleration seen through classic risk factors for atherosclerosis. Two main risk factors impact cardiovascular morbidity and mortality of the patient—one is hypertension, which has deleterious effects in diabetes due to its critical role in coronary artery disease and stroke.

Hypertension and diabetes have additive adverse effects on the progression of diabetic kidney diseases, and once the kidney is impaired, hypertension tends to exacerbate nephropathy in diabetics. Dyslipidemia, with elevated triglycerides and decreased high-density lipoprotein cholesterol that occur together with the abnormal LDL, is commonly found in type 2 diabetic patients, which accelerates vascular disease. Interventions to lower lipids mainly in type 2 diabetes include lifestyle therapy. Several small studies of this type have demonstrated a reduction in coronary stenosis within a short period of time. As reviewed above, the magnitude and the timing of the cardiovascular risk factor relationships suggest early intervention would be especially beneficial; the challenge is to find the optimal low-risk patients for whom such early intervention would most cost-effectively be applied. Patients with diabetes have an increased long-term risk of myocardial infarction and cerebrovascular events. This increased risk may range from double in patients with newly diagnosed diabetes to six times that of non-diabetic subjects in older cohorts. Numerous studies have shown that the risk of coronary artery disease starts to rise steeper with increasing glucose levels already at the non-diabetic plasma glucose range. The possibilities that these findings could ultimately provide a further rationale for aggressive management of plasma glucose levels and the regimens favoring the role of insulin sensitizers. [12][13][14]

3.1. Coronary Artery Disease

Coronary artery disease (CAD) is an important and major macrovascular complication in both type 1 diabetes and type 2 diabetes. People with diabetes are at a two- to threefold increased risk of cardiovascular events compared to people without diabetes. The increasing prevalence of pancreatic disease along with obesity, which are the main representations of a sedentary lifestyle, have led to an increase in risk factors for heart disease, including coronary artery disease. Diabetics have long been recognized to have an increased duration of symptoms before the development of CAD. It is known that diabetes not only increases the likelihood of the development of coronary artery disease but also accelerates the rapid progression of the disease through shared risk factors such as hypertension and dyslipidemia. The cause of diabetes accelerates atherosclerosis due to the function and anatomy of the coronary arteries.

Thus, diabetes can lead to various types of heart disease, from infarction to heart failure, when compared with people without diabetes. The pathogenesis of the development of CAD in diabetics is indeed still controversial. It seems to be a result of the combination of insulin resistance, hypertriglyceridemia, and hyperglycemia. Hyperglycemia increases inflammation and endothelial dysfunction. Disorders of mitochondrial calcium regulation are thought to play an important role in diabetic heart disease. Hyperglycemia, in accordance with other symptoms, can lead to the production of oxygen radicals, both by increasing the nutrients to the mitochondria from donor substrates and by reducing the use of oxygen in the electron transport chain. The relationship between the duration of diabetes and the increased incidence of cardiovascular disease is related to the increased expression of VCAM-1 protein in plasma, which plays a role in monocyte attachment in blood vessels. In addition, it is recommended that all diabetics aged 40 years and older for men and more than 50 years for women, with a history of smoking, should be screened for atherosclerotic heart disease (ASvD) risk factors. Management of coronary heart disease includes increased physical activity, counseling related to nutrition, smoking cessation, and medication therapy. Balancing blood sugar levels, controlling high blood pressure, and managing the intake of cholesterol-lowering drugs are essential in diabetic heart disease management. Prevention of coronary heart disease in diabetics or those with metabolic syndrome needs to be screened, especially in people aged 40 years and older for men and 50 years and older for women.

