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Review Article

The Relationship in Renal disease in individuals with diabetes

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Abstract

The historical era of the past was not favorable, particularly in terms of managing individuals with type 2 diabetes. During the 1960s, the innovation of a radioimmunoassay for insulin enabled the identification of the unique characteristics of type 1 and type 2 diabetes. Type 2 diabetes was initially treated with sulfonylureas and later phenformin, despite the fact that the mechanisms of action were not fully understood at that time. Subsequently, thiazolidinediones were introduced. Although all medications were linked to weight gain and the actual benefits were uncertain, advancements in basic science elucidated the mechanisms by which glucose is detected and even identified a subset of patients who benefitted from sulfonylureas. The subsequent focus on renin-angiotensin-aldosterone system blockade was considered a significant advancement by many, although the benefits were not as remarkable as anticipated. Various other promising medications emerged and faded over time. Progress was made over the years in understanding the pathology of diabetic kidney disease, which is crucial given that it has become a leading cause of end-stage renal failure. Nevertheless, recent breakthroughs have transformed a bleak scenario and offer hope for the future. Presently, there are medications available that have the potential to significantly benefit individuals with type 2 diabetes. A century after the introduction of insulin, it is indeed a pivotal moment.

Keywords: diabetes; renin-angiotensin; kidney desease; sulfonylureas; thiazolidine

1.Introduction

In his work "The Canon of Medicine," Avicenna, a Persian physician from the 10th to 11th century, not only observed abnormal appetite and diabetic gangrene but also developed a mixture of seeds (lupin, fenugreek, zedoary) as a treatment [1]. The term "mellitus," meaning sweet like honey in Latin, was coined by British Surgeon General John Rollo in 1798 to distinguish this form of diabetes from the tasteless urine associated with diabetes insipidus. A retains the Cappadocian, who introduced the term "diabetes" from the Greek word for siphon, vividly described the excessive urination and loss of flesh in individuals with diabetes [2,3]. Ancient Indian physicians Sushruta and Charaka identified the two types of diabetes, one affecting young individual who died quickly and the other affecting older individuals. In the early 20th century, diabetes was classified as either juvenile or adult-onset, based on age of onset and insulin dependence [3,4]. However, these terms were replaced by type 1 and type 2 diabetes in the 1970s, with the distinction being made possible by the ability to measure insulin levels. It has now been a century since the introduction of insulin, which has greatly improved the survival of patients with type 1 diabetes. However, the benefits of insulin treatment for patients with type 2 diabetes are still not fully understood [5].

Distinguishing between type 1 diabetes and type 2 diabetes in the present day is not a challenging task (Fig. 1). Type 1 diabetes is characterized as an autoimmune disease, where the body fails to produce sufficient insulin. On the other hand, type 2 diabetes is a condition where the body does not effectively utilize insulin due to insulin resistance. It is now understood that type 1 diabetes affects only 5% of individuals with diabetes, while type 2 diabetes encompasses the majority, which is the focus of our current discussion. These individuals are often overweight, exhibit unhealthy dietary habits, and lack physical activity. However, during the 1960s, as junior physicians, we did not have such clear distinctions [6,7].

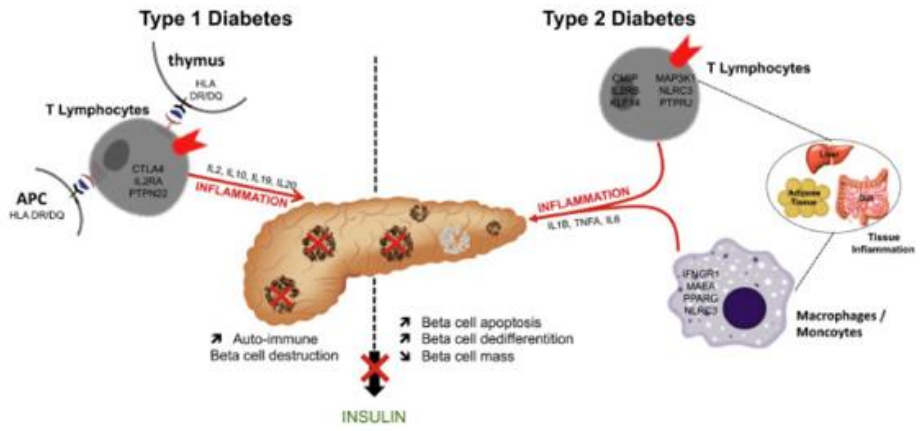

Figure 1. Types of Diabetes.

