Clinical Journal of Diabetes Care and Control

Chembio Publishers
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Research Article *Volume 1; Issue 3*

A Primary Goal of Diabetic Management--- (The Sugar Disease)

Raghavendra Rao MV[1]*, Ponnusamy K[1], Sateesh Babu A[1], Sripada Pallavi T[2], Krishna Sowmya M[3], Ramanaiah CJ[4], Fatteh S[1], Fateh A[1], Verma MK[5], Gokul Kumar SS[6], Fateh R[1], Sireesha Bala A[1] and Vijay Raj B[7]

[1]Avalon University School of Medicine, Central America

[2]Apollo Institute of Medical Science and Research Institute, India

[3]Burjeel Hospital, United Arab Emirates

[4]Amina Hospital Sharjah, United Arab Emirates

[5]Acharya Nagarjuna University, India

[6]Pondicherry Institute of Medical Sciences, India

[7]Loyola College, India

***Corresponding author:** Dr. M.V Raghavendra Rao, MD (US), M.Sc., Ph. D., FIBMS, FIMSA, FABAP, Professor and Head of the Department of Diseases, Immunity and Therapeutics (DIT)Dean (Student affairs) and Research Director, Avalon University School of Medicine, Sta. Rosaweg 122-124, Willemstad, Curacao, Central America, Tel: +5999 788-8008, Fax: +5999 788-8102; Email: reachdrmvrrao@gmail.com

Received Date: November 17, 2018; **Published Date:** November 23, 2018

Abstract

We can do better when patients get recommended preventive care and treatment, complications such as heart disease, kidney failure and amputations can be prevented. Children who drink one or more cups of coffee or tea each day greatly increased their risk of developing Type-1 diabetes. So keep that coffee break for the adult Children have enough energy their own. Daily magnesium supplements may help people with diabetes handle their extra blood sugar better. Magnesium helps insulin work well, which can lower the amount of sugar in the blood and raise the amount of sugar inside the cells. Many people with diabetes have mild magnesium deficiency. Cow's milk for babies can cause diabetes. Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct Types of DM are caused by the complex interaction of genetics and environmental factors.

In the United States, DM is the leading cause of end-stage renal disease (ESRD), non-traumatic lower extremity amputations, and adult blindness. It also predisposes to cardiovascular diseases. With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future. Diabetes mellitus is a heterogenous group of syndromes characterized by an elevation of fasting blood glucose that is caused by a relative or absolute deficiency of insulin. Diabetes is the leading cause of adult blindness and amputation and a major cause of renal failure, nerve damage, heart attacks, and stroke. Diabetes can be classified into two groups, type 1 (T1D) and type 2 (T2D). Type 1 diabetics constitute approximately 10% of the nearly 28 million diabetics in the United Status. The disease is characterized by an absolute deficiency of insulin caused by an autoimmune attack on the β-cells of the pancreas. This destruction requires a stimulus from the environment (such as a viral infection) and a genetic determinant that allows

Citation: Raghavendra Rao MV. A Primary Goal of Diabetic Management--- (The Sugar Disease). Clin J Dia Care Control 2018, 1(3): 180012.

the β-cells to be recognized as "non-self". The metabolic abnormalities of T1D mellitus include hyperglycemia, ketoacidosis, and hypertriglyceridemia that result from a deficiency of insulin. Type 1 diabetics must rely on exogenous insulin delivered subcutaneously to control hyperglycemia and ketoacidosis. T2D has a strong genetic component.

Keywords: End-stage renal disease; Diabetic kidney disease; Type 2 diabetes mellitus; Gestational diabetes; Glycolysis; Gluconeogenesis; Insulin pump; Glucose transporter

Abbreviations: ESRD: End-Stage Renal Disease; DKD: Diabetic Kidney Disease; T2D: Type 2 Diabetes Mellitus; GD: Gestational Diabetes; T1D: Type 1 Diabetes Mellitus; DNs: Diabetic Neuropathies; DSP: Distal Symmetric Polyneuropathy; DPN: Diabetic Peripheral Neuropathy; IDDM: Insulin-Dependent Diabetes Mellitus; VNTRs: Variable Number of Tandem Repeats; APS: Autoimmune Polyendocrinopathy Syndrome; ICU: Intensive Care Unit; IRS: Insulin Receptor Substrates