People under 40-50 years old should be screened if they have advanced diabetes, with LDL cholesterol > 100-129 mg/dL, physical activity > 3 times per day, HDL cholesterol < 40 mg/dL, and a history of other diseases. [15][16][17]

4. Microvascular Complications

Diabetes affects not only systemic macrovessels but also smaller blood vessels, leading to various complications such as retinopathy, nephropathy, and neuropathy. These microvascular complications have been associated with chronic hyperglycemia, the key characteristic of diabetes. Chronic hyperglycemia in diabetes has been demonstrated to cause various adverse effects on the vascular endothelium, the monolayer of cells lining blood vessels. Multifactorial effects of hyperglycemia include activation of the protein kinase C pathway, excessive production of sorbitol through the polyol pathway, and increased production of advanced glycation end-products that activate their receptor, finally inducing an abnormality in a variety of cellular functions. The resulting dysfunctional vascular endothelium then causes various physiological changes in the proper function of organs. For instance, abnormal blood flow caused by activation of thromboses, angiogenesis, or coagulation results in alterations in the function of the eyes, leading to retinopathy. Similarly, endothelial dysfunction caused by imbalances in vasodilation and constriction modulators affects the kidneys and results in nephropathy. Increased oxidative stress from mitochondrial dysfunction, activation of the AGE-RAGE axis, and hypocytokinesis leads to disturbances in neuronal function in the nerves, causing neuropathy. However, normoglycemic newly diagnosed patients did not exhibit any signs of microvascular complications. Risk factors include older age, longer diabetes duration, poor glycemic control, hypertension, and hyperlipidemia. Diabetic retinopathy is characterized by microaneurysms, dot, and blot hemorrhages; hard exudates; and cotton wool spots among others on the retina. Late-stage diabetic retinopathy can cause irreversible vision loss or blindness. This is why early detection and proper management of diabetic retinopathy are important to prevent or slow permanent damage. Currently, comprehensive management strategies aim to slow or prevent microvascular complications. However, developing the most effective ways to manage and lower the risk or slow the progression of these complications is crucial in reducing the morbidity and mortality associated with diabetes. [18][19][20]

4.1. Diabetic Retinopathy

Diabetic retinopathy is the leading cause of blindness in adults. It occurs in two severe forms, an exudative or proliferative phase and an advanced stage with resultant ischemia of the retina and neovascular changes (severe non-proliferative retinopathy and proliferative retinopathy). Less serious forms are detected through regular eye examinations often before the patient is aware of any symptoms: mild non-proliferative retinopathy characterized by small retinal hemorrhages; and moderate non-proliferative retinopathy with extensive retinal hemorrhages and venous beading. The pathogenesis or pathophysiological mechanisms that link uncontrolled diabetes to changes in the retina have been described over the years: microvascular changes in the retina can lead to ischemia of the retina which in turn leads to neovascularization—the accurate mechanism of which is not completely elucidated. Several risk factors have been identified including duration of diabetes, hypertension, and hyperglycemia. Regular eye examinations for early detection of retinopathy are recommended which, if detected early, can lead to better treatment success in limiting progression of vision loss along with other forms of interference such as vitreous hemorrhages and the consequence of surgery for vitreous hemorrhage. Current treatment options include a form of laser therapy or a series of injections with anti-vascular endothelial growth factors to prevent progression of more severe forms of retinopathy. Laser surgery has been shown to reduce the risk of severe visual loss by 55% whereas there are consistent clinical trial data to suggest that intravitreal injections of anti-VEGF can improve, by approximately 3% after one year, 2 letters or more improving vision which is associated with an improvement in length of time before progression of disease to retinopathy.