The 1960s brought about significant political and scientific changes that revolutionized our understanding. Suddenly, we were able to measure and comprehend concepts that were previously only speculated upon, despite being administered as a form of treatment. What exactly was insulin? Its sequence was unknown at the time, but this problem was resolved by Sanger [7]. Yalow and Berson then made it possible to measure hidden molecules and their functions. Insulin was the first molecule to be studied in this manner. As a result, certain significant discrepancies in the progression of diabetes mellitus could finally be addressed. In medical school, we were taught that diabetes had been recognized for centuries, and a treatment had been available since the 1920s [8].

The recognition of the potential benefits of pancreatic extracts was acknowledged. However, the question arises whether a universal approach is suitable for all individuals. Furthermore, the existence of different sizes and variations in treatment options must be considered. The well-known association between long-standing diabetes and kidney disease was not a hidden fact. A seminal study provided a detailed description of the fundamental histopathology [9-11].

2. Methods and materials

The following databases were searched for this review article: To find the most significant comparative research on the relationship between diabetes and kidney disease, its therapeutic options, search engines like Google Scholar, PubMed, and Directory Open Access Journal databases. Keywords like diabetes, hyperglycemia, blood glucose, insulin, pharmacotherapy, sulfonylureas, kidney disease, Thiazolidine, gestational diabetes, insulin resistance metabolic disorders, diabetes management, and drugs are also used. After assessing the quality and strength of the findings, meta-analyses, systematic reviews, large epidemiological studies, and randomized control trials were used as the main sources of information where they were available.

3. Results

3.1Sulfonylureas

The introduction of sulfonylureas and the initiation of the first clinical trials marked a significant milestone in the understanding of type 1 and type 2 diabetes mellitus as distinct conditions. The University Group Diabetes Program (UGDP), a groundbreaking research endeavor supported by the National Institutes of Health, shed light on the efficacy of treatments for type 2 diabetes over a two-decade period. This study served as an educational platform for medical students, introducing them to the concept of prospective, randomized, placebo-controlled clinical trials. The historical significance and complexity of the UGDP trial warrant further examination beyond the scope of this discussion. The aftermath of the trial included congressional inquiries, audits, legal proceedings, and a request for data under the Freedom of Information Act that reached the US Supreme Court [12]. The initial findings in 1970 revealed that the combination of diet and tolbutamide therapy with sulfonylureas did not significantly improve life expectancy compared to diet alone. Additionally, the results suggested that tolbutamide and diet were potentially less effective than diet alone or diet combined with insulin in reducing cardiovascular mortality. These revelations had a profound impact on junior house-staff physicians, who were also introduced to the concept of surrogate endpoints. A delayed arm of the UGDP study further explored the effects of the newly introduced drug, phenformin, with findings reported a year later.

The researchers did not find any evidence to suggest that phenformin was more effective than diet alone or diet combined with insulin in prolonging life. In fact, the mortality rates for patients in the phenformin treatment group were higher for all causes of death and specifically for cardiovascular causes compared to the other treatment groups. As a result, the UGDP investigators recommended against the use of tolbutamide and phenformin, and these drugs were discontinued from the trial. This decision caused significant distress among industry professionals. Consequently, those of us working in healthcare were left with the belief that diet alone was the only viable treatment option for patients with type 2 diabetes.

The UGDP barely addressed the issue of chronic kidney disease (CKD). However, the group receiving insulin, when compared to the placebo group, only showed an 8.3% increase in creatinine concentration, while the placebo group showed an 18.5% increase (P = .005), as reported in 1981. The Food and Drug Administration's audit of the UGDP concluded that there were no major discrepancies between the information available on deaths and the causes of death as determined by the UGDP investigators.

The Diabetes Control and Complications Trial, published in 1993, significantly advanced the treatment of type 1 diabetes [13]. This randomized controlled trial demonstrated that intensive glycemic control, which aims to maintain blood glucose levels as close to normal as possible, reduces the incidence and progression of microvascular complications such as retinopathy, nephropathy, and neuropathy in type 1 diabetes. However, since most healthcare professionals primarily dealt with type 2 diabetes, they felt neglected. The UK Prospective Diabetes Study aimed to address these gaps [14]. The study included interventions such as diet only, sulfonylurea, insulin, and metformin (for obese patients). Notably, this study was five times larger than the UGDP.

