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Mitigating the Impact of Diabetes Mellitus: Highlighting Treatments and Trials for Customary Complications

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ABSTRACT

The prevalence of Diabetes Mellitus (DM), more commonly referred to as diabetes, has surged exponentially over the last decades [1]. The rise of the disease further denotes the rise of its complications. The condition is associated with several complications ranging from various levels of severity, and understanding these complications is critical for diabetes management. In this research paper, I discuss the short- and long-term complications of diabetes, focusing particularly on Type 1 and Type 2 Diabetes. Each complication is introduced and thoroughly examined, with emphasis on the methods used for its detection and the functioning of various treatments. Given that many DM complications lack distinct treatments, I also specify relevant clinical trials for potential treatments, highlighting the trial's statistics, results, and limitations, if any. I conclude by highlighting the personal experience of Mohammad Osama Minhas, a diabetic patient of 16 years, providing a valuable perspective to the daily challenges in managing the disease.

Introduction: Overview/Historical Background of Diabetes Mellitus

Diabetes Mellitus is a chronic health condition in which, from a medical perspective, the body is unable to produce sufficient insulin or is unable to effectively use any insulin it produces as a result of its delivery to the body being partially or totally blocked, resulting in an imbalance of blood sugar called hyperglycemia [1,2]. From an individual perspective, Diabetes is the regulation and management of the blood glucose levels in the body through controlling diet and pursuing a healthy lifestyle. The name for the condition is split into two words - diabetes and mellitus. Diabetes was first used to describe the disease by Araetus of Cappodocia (81-138 AD), who labeled diabetes as a polyuric condition. Araetus described the condition as follows, "Diabetes is a wonderful affection…being a melting down of the flesh and limbs into urine. The patient never stops drinking water but the flow is incessant as if from the opening of aqueducts. The patient is short lived" [3]. This led to the adoption of the Greek work diabetes, meaning to siphon or to run through, as a descriptor for the disease. Thomas Willis, a British physician, later rediscovered the remarkable sweetness of urine excreted by diabetic patients in 1675 by taking the daring step of tasting his patient's urine, stating that the diabetic urine is "wonderfully sweet as if it was imbued with honey or sugar." To capture this characteristic, Willis appended the Latin word mellitus, meaning honey sweet, to the term 'diabetes' [4].

Diabetes is split into two primary types: Type 1 and Type 2. Type 1 diabetes, also known as juvenile diabetes, is caused by an autoimmune response which leads to the immune system's T-cells attacking the insulin producing β (beta) cells in the pancreas. β cells sense glucose levels and release insulin according to the body's needs. Without β cells, glucose control is lost, causing hyperglycemia - or worse - if untreated [5]. Type 1 diabetes has no known risk factors apart from family history and a few unknown environmental factors [6]. Type 1 is one of the most common chronic diseases during childhood, with nearly all patients diagnosed being between ages 5-12 [7]. The correlation between the condition and its prevalence in younger age groups is why type 1 diabetes is referred to as juvenile diabetes [8]. Type 2 diabetes, on the other hand, makes up for 90-95% of diabetes mellitus diagnoses [9], and it is caused mainly by visceral fat buildup preventing insulin from entering certain parts of the body, causing insulin

resistance [10]. Insulin resistance occurs when the body's cells do not react well to insulin, and don't store enough glucose from the blood stream, thus raising blood sugar levels and causing hyperglycemia, and the only way for the body to combat this is for the pancreas to excrete more insulin [11]. Unlike type 1, type 2 diabetes is most likely to be diagnosed in patients over the age of 45 [9]. Although neither type 1 nor type 2 diabetes has a cure, they can be managed through modern insulin pumps and other diabetic supplies. Diabetes Miletus is an important and widespread disease that constitutes a major health problem today, but this was not always so. According to the World Health Organization, diabetes incidence rates quadrupled in only 34 years, going from 108 million in 1980 to 422 million in 2014. This increase is due in great part to the increase of obesity and physical inactivity [12]. Elliot Joslin, the first medical doctor in the United States specializing in diabetes, first hypothesized a relationship between high glucose levels and diabetic complications. By meticulously observing and recording the wellbeing of his patients over several years, Joslin noticed patterns of complications such as retinopathy, nephropathy, and neuropathy in those with poorly controlled glycemic levels [13]. As stated before, the rise of incidence rates for diabetes mellitus also means the rise of its complications. Type 1 and Type 2 have many complications that must be addressed, as some are as severe of health problems as diabetes itself. This paper dives into the short- and long-term complications of diabetes mellitus with intricate detail and compiles methods of detection and treatment for such complications.