Recent findings from large and well-designed clinical trials have demonstrated that the progression of retinopathy in patients with diabetes type 1 or severe diabetes type 2 (reducing the level of hemoglobin A1c via intensive glycemic control) can be slowed. In the type 2 Diabetic Retinopathy Vitrectomy Study, the incidence of both moderate visual loss and vitrectomy surgery was lower by 100 per 1000 person-years in eyes treated with immediate vitrectomy as compared with deferral of vitrectomy. [21][22]

5. Neuropathic Complications

There are a number of neuropathic complications that are seen in diabetes of various durations. The prevalence of peripheral neuropathy varies from 16% to 26% based on the presence of symptoms, foot deformities, plantar ulcers, Charcot joints, or lower extremity amputations in diabetes. There are different types and several pathophysiological events involved in these neuropathies. Sensory polyneuropathy is the nerve complication that can affect any one or more of the glucose-genic plus the non-glucose-genic types. Two syndromes are commonly seen in sensory neuropathies: somatic (peripheral) and autonomic. Peripheral neuropathies appear to be more common and share several pathophysiological mechanisms. Insufficient insulin and/or its action with or without antioxidant treatment may culminate in intense reiterative metabolic and ischemic processes, which disrupt quality of life and functional independence. Early identification or awareness of neuropathy is paramount in the management of diabetes in order to prevent its long-term complications. It is pain and paresthesia that initially suggest the development of neuropathy. Impaired proprioception or fine motor coordination due to numbness can result in postural and motor imbalance during walking, leading to ulcers in the feet. The double lesion of the autonomic and either glucose-genic or non-glucose-genic sensory nerve fibers constitutes the clinical phenotype of both autonomic and sensory neuropathy in diabetes. Management of these complications is to contain hyperglycemia and provide some anti-hyperalgesic agents. Electroanalgesia, which utilizes microcurrent effect technology, would be a rationale-based addition as it will add no adverse effects and also prevent further impairment since it is tested on diabetic neuropathies as a non-pharmacological delivery of treatment in palliative care. Management of neuropathy is devoid of any disease-modifying drugs; it mainly comprises pharmacological and non-pharmacological management. The proactively emphasized non-pharmacological treatment is the provision of comprehensive foot care to prevent foot complications in diabetes. Such advice includes encouraging and educating diabetic patients to wear appropriate footwear, self-inspection of the feet at regular intervals, controlling and maintaining blood sugar levels as near normal as possible, and those with healed ulcers attending regular preventive foot care clinics. The management of diabetic sensorimotor polyneuropathy usually follows a stepwise approach; these are to contain the underlying etiology, relieve pain, and provide physical, psychological, and occupational therapy in addition to maintaining an adequate level of physical activity, which reinforces prescribed medication. Opioids, tramadol, pregabalin, alpha-lipoic acid, or capsaicin patches are the first-line treatments for neuropathic pain in diabetes. The neuropathic symptoms may persist long after better control of hemoglobin A1c, indicating the need for early intervention, effective treatment, and continual assessment of neuropathic signs and symptoms. [23][24]

5.1. Diabetic Peripheral Neuropathy

The Commission recommends annual screening for diabetic neuropathy by the 10g monofilament where possible to identify peripheral neuropathy in high-risk groups. It is an attempt not only to find people with diabetic neuropathy who require neurological assessment and possible management but also to identify those with sensory neuropathy causing unsteadiness and falls who could then be referred to fall clinics for potential benefit. In summary, although asymptomatic until very late in their evolution, these complications result in lifelong disabilities for a patient who eventually, having cutaneous insensibility, suffers from bruises and infections which very often progress to gangrene and amputation. All these could occur without feeling any pain. Therefore, it warrants early identification and management to maintain the quality of life.

Diabetic peripheral neuropathy (DPN) is a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic or microvessel alterations resulting from chronic hyperglycemia exposure and cardiovascular risk covariates, commonly of long duration. Clinically, subjective symptoms that may be accompanied by objective signs and always by sudomotor dysfunction are the preferred diagnostic standard at the original presentation. Painful diabetic neuropathy (PDN) is a neurogenic pain diagnosing 25% of the individuals with diabetes and comprises 11%-26% of the diabetic neuropathy population. PDN is proof of diabetic nerve damage and is delineated by tingling, squeeze or pinch in feet and legs, radiance, burning, pain at night while in bed, and loss of sensory function leading to numbness. Despite presenting no signs and symptoms, the following are the advent of the nerve damage: loss of sense of weight, temperature, touch, or pinprick in feet. Diabetic sensorimotor polyneuropathy is a rare condition which usually progresses gradually; however, it is likely sometimes to escalate. [25][26]