The predominant effect of tighter control was a reduction of microvascular disease by a quarter, largely owing to a reduction in laser photocoagulation. There also was a trend toward a reduction in macrovascular disease. No

threshold was seen, namely, any improvement in blood sugar control was beneficial. Metformin use was associated with fewer aggregate end points (including overall mortality) in obese patients. However, the number of patients allocated to metformin was less than 10% of all patients randomized. Therefore, we still were left with the questions, "What are we to do? And what about CKD resulting from diabetes?" Next-generation sulfonylureas came about, and enthusiasm for the clinical application of these drugs continued largely unabated. The development of patch-clamp technology, identification of ion channels—specifically adenosine triphosphate potassium channels, their cloning, and the discovery of how sulfonylurea drugs actually work not only elucidated glucose sensing, but also provided a defined structure on how these drugs (and in whom they) should be used.[15] Ashcroft and Rorsman,[16] major contributors in this area, have reviewed more recent progress (Figure. 2).

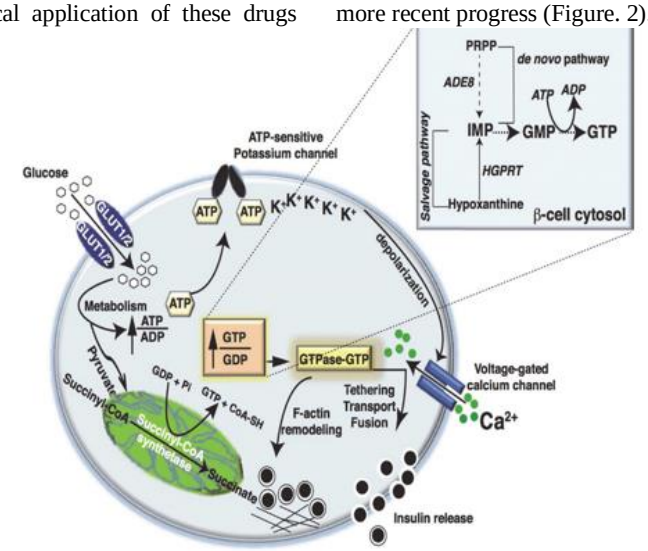

Figure 2. Glucose-stimulated insulin secretion

3.2 Thiazolidine

The controversy surrounding thiazolidinediones, commonly known as TZDs, was a significant issue in the early 2000s. These drugs were designed to target insulin resistance in individuals with type 2 diabetes by activating peroxisome proliferator-activated receptors (PPARs), specifically PPARg. The natural ligands for these receptors are free fatty acids and eicosanoids. When activated, PPAR binds to DNA alongside the retinoid X receptor, leading to the upregulation of certain genes and the downregulation of others. The potential of these drugs seemed promising, both from a molecular standpoint and in terms of clinical outcomes [17].

One prominent member of this drug class was rosiglitazone, which gained popularity. However, a meta-analysis conducted by Nissen and Wolski raised concerns about its safety [18]. They found that rosiglitazone was associated with a significant increase in the risk of heart attacks and a potential increase in cardiovascular-related deaths. It is unclear whether the manufacturer was aware of these risks before the meta-analysis was published.

Another member of the TZD class is pioglitazone. While it remains uncertain why other drugs in this class may have different effects, some claims suggest that pioglitazone may reduce the risk of stroke in individuals with type 2 diabetes. However, the mechanism behind this potential benefit is not yet fully understood. Despite these claims, the overall effectiveness of TZDs in improving outcomes for patients with type 2 diabetes is questionable, and their future remains uncertain.

Furthermore, aleglitazar, a dual PPARa and g agonist, did not provide any significant improvements in the outlook for these compounds. In fact, patients treated with aleglitazar experienced higher incidences of hypoglycemia, gastrointestinal hemorrhage, bone fractures, heart failure, cardiovascular death, and malignancy compared to those who did not receive this drug. Despite its efficacy in glycemic and lipid control, aleglitazar's poor safety profile raises concerns about its use [19].