Complications of Diabetes Mellitus

Diabetes is a condition in which patients are unable to control blood sugar levels, which constitutes a major problem because excessive high blood sugar levels (hyperglycemia) along with excessive low blood sugar levels (hypoglycemia) affects every organ in the body, as they contain passages for blood vessels. This is the main factor contributing to the vast number of diabetic complications [14], such as cardiovascular disease, kidney disease/failure, diabetic retinopathy, diabetic neuropathy [15], all of which will be discussed in this section of the research paper.

Cardiovascular Disease

Cardiovascular disease is the most common cause of mortality among patients with Type 1 and Type 2 diabetes [16,17]. Adults with diabetes are 2 to 4 times more likely to die due to heart disease [18], and this comes down to the damaging effect of hyperglycemia on the blood vessels and nerves found inside the heart [19].

While the risk of cardiac issues is heightened with poor glycemic control, studies show that ~50% of patients with a regulated A1c and no history of hypertension evince some form of cardiac issues [20]. Patients with earlier stages of cardiovascular disease are typically asymptomatic, making it exceptionally difficult to detect until the latter stages, where it becomes more malignant [21]. It is well established that the left ventricular dysfunction is a common indicator of a disease in the diabetic heart, and can be spotted using a cardiac magnetic resonance imaging (CMRI) [22]. CMRI evaluates cardiac function and can detect any signs of infarction in the right and left ventricles caused by the buildup of excess blood sugar in the blood vessels. The accuracy of CMRI, coupled with its avoidance of ionizing radiation and nephrotoxic contrast agents makes it the safest and best methods for diagnosing cardiovascular disease [23]. However, CMRI and other similar instruments are not always available. Echocardiography through ultrasound has made several advancements in recent years, and can produce somewhat high-resolution scans of the heart without the availability restraints posed by CMRI, making it the favorite for the majority of clinical assessments for cardiovascular disease [24].

Several clinical trials have examined the impacts of intensive treatment of hyperglycemia on reducing the risk of cardiovascular disease, with the trials having an emphasis on both Type 1 and Type 2 diabetes, but the trials produced conflicting results. The Diabetes Control and Complications Trial (DCCT) study demonstrated enduring improvements in cardiovascular health for Type 1 patients as a consequence of intensive glycemic control spanning 6.5 years, followed by a comprehensive 10-year observational period. The culmination of the 17-year trial revealed a

remarkable 42% reduction of the risk of any cardiovascular event, accompanied by a maintenance of glycemic hemoglobin levels below 7% (~154 mg/dL) [25]. The United Kingdom Prospective Diabetes Study (UKPDS) examined the impact of intensive treatment of hyperglycemia in newly diagnosed Type 2 patients (patients with 5 years or less with the disease), presenting long-term cardiovascular benefits beyond the five-year trial period [26]. Conversely, other large clinical trials focused on T2D patients produced different results. The Veterans Affairs Diabetes Trial (VADT), also implemented intensive glycemic control, but specifically targeted older patients (those with a minimum of 10 years of T2D) and included 40% of patients with a cardiovascular disease history. However, the results of the VADT trial did not yield any cardiovascular benefits [27]. These results were comparable to two other similar trials - Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial [28], and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [29]. In contrast to the UKPDS trial, all three trials encompassed a higher average age and longer diabetes duration among the patient population. The key takeaway from these trials is that the implementation of intensive glycemic control with a focus to achieve an HbA1c level below 7% delivers cardiovascular benefits when initiated early in younger patients who have been recently diagnosed with diabetes and have a low risk of cardiovascular disease. Attempting to achieve such glycemic targets in older patients with a lengthier history of hyperglycemia and an increased cardiovascular risk profile does not yield the same advantageous outcomes [30].

Kidney Disease/Failure

According to the Centers for Disease Control and Prevention, 1 in 3 diabetic patients are likely to have chronic kidney disease (CKD), an issue affecting 37 million Americans [31]. Diabetic nephropathy, the term used to describe the effect of kidney failure caused by diabetes, refers to the slow deterioration of the kidney as a consequence of hyperglycemia eventually progressing to its final stage, where it is classified as kidney failure or end-stage renal disease (ESRD) [32].

Hyperglycemia, a prevalent risk factor in various diabetic complications, also plays a significant role in the development of diabetic nephropathy. High blood glycose can damage the kidney's blood vessels and nephrons [33] – hence the name "diabetic nephropathy." Nephrons are the basic structural and functional unit of the kidneys carrying out functions such as blood filtration, pH regulation, and water reabsorption [34]. Another risk factor of diabetic nephropathy include hypertension, which causes the loss of renal autoregulation in diabetes [35]. Blood lipid abnormalities, insulin resistance, and obesity are further contributors to the progression of this condition [36]. While there aren't any early symptoms for diabetic nephropathy, the symptoms of the later stages of include worsening blood pressure control, protein in urine, difficulty breathing, and swelling of eyes, feet, ankles, and other joints [37]. Diabetic nephropathy, like many other diseases, is hard to treat but has a substantially higher likelihood of being treated when diagnosed early [38]. Typical screening for diabetic nephropathy, or chronic kidney disease as a whole, involves a test for albumin excretion in urine or a measurement of overall kidney health through a glomerular filtration rate (GFR), which is a measure of the kidneys' ability to filter blood. Albumin, on the other hand, is a family of proteins found in blood plasma manufactured by the liver. Persistent abnormalities in either the albumin levels in urine or the GFR levels lead to the diagnosis of diabetic nephropathy in patients with diabetes or CDK in patients without diabetes [39].