6. Renal Complications

Renal complications are the second most common cause of morbidity and mortality in patients with diabetes. Diabetic nephropathy is a well-documented chronic complication of both type 1 and type 2 diabetes. Studies have estimated the prevalence of nephropathy in patients with insulin-dependent diabetes to range from 28 to 35% based on a urinary albumin excretion rate of 20–200 µg/min. The cumulative ten-year risk for patients with diabetes developing macroalbuminuria is approximately 40%. Renal complications are a common cause of death in patients with diabetes, with over 50% of patients with end-stage renal disease on long-term haemodialysis programs suffering from the condition. The economic and social burden is high, with each haemodialysis patient costing the healthcare system over $100,000 per annum. Therefore, the early recognition and prompt treatment of nephropathy is important in order to slow the development of end-stage renal disease.

Pathophysiologically, diabetic nephropathy has a number of features. Initially, there is a hyperdynamic phase, with intraglomerular hypertension referred to as glomerular hyperfiltration, and kidney growth. This is followed by a prolonged phase with more characteristic pathological features. There are a number of key factors that are well documented to contribute. Hypertension and the presence of metabolic syndrome significantly increase the risk of developing diabetic nephropathy. Genetic determinants of diabetic nephropathy are also increasingly identified. Combined, these factors provide the opportunity for considerable reduction and possibly avoidance of diabetic renal disease in an “at risk” patient with diabetes. In a patient with diabetes and renal disease, in addition to tight management of diabetes and blood pressure, specific renoprotective interventions should be made. These include blockade of the renin-angiotensin system with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. These medications have been found to slow the rate of decline of renal function, as measured by both the change in the glomerular filtration rate and the onset of microalbuminuria. These medications have also been found to have anti-proteinuric effects. However, proteinuria is not abolished even in patients with microalbuminuria. As such, other non-pharmacological interventions are critically important. These are diet and lifestyle change, and include healthy eating, exercise, weight management, smoking cessation, and management of lipids. Optimisation of renal care requires a team approach and can be optimally administered in a multidisciplinary setting. [27][28]

6.1. Diabetic Nephropathy

Diabetic nephropathy (DN) leads to end-stage renal disease (ESRD) in a high percentage of patients with diabetes mellitus (DM). Several stages characterize the progression of DN, and treatment strategies differ for each one. Early diagnosis is a paramount issue that may allow for improved outcomes. DN has a multifactorial pathogenesis that includes metabolic and hemodynamic pathways. From the point of view of the kidneys, DN is a glomerulosclerosis and a tubular disorder. The evolution of DN is influenced by risk factors such as hyperglycemia, high

levels of blood pressure (BP), male gender, and genetic predisposition. DN treatment should aim to address these risk factors. The gold standard for diagnosing early DN is microalbuminuria, which is the only marker of DN severity. In clinical practice, the management of DN is substantially supportive, aimed at slowing the progression toward ESRD. Lifestyle and nutritional suggestions are essential. They include weight reduction, salt and protein intake restriction, increased physical activity, and smoking cessation. An early and rigorous control of glycemia and blood pressure, with aggressive lipid-lowering therapy, is essential. Other strategies toward slowing DN progression include antihypertensive agents in both nondiabetic and diabetic patients with microalbuminuria or overt proteinuria. The use of angiotensin-converting enzyme inhibitors has been recommended among other types of antihypertensive therapies.