Introduction

Diabetic kidney disease is a major cause of morbidity and mortality in diabetes. Indeed, the excess mortality of diabetes occurs mainly in individuals with diabetes and proteinuria, and results not only from end-stage renal disease (ESRD) but also from cardiovascular disease, with the latter being particularly common in patients with type 2 diabetes [1,2]. Type 2 diabetes is the most common cause of CKD and ESRD worldwide. In the United States, .40% of the .29 million individuals with type 2 diabetes have diabetic kidney disease (DKD) [3]. Phytotherapy has long been a source of medicinal products and over the years there have been many attempts to use herbal medicines for the treatment of diabetes. Several medicinal plants and their preparations have been demonstrated to act at key points of glucidic metabolism. The most common mechanisms of action found include the inhibition of α-glucosidase and of AGE formation, the increase of GLUT-4 and PPARs expression and antioxidant activity [4]. Skeletal fractures can result when there are co-morbid conditions that negatively impact bone strength. Fractures represent an important source of morbidity and mortality, especially in older populations.

Diabetes mellitus is a metabolic disorder that has reached worldwide epidemic proportions and is increasingly being recognized as a risk factor for fracture [4]. As a result of this trend, it is fast becoming an epidemic in some countries of the world with the number of people affected expected to double in the next decade due to increase in ageing population, thereby adding to the already existing burden for healthcare providers, especially in poorly developed countries [6]. It is well-established that pre-diabetes is reversible but it is unclear whether diabetes is reversible once it has been diagnosed [7]. Diabetes mellitus elicits cellular, epigenetic, and post-translational changes that directly or indirectly affect the biology of the vasculature and other metabolic systems resulting in the apparition of cardiovascular disease [8]. Diabetic neuropathies (DNs) differ in clinical course, distribution, fiber involvement (type and size), and pathophysiology, the most typical type being a lengthdependent distal symmetric polyneuropathy (DSP) with differing degrees of autonomic involvement [9]. Diabetic foot ulcers remain a major health care problem. They are common, result in considerable suffering, frequently recur, and are associated with high mortality, as well as considerable health care costs. While national and international guidance exists, the evidence base for much of routine clinical care is thin [10].

Diabetic retinopathy is clinically defined, diagnosed and treated based on the extent of retinal vascular disease detected by ophthalmoscopy. Three distinct forms of diabetic retinopathy are described [11] macular edema, which includes diffuse or focal vascular leakage at the macula [12] progressive accumulation of microvascular change that includes microaneurysms. Diabetes mellitus is nowadays one of the foremost non-communicable diseases affecting more than 387 million people worldwide [13] Type 2 diabetes mellitus (T2D) is a disorder of glucose metabolism. It is a complex process involving the regulation of insulin secretion, insulin sensitivity, gluconeogenesis, and glucose uptake at the cellular level. Deregulations of one or more of these processes due to environmental or genetic factors can lead to altered glucose metabolism causing diabetes mellitus [14,15]. Type 2 diabetes mellitus (T2D) is a disorder of glucose metabolism. It is a complex process involving the regulation of insulin secretion, insulin sensitivity, gluconeogenesis, and glucose uptake at the cellular level. Diabetic peripheral neuropathy (DPN) is one of the debilitating complications that are present in approximately 50% of diabetic patients. It is the primary cause of diabetes-related hospital admissions and non-traumatic foot amputation [16]. Uncontrolled T2D can complicate pregnancy outcomes. Different kinds of birth defects are more commonly seen in babies born to women with diabetes [17]. Twin studies can estimate the multifactorial genetic involvement in T2D more precisely [18] cardiovascular disease remains the principal cause of death and disability among patients with diabetes

mellitus. Diabetes mellitus exacerbates mechanisms underlying atherosclerosis and heart failure. Unfortunately, these mechanisms are not adequately modulated by therapeutic strategies focusing solely on optimal glycemic control with currently available drugs or approaches [19]. Atherosclerotic cardiovascular disease remains the principal cause of death and disability among patients with diabetes mellitus, especially in those with type 2 diabetes mellitus in whom it typically occurs 14.6 years earlier, 1 with greater severity, and with more diffuse distribution than in individuals without diabetes mellitus [20,21].