Avoiding the inception of hyperglycemia is the best method to prevent diabetic nephropathy. However, prospective treatments for CKD have emerged: In a study published in the American Diabetes Association, researchers investigated the potential of high-dose thiamine and benfotiamine in preventing the development of diabetic nephropathy. Using rats induced with experimental diabetes, they found that hyperglycemia triggered biochemical dysfunction in the kidney's characterized by an accumulation of triosephosphates, leading to an activation of pathogenic pathways including protein kinase C, glycation, and oxidative stress. High-dose thiamine and benfotiamine directly opposes the effects of triosephosphate through stimulation of the reductive pentosephosphate pathway, proliferating and converting triosephosphates into ribose-5-phosphate. As a result, the therapy decreased activation protein kinase C, protein glycation, and oxidative stress. Crucially, the treatment inhibited the development of CKD, as evidenced through

decreased levels of albumin. Overall, the study suggests that high doses of thiamine and its derivative benfotiamine could be a novel strategy for preventing the development of kidney disease in diabetic patients [40].

Diabetic Retinopathy

The eye contains several blood vessels that, due to their miniscule size, are easily susceptible to impairment through diseases that impact the flow of blood [41], such as diabetes. Prolonged exposure to high and low blood glucose levels can inflict partially irreversible damage on the delicate ocular blood vessels, giving rise to a condition known as diabetic nephropathy. As a leading cause of blindness among adults, diabetic nephropathy underscores the need for proactive measures in monitoring ocular health in patients with diabetes [42].

Non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) are the two main classifications of DR. The earliest indication of NPDR is the formation of microaneurysms, characterized by small protrusions in the capillary walls typically observed near the temporal fovea. While usually asymptomatic, these microaneurysms may lead to intraretinal hemorrhages upon rupture. Progression of the condition can lead to blot hemorrhages, venous caliber fluctuations, and the presence of intraretinal microvascular anomalies, which serve as indicators for the advancement into PDR. The latter stages of diabetic retinopathy, PDR, involves the formation of new blood vessels in response to tissue ischemia. These abnormal vessels can lead to complications such as vitreous hemorrhages and can precipitate tractional retinal detachment, leading to vision loss if untreated [43]. For both classifications, diabetic retinopathy is diagnosed most commonly through a dilated eye exam. The procedure is painless and simple, consisting of several common eye tests such as visual field tests and acuity tests. Finally, a doctor uses dilation to check for any issues. By using eye drops, the pupil widens, allowing a clear view of the blood vessels and nerves within the eye. It is crucial to diagnose diabetic retinopathy while it is the NPDR stage, as most of its effects can be easily reversed, a trend that doesn't apply to PDR [44].

The common treatment for diabetic retinopathy is laser treatment, in which lasers are used to shrink abnormal blood vessels, which form during the stage of PDR [45]. However, the introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy has revolutionized not only the treatment of diabetic retinopathy but also the treatment of various other cancers and diseases causing the growth of harmful blood vessels in the eye. Several studies analyzed the impact in visual acuity in patients with diabetic retinopathy treated by anti-VEGF agents including bevacizumab, ranibizumab, pegaptanib, all of which yielded promising results. The study by the Diabetic Retinopathy Clinical Research Network (DRCR) have shown notable improvements in visual acuity and reductions in retinal thickening when injected ranibizumab, particularly when used alongside traditional laser therapy. Bevacizumab produced similar results when triamcinolone. Both drugs were especially effective in treating diabetic macular edema (DME), a common subtype of diabetic retinopathy [46]. Life-threatening side effects from anti-VEGF drugs are very rare; in the DRCR study, only 0.08% of all patients given ranibizumab were diagnosed with endophthalmitis, with similar statistics present with retinal detachment. As a result, safety of the drug remains minimal [47]. Overall, anti-VEGF medications represent a significant advancement in diabetic retinopathy treatment, especially for DME, but the number of clinical trials analyzing the drug is still insufficient, and more studies are necessary to refine treatment approaches.

Diabetic Neuropathy

Diabetic neuropathy is classified as the extensive damage of bodily nerves caused by prolonged exposure to hyperglycemia, affecting up to 51% of diabetic patients worldwide [48]. While the condition affects nerves all around the body, its effects are usually concentrated in the hands and feet, where many of the body's nerve endings are located. The most common symptom of the disease is extreme pain and numbness in the specified areas. The outcome of diabetic neuropathy can sometimes be fatal, as it severely damages several key organs in the body such as the heart, urinary tract, and digestive system [49].