Patients with diabetes and their healthcare providers need to be aware of the kidney health consequences of their disease. Early identification of the patients at risk is based mainly on the assessment of glomerular hyperfiltration, which may be particularly dangerous for kidney function. Albuminuria is not a simple marker of kidney injury. Once an impairment of renal function is present, markers of kidney injury are more accurate in predicting the outcomes. Psychosocial issues are also important and should be managed with the help of the whole healthcare team, including kidney specialists or nephrologists in those at higher risk of developing ESRD. Several clinical and laboratory markers may be used in the care of these patients. Parameters should be used in combination rather than individually. This approach should provide prognostic stratification, early diagnosis, and diagnosis of diabetic kidney disease complications. The international society of accuracy was proposed to validate new markers of diabetes and kidney disease. Because type 2 diabetes is the main cause of ESRD in most individual countries, the campaign of awareness groups, patient organizations, and health advocacy bodies is of great importance to improve the knowledge of the medical community and to show the burden of ESRD in each country. The main message in the campaign of this year is: "Diabetes is the leading cause of chronic kidney disease. Screening for kidney disease is important for everyone with diabetes." [29][30]

7. Diabetic Foot Complications

Diabetic foot complications and amputation are a large cause of morbidity and mortality. Diabetic foot problems typically present as neuropathy, peripheral vascular disease, and strong infections with ulcerations. Ulceration is due to mainly two reasons: neuropathy and ischemia. Neuropathy results in a situation where pain is not felt, and a small injury creates an enormous wound because the pressure-induced tissue breakdown goes unnoticed. Neovascularization is also limited, creating an ischemic microenvironment, which impairs healing, increasing the risk of infection and amputation. The foot complications can be ulcerations or infections of the skin and muscle. Ulcerations of the proximal interphalangeal joint, at the fifth metatarsal or the lateral part of the sole, and amputations are associated with shorter amputation-free survival.

The most severe lower leg complications are seen in the neuropathic foot. Neuropathy, peripheral vascular disease, poor glycemic control, and increased duration of diabetes are the main risk factors for the development of foot complications. Additional risk factors include chronic ulceration and previous amputation. In relation to the foot, there is sometimes an increased risk of pressure due to a Charcot foot or inappropriate footwear. After intact sensibility, reduced or absent blood flow to the foot is the second most important risk factor. Regular foot examination and education for the patients, as well as measures to prevent ischemia and loss of sensibility, and treatment of bacterial contamination, are important issues in prevention. Treatment of the ulcers includes cutting away necrosis, wound care, and treating bacterial contamination. If arterial blood flow is insufficient, surgical interventions will be necessary.

Diabetic foot and chronic complications are a multidisciplinary issue that is most effectively managed by a team. Early and appropriate treatment of wound and soft tissue complications is essential. Promoting patients' awareness and reducing their ulcer incidence by at least 50%

through the application of best practice evidence in everyday care and preventing or limiting the underlying pathology is possible. Failure to recognize early-stage complicating ulceration may result in significant amputation. Early detection and prompt specialist care will help to reduce this morbidity and subsequent mortality. [31][32]

7.1. Ulcers and Infections

Pathophysiology: The development of a foot ulcer in diabetic patients is multifactorial. Various factors contribute, but mainly it is peripheral neuropathy that leads to increased plantar pressures and the development of skin breakdown. Ischemia may be of lesser importance in sizeable wounds and mostly plays a role in the ultimate healing process. Infection, often a secondary process, not only aggravates the problem but may finally result in an amputation of the affected foot.

Risk factors: Diabetes-related complications like peripheral neuropathy, especially with increasing loss of sensation and motor function, are significant risk factors in ulcers. Impaired glycemic control, male gender, and social restrictions related to occupation, quality of life, and vision play a role as well. Other factors not directly related to the patients' disease that contribute to ulceration and infection are mainly anatomic deformity and previous amputation. Wearing inadequate and ill-fitting footwear is an important behavioral risk factor. Also, an impaired host immune response will increase the chance that bacteria resulting from an infected ulcer will breach the defense mechanism of the body.