In conclusion, the thiazolidinedione debacle highlights the challenges faced in developing effective treatments for insulin resistance in type 2 diabetes. While these drugs initially showed promise, their safety and overall effectiveness have come into question. Further research and development are needed to find safer and more efficacious alternatives for managing this complex condition [20]

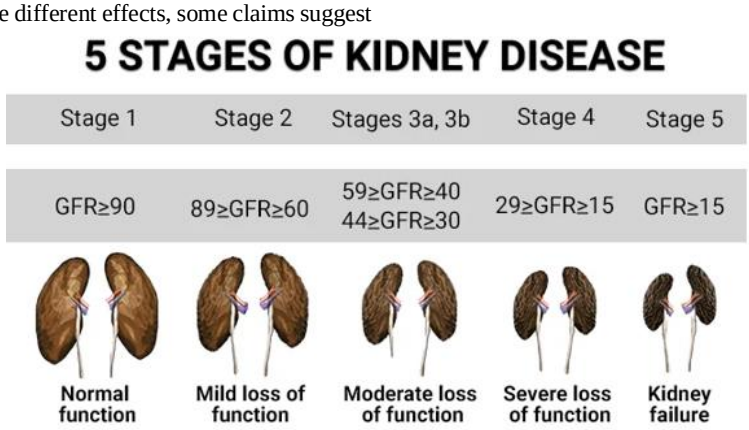

Figure 3. kidney desease

3.3 have a diet.

Encouraging individuals to consume only half of their usual caloric intake is a challenging endeavor. It is widely known that a significant number of type 2 diabetes patients are overweight. The concept of reducing caloric intake to improve this condition was first proposed by Kempner et al. However, Kempner et al. also acknowledged that people are generally reluctant to decrease their food consumption. As a result, surgical procedures have been developed to address this issue. Recent reviews have evaluated the outcomes of these surgical interventions. In the United States, around 252,000 bariatric procedures are performed annually, with approximately 15% of them being revisions. Despite this statistic being somewhat concerning, modern bariatric procedures have been shown to be effective and safe. The authors of the review recommended that all severely obese patients, particularly those with type 2 diabetes, should engage in discussions about the risks and benefits of surgery versus traditional medical and lifestyle treatments. The decision to undergo surgery should primarily be based on the informed preferences of the patient. The future outlook for marketing these procedures appear promising [21,22].

3.4 The Renin-Angiotensin-Aldosterone System

The Renin-Angiotensin-Aldosterone System plays a crucial role in the treatment of diabetic kidney disease, with Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin-Receptor Blockers (ARBs) being highly regarded in this regard. A significant study was published in 1993 by Lewis et al., who conducted a randomized controlled trial comparing captopril with a placebo in patients with type 1 diabetes mellitus and high levels of urinary protein excretion and low serum creatinine concentration [23].

The main objective was to observe a twofold increase in the initial serum creatinine levels. In the captopril group, 25 patients experienced a doubling of serum creatinine concentrations, while in the placebo group, this occurred in 43 patients (P = .007). The key issue, in my opinion, revolves around blood pressure. The reduction in average baseline mean arterial pressure among the 155 captopril group patients with preexisting hypertension was 7 ± 11 mm Hg, compared to 5 ± 11 mm Hg in the 153 placebo group patients with preexisting hypertension. The difference in blood pressure management was not statistically significant (P = .16). Some patients in both groups did not have hypertension. Therefore, did captopril fail to lower blood pressure (75 mg in some) in these patients? There is no need to delve further into this matter [24].

Aliskiren, a direct renin inhibitor, could potentially be the most innovative RAAS inhibitor ever developed. However, a delayed introduction ultimately determined the fate of this groundbreaking compound. Could aliskiren reduce cardiovascular and renal events in patients with type 2 diabetes and chronic kidney disease, cardiovascular disease, or both? Theoretically, dual RAAS blockade should be more effective than a single agent, yet the outcomes of both the Valsartan in Acute Myocardial Infarction Trial and the Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial did not support combined therapy with an ACE inhibitor and an ARB. In the Aliskiren type 2 diabetes trial, half of the patients in each group were already receiving an ACE inhibitor [25]. Half were receiving an ARB. Half were receiving β2-receptor blockade. How could aliskiren ever stand a chance? It did not. However, a recent randomized controlled trial utilizing chlorthalidone to lower blood pressure in patients with advanced nephropathy highlighted the significance of blood pressure reduction [26].

The ongoing debates are focused on the mineralocorticoid receptor. Our initial diuretic, spironolactone, targeted this receptor. Nevertheless, finerenone is currently being promoted as a replacement for this reliable old medication [27].