Studies have proven that diabetic neuropathy can be present in prediabetes, signifying that an HbA1c test with results ≥6.0%, while not a concrete sign of neuropathy, is received as a major sign pointing in its direction [50]. As such, advanced tests must be taken to further analyze the specific variant of neuropathy that may be present. Diabetic Peripheral Neuropathy (DPN) and other sensorimotor neuropathies primarily affect peripheral nerves, originating in distal extremities of the body before progressing proximally in a "stocking glove" pattern. Small fiber disease affects temperature and pain perception, while large fiber disease affects proprioception and touch, both of which occur in respective order as DPN advances into latter stages. Simply put, DPN is classified by sharp pains, paraesthesia, and dysesthesia; with final stages manifesting complications such as ulcerations and neuroarthropathy [51]. The novel method of diagnosis is in the form of the Clanging Tuning Fork (CTF) test. By using a C-128 Hz tuning fork, physicians can more accurately and consistently detect early signs of DPN and ulcers than the monofilament test[51]. Screening tools and questionnaires may also be useful in detecting DPN, although such methods miss 10-20% of clinician-diagnosed cases, highlighting the need for careful judgement for sensorimotor neuropathy. Autonomic neuropathy, often known for having more severe affects, relies mostly on screening for diagnosis, although questionnaires are also used to relate a patient's disease to neuropathy [52].

Treatment for diabetic neuropathy primarily extends to strict glycemic control to slow disease progression, as there is currently no cure. However, numerous trials are ongoing to change this, each with different approaches to neuropathy. Among these, trials for Nerve Growth Factor (NGF) as a novel treatment for neuropathy have gathered significant interest. NGF is a neurotrophic protein essential for the growth of sensory neurons, making it useful for preventing several different neurodegenerative diseases, including diabetic neuropathy. Preclinical studies with the protein showed promising results, demonstrating the potential to prevent and even reverse the effects of neuropathy in animal models. Furthermore, Phase I and II trials produced similar, desirable outcomes, showing improvements in a variety of sensory tests and questionnaires. Genentech's large-scale phase III trial consisted of 1019 patients, randomized to receive either the NGF protein or a placebo for 48 weeks. Analogous efficacy in this phase weren't present, with nearly identical improvement or deterioration in the disease between the placebo and NGF groups. Moreover, 41% of patients receiving NGF treatment reported injection-site pain. Dose-limiting toxicity due to hyperalgesia proved to be a major and widespread side-effect of the trial. These issues, combined with insufficient improvements to disease outcomes, discouraged Genentech from advancing further trials with NGF [53].

Conclusion

Diabetes Mellitus is far more than an autoimmune disease characterized by high blood sugar; it is a condition that can affect nearly every organ in the body and disrupt key functions, often leading to severe complications if not carefully managed. This paper explored several common complications of the disease, including cardiovascular disease, kidney failure, retinopathy, and neuropathy and highlighted methods of early detection, the functioning of its treatments, and potential management strategies. The impact of DM on cardiovascular health, as demonstrated by various clinical trials, suggests that intensive glycemic control can provide significant benefits, particularly in younger patients with a shorter history of diabetes. However, this improvement is not universally seen in older populations with long-standing disease, emphasizing a need for treatment approaches based on age, diabetes duration, and overall health. Complications such as kidney disease, or diabetic neuropathy, and retinopathy, are especially difficult for detection and sufficient treatment. However, advancements in the CMRI for cardiovascular disease, the Clanging Tuning Fork test for neuropathy, and dilated eye exams have allowed for significant strides in early detection. Still, while early detection is critical, treatment for many complications remain limited. Emerging therapies such as high-dose thiamine and benfotiamine for kidney disease, anti-VEGF treatments for retinopathy, and nerve growth factors for neuropathy, show promising results in clinical trials, with the primary hurdle being the failure to present benefits in large-scale human trials. The account of Mohammad Osama Minhas, a diabetic patient of 16 years, highlights the personal perspective to the disease. His experience illustrates the challenges faced by patients with diabetes with an emphasis on the importance of strict blood glucose management to minimize the risk of complications. Despite the advances in glucose

monitoring, many still struggle with keeping up with the burden of constant monitoring and lifestyle adjustments, including a focus on diet and physical activity. This personal account signifies the need for not only medical advancements but strides in patient and lifestyle education. In conclusion, while significant progress has been made in understanding and effectively treating diabetes, there still remains a lot of work that needs to be done. As the prevalence of the disease continues to rise, effective treatment, patient education, and support for ongoing research is critical to mitigate the impact of diabetes mellitus.

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