Preventing ulcers and managing foot problems: Preventive measures include daily foot care and wearing protective footwear. Many professionals regard comprehensive education as an effective tool in achieving a lower incidence of ulcers. Although most foot problems in diabetes are managed conservatively, options include the removal of callus, debridement of infected and dead tissue, and finally, in some cases, there may be new treatment modalities, such as advanced wound care therapies, skin substitutes, and matrix products to support healing after ulceration. For a minority of patients, revascularization is indicated. It is essential that a multidisciplinary team approach must be adopted. Preferences for one or another of these techniques are not based on randomized trials but on the expertise of the professional, availability, patient characteristics, and economic factors.

Infections: Most often, ulcer infections are polymicrobial, consisting of gram-positive cocci and/or gram-negative rods. An estimated 40–70% of infections are infected with methicillin-resistant Staphylococcus aureus. This pathogen is especially difficult to eradicate, as well as the possibility of an increased rate of amputation in infected patients. Antibiotics are usually prescribed for a shorter or longer period of time to avoid systemic spread or limb-threatening complications. Oral therapy is preferred as soon as it can be established that the antibiotic is effective. The length of therapy is not the same for all patients and depends on various patient characteristics and the response. Unfortunately, several studies have demonstrated that in more than one-third of patients the organism is cultured from the bone, a so-called osteomyelitis, with a reduced chance of a timely eradication of the bacteria and thus also the ulcer. When more devastating infections spread and when the general state worsens, sepsis or other life-threatening issues will need aggressive fluids, oxidative breathing support, and perhaps, in lesion or life-threatening infections, hyperbaric oxygen may help as an add-on to antibiotics.

When to refer to a specialist: It may not always be easy to decide who needs to be seen by a specialist when the problem exacerbates. Points for referral are the possible presence of an infection, the presence of ischemia, the risk of amputation of the limb, or the presence of an ulcer or healed ulcer that is considered to be complicated. In every case, a serious condition like a life-threatening or limb-threatening problem certainly demands an urgent referral. When few or none of these signs are present and depending on the infrastructure and support, a more conservative approach can be advocated. The role of the specialist is to support the treating physician to achieve an optimal closure of the ulcer, preferably by a closed referral system. It must be accepted that in many cases this closure can be achieved short term by solely conservative care. [33][34]

8. Psychosocial Impact of Long-term Diabetes

Diabetes is known to have significant psychosocial implications, with the lifelong commitment to managing the condition affecting an individual both emotionally and psychologically. Living with a chronic condition, such as diabetes, can have psychological effects of stress and isolation, and can be traumatic and frustrating. It is therefore not surprising that many patients living with diabetes may have some level of emotional or psychological distress or morbidity as a result of this ongoing management of their condition. This is amplified further when considering individuals also living with long-term complications. Depression is both related to and predictive of complications development, with some suggesting that major depression could be a risk factor for microvascular complications. Depression, anxiety, and emotional distress all have bidirectional relationships with depression, with each influencing the course and the morbidity of the other.

Feelings of frustration and isolation can also extend to all aspects of life including employment, education, travel, sports, hobbies, and insurance, and are not limited to social occasions. This can significantly impact not just the person living with diabetes, but also their family, and therefore can also impact social interactions and family dynamics as a result. The person living with diabetes may also feel as though they are putting their family under pressure or financial strain as further complications develop, with children of a parent with T1D at higher risk of depression and anxiety. Similarly, caregivers of a person with long-term complications were found to have higher levels of anxiety and depression, and an increased caregiving burden, further highlighting the multifaceted impact that long-term diabetes complications can have. In today's society, the development of diabetes-branded products and language can also increase the stigma associated with diabetes, which an individual may experience, and further compound stress.