3.5 Sulodexide

Sulodexide is a purified mixture of glycosaminoglycans consisting of low-molecular-weight heparin (80%) and dermatan sulfate (20%). It is commonly used in clinical practice for the prevention and treatment of thromboembolic diseases. Recent studies have also demonstrated the positive effects of sulodexide in animal models of reperfusion injury and in the management of diabetic nephropathy. Experimental evidence suggests that the administration of heparin and other anionic glycoproteins can prevent biochemical alterations associated with albuminuria in diabetic nephropathy. However, the efficacy of sulodexide in human trials remains uncertain [28].

Bardoxolone methyl, on the other hand, is an experimental semisynthetic triterpenoid that activates the Kelch-like ECH-associated protein 1-Nuclear factor erythroid 2-related factor 2 pathway in mice. It also inhibits the proinflammatory transcription factor nuclear factor-kB in human cell cultures. Short-term studies have shown promising results of bardoxolone methyl in patients with type 2 diabetes, but its long-term effects and optimal dosage have not been established. In patients with advanced chronic kidney disease and type 2 diabetes, bardoxolone methyl has been associated with an improvement in the estimated glomerular filtration rate at 24 weeks. However, a clinical trial involving patients with type 2 diabetes and stage 4 chronic kidney disease did not demonstrate a reduction in the risk of end-stage renal disease or cardiovascular-related deaths with bardoxolone methyl, leading to the premature termination of the trial due to a higher rate of cardiovascular events compared to the placebo group [29,30].

3.6 Renal disease in individuals with diabetes.

Eptstein highlighted that individuals with diabetes mellitus may develop nephrotic-range proteinuria. Kimmelstein and Wilson brought attention to diabetic renal disease. It was not widely known that nephrotic-range proteinuria could occur in individuals with diabetes mellitus. Nevertheless, Kimmelstiel and Wilson emphasized diabetic renal disease [31]. The Renal Pathological Society membership has given us a contemporary pathological classification of diabetic nephropathy. The disease typically takes around 15 years to progress, starting with thickening of the glomerular basement membrane, expansion of mesangial cells, and accumulation of hyaline in arterioles [32]. The mesangial lesions may evolve into nodules, as observed by Kimmelstiel and Wilson [11]. Both afferent and efferent arterioles are affected, as clearly seen through electron microscopy. Podocyte loss and disrupted glomerular outflow may occur. Murine models, especially with modern techniques, offer promising insights into the mechanisms involved [33].

3.7 Ample space for optimism

Advancements in recent years have significantly enhanced the prognosis for type 2 diabetic patients and have impacted cardiovascular and renal diseases, even in non-diabetic patients [34]. Various glucagon-like peptide-1 receptor agonists with different structures and durations of action have been introduced, reducing cardiovascular mortality and kidney outcomes [35]. The effects of sodium-glucose cotransporter-2 inhibitors on specific cardiovascular and renal outcomes are equally remarkable. Consequently, we now have treatments to offer these patients. This progress represents a significant improvement compared to the early days in the 1960s!

The recent advancements have resulted in updated recommendations for managing diabetes in individuals with kidney disease [36]. These guidelines suggest the use of seven medications (metformin, sodium-glucose cotransporter-2 inhibitor, RAAS blockade, statins, glucagon-like peptide-1−receptor agonist, antiplatelet drugs, and a nonsteroidal mineralocorticoid receptor antagonist) to achieve glycemic control, lower blood pressure, and modify risk factors. Regular reassessment every 3 to 6 months is also advised. This approach may seem tailored for those with financial means [37]. The treatment strategy is depicted as a pyramid, but perhaps a preventive pyramid is what is truly needed. Obesity is identified as the primary driver of type 2 diabetes. Evidence indicates that children who are

obese at a young age are likely to remain obese into adulthood. Therefore, addressing childhood obesity should be a key objective [40-44]. Apart from regulating the food industry, limited strategies come to mind. A good starting point could be removing junk food vending machines from schools and campuses. While exercise may not be the most effective method for weight loss, it offers various other health benefits. In today's sedentary society, there is a widespread lack of physical activity. A recent study involving 30 million individuals demonstrated a significant reduction in cardiovascular and cancer-related deaths with just 11 minutes of daily exercise. Surprisingly, the majority of these individuals engaged in less than 2.4 hours of moderate physical activity per week, which is equivalent to short trips to the refrigerator. While new medications and bariatric surgery can be beneficial, a fundamental shift in human nutrition is essential if we are to sustain a global population of 8 billion people [38,39].

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