In clinical practice, consideration of holistic care of patients with diabetes embraces psychosocial factors, with treatment and management plans acknowledging mental health as much as physical health. Interventional studies have shown that in T1D both depression and distress can be improved with patient-focused education around diabetes, with further improvements noted through cognitive and behavioral therapies. Online support groups can also help individuals feel less socially isolated, as well as reducing feelings of social isolation and improving emotional well-being for both those with diabetes and their caregivers. This highlights the need for health care professionals to be mindful of psychosocial factors for the patient as well as the condition in managing diabetes. Recognizing and addressing these issues is integral to improving an individual's diabetes management. Integrating mental health services into diabetes care can have a large impact on well-being and on reducing the severity of the psychological conditions that many experience. Building good relationships is critical to providing high-quality, overarching care for those living with diabetes, including those living with long-term complications. [35][36]

8.1. Depression and Anxiety

With an estimated prevalence of approximately 20% and 40%, respectively, increased rates of anxiety and depression have been reported in individuals living with diabetes compared to the general population. Untreated depression has been shown to be associated with higher levels of HbA1c. It has also been reported as the leading cause of symptomatic hyperglycemia among those suffering from type 1 diabetes and can be associated with insulin resistance in type 2 diabetes. Additionally, diabetes-related distress is a strongly significant, yet entirely separate, psychological comorbidity in type 2 diabetes and also correlates with higher levels of HbA1c. One can therefore appreciate how profound an impact comorbid mood disorders have on an individual's ability to accept their lifelong condition, managing it each day with recommended lifestyle interventions and treatment regimens, particularly regarding the more effective use of insulin.

Methods have been developed to screen and diagnose mood disorders in this cohort; the PHQ-2 or HADS, or the PHQ-4 or GAD-2, are easy to use and were developed for people with diabetes. In addition, cognitive behavioral therapy has also been adapted specifically to improve glycemic outcomes in people with type 1 diabetes. These are time-consuming and, for individuals that may

have fluctuating diabetic clinic attendance, may become obsolete in the interim between attending appointments. It is imperative that treatment involving various pathways, medication, and psychosocial support in people enable the provision of adequate and robust support in addition to improved glycemic management techniques, recommendations, and the tools to sustain these improvements. Healthcare professionals working at such a clinic should be part of multidisciplinary teams and should be well-versed in being supportive rather than dismissive of the fact that these mood disorders exist. In summary, a collaborative approach to managing a lifelong disorder requires the needed synergy and motivation to alter variables such as blood glucose levels. [37][38]

9. Preventive Strategies and Management

Successful management of type 1 diabetes mellitus and type 2 diabetes mellitus is essential to reduce the risk of long-term complications and to increase the expectancy and quality of life. Long-term hyperglycemia is the basic element of the pathogenesis that guides the treatment in diabetes mellitus. At least 40% of patients with diabetes mellitus will not achieve normal values of glycosylated hemoglobin with current personalized management strategies. Behavioral changes can prevent the development of type 2 diabetes mellitus in people with prediabetes and are effective in type 2 diabetes mellitus treatment. If good blood glucose control is not achieved, early introduction of different glucose-lowering drugs according to basal insulin or sulfonylureas leads to better control of blood glucose levels than the introduction of these drugs when the blood glucose is not controlled anymore by the initial treatment from the very beginning. In general, the management of diabetes can account for an approximate 50% reduction of long-term complications for both type 1 diabetes mellitus and type 2 diabetes mellitus.

Recent guidelines suggested individualized targets for suitable glycemic control. These clinical practice guidelines have three main points in common: a) There is no one-size-fits-all approach in setting glycemic targets; b) Routine monitoring of HbA1c is necessary with consideration of individual priorities and comorbidities, as well as evidence-based targets and validated assessment of renal function; c) When medication to control hyperglycemia has to be initiated or progressed, the choice depends on health status, life expectancy, and the degree of glycemic control. In addition to the special situation of recent diagnosis of type 2 diabetes mellitus, influencing factors are age, comorbidities, the patient's understanding, and acceptance of management plans. Since diabetes mellitus management is complex and deeply connected with well-organized educational strategies to be efficient, diabetes centers are generally recommended as providing the multidisciplinary skills necessary to integrate care of diabetic patients. Adherence improvement strategies are becoming more important in the diabetes field, and information and communication technology, including telemedicine, smartphone telemonitoring, desktop computers, and other media, increase adherence and patient satisfaction in general and for self-monitoring of blood glucose and type 2 diabetes treatment specifically in conjunction with individualized feedback, education, and coaching. This is especially relevant as low-income patients have a higher premature mortality from diabetes mellitus and thus are in major need of quality counseling. [39][40]

9.1. Glycemic Control

A focus on glycemic control is critical to the management of diabetes and the prevention of its complications. A study in type 1 diabetes (T1D) showed a reduction in cardiovascular complications of 42% with intensive insulin therapy compared with conventional therapy in patients with T1D. Another trial that included patients with type 2 diabetes (T2D) reported that a 1% reduction in hemoglobin A1c (HbA1c) was accompanied by a 21% reduction in any endpoint related to diabetes and a 37% reduction in microvascular complications. During a follow-up period, a significant risk reduction in myocardial infarction, sudden death, stroke, peripheral amputation, and microvascular complications was observed among patients with T2D who received an intensive glucose-lowering intervention that aimed to achieve an HbA1c level below

7%. An HbA1c target below 7% has now been established in patients with T2D to reduce the development and progression of microvascular complications.

Glycemic treatment targets for major stakeholders in diabetes typically involve lower HbA1c levels for more time, ranging from less than 6% to less than 8% across organizations and independent of the estimated life expectancy and concurrent diseases. HbA1c targets of less than 6.5%, less than 7%, and less than 7.5% are most common for younger patients without complications, for older patients with multiple comorbidities including vascular disease, and for other populations, respectively. However, within the same guideline, it is noted that the decision should be individualized, taking into account both patient characteristics and age and potential comorbidities. Overall, the most effective HbA1c target for each individual patient is determined by integrating the absolute reduction in HbA1c at a given treatment with the certainty of the benefit, the risk and magnitude of hypoglycemia and other adverse effects, the impact on quality of life, the burden of treatment, and cost. [41][42]

10. Conclusion and Future Directions

Diabetes is an extremely heterogeneous disease that presents with many complexities and interrelated issues, especially regarding the risk screening and management of long-term complications. Similarly, while glycemic control is important, preventing and managing complications or co-occurring conditions also directly impacts outcomes. A multitude of scanning exams and screening practices have not been found to be cost-effective and may do more harm than good. One strong recommendation brought to the fore by our experienced panel was the importance of early detection and prevention: if diabetes, its associated vascular complications, and associated manifestations are discovered early, treatment is far more likely to be successful.

For the future, new approaches to prediction, prevention, and management are needed. This will involve lifestyle and behavioral factors as well as a more personalized assessment of genetics, biochemistry, and physiology. The targeting of these underlying processes requires a system change in practice to develop team-based approaches. For example, podiatrists focus on foot care, ophthalmologists on eye care, and other specialists on specific issues such as hearing with audiologists and cardiologists. New approaches for prevention and care delivery at the primary care level, which is where the majority of patients receive care, should also be a research focus. New strategies should expand from our current model of multi-factorial treatment in a clinical trials setting to how complications are prevented, screened, and treated in the real world. The hope is that newer tools, including sophisticated biomarkers, genomic, and accurate non-invasive measures of mechanics throughout the body, will be of more utility in future research than is currently available. At the same time, these technologies are likely to change our management strategies.

In terms of overall adoption into clinical care, it is clear that diabetes specialists must dramatically increase their commitment in time, skills, and resources to train health professionals in diabetes and its vascular complications, instead of only focusing on the use of glucose-lowering agents. This gap in training of the primary care and other health teams needs to be addressed because of the rapidly increasing prevalence and incidence of these complications that is occurring as the burden of diabetes increases worldwide. It should be noted that this may need to be a multi-disciplinary focus to be more effective in training health team members.

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