History

Diabetes was one of the first diseases described [22], with an Egyptian manuscript from c. 1500 BCE mentioning "too great emptying of the urine" [23]. The Ebers papyrus includes a recommendation for a drink to be taken in such cases [24]. The first described cases are believed to be of type 1 diabetes. . He described the symptoms and the course of the disease, which he attributed to the moisture and coldness, reflecting the beliefs of the "Pneumatic School". He hypothesized a correlation of diabetes with other diseases, and he discussed differential diagnosis from the snakebite which also provokes excessive thirst. His work remained unknown in the West until 1552, when the first Latin edition was published in Venice [25].

Type 1 and type 2 diabetes were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400–500 CE with type 1 associated with youth and type 2 with being overweight. The term "mellitus" or "from honey" was added by the Briton John Rolle in the late 1700s to separate the condition from diabetes inspidus, which is also associated with frequent urination. Babies born to mothers with poorly treated gestational diabetes are at increased risk of being too large, having low blood sugar after birth, and jaundice. If untreated, it can also result in a stillbirth. Long term, children are at higher risk of being overweight and developing type 2 diabetes [26].

Significant Gap in Research

There are several kinds of diabetes. All of them have one thing in common; higher than normal levels of blood glucose. Glucose is a sugar that your body produces from digested food. In order for your body to use glucose properly, a hormone called insulin, which is produced by the pancreas, is necessary. Insulin helps to transport glucose from your blood stream into your body's cells where it can be burned for fuel or stored for future energy use. If you have diabetes, your pancreas either does not produce insulin, or the insulin that it produces does not work effectively in your body. This booklet discusses those three most common kinds of diabetes: type 1, type 2, and gestational diabetes. If you have type 1, or insulin-dependent diabetes (also called IDDM or in the past, juvenile diabetes), you probably have had it since childhood. Your pancreas can't produce the insulin you need, and therefore, you are dependent on injections of insulin every day. You also follow a special meal plan to keep your body in healthy, working order. During pregnancy, you will need to take special care in managing your diabetes. If you have type 2, or non-insulin-dependent diabetes (also called NIDDM, or in the past, late-onset, or adult-onset diabetes), your pancreas does produce some insulin. However, you do not produce enough insulin for your body's needs, or your body doesn't effectively use the insulin that is produced. You will need to closely watch your meal plan and will most likely need to take insulin injections during your pregnancy. Perhaps you did not have diabetes before you become pregnant, or perhaps you had diabetes but did not know it. In either case, you may develop gestational diabetes during pregnancy. Your "bag of water" (amniotic fluid) breaks. This bag of water surrounding your baby may break at the beginning of labor, during labor, or just before your baby is born. Itmay break spontaneously or your doctor may want to break your bag of water to help your labor progress. In case a large amount of fluid escapes from your vagina.

As soon as it does, go to the hospital. Management of diabetes during labor and delivery is highly dependent upon your individual doctor's preference. Your blood glucose levels will be checked frequently when your labor begins and during labor so your doctor can give you insulin as you need it (either by injection or into your vein), as well as glucose through an intravenous line. If you have gestational diabetes there is good chance that you will not need any insulin during labor. Labor is exercise and, as you knows exercise lowers blood glucose levels. Rest assured, no matter what type of diabetes you have, you will be closely watched. Regardless of whether you have type 1, type 2 or gestational diabetes, be encouraged to breast-feed your baby. Your breast milk is nutritious and contains substances that protect your baby from some infections and illness. If you decided to do breast-feed you will continue to need extra calories to provide adequate nutrition for your baby. Be sure to discuss this with your doctor as well as any medication that you are taking which might appear in breast milk [26].

Gluconeogenesis is the process of synthesizing glucose or glycogen from non-carbohydrate precursors. It is of particular importance when carbohydrate is not available

from the diet. Significant substrates are amino acids, lactate, glycerol, and propionate. The pathways of gluconeogenesis in the liver and kidney utilize those reactions in glycolysis that are reversible plus four additional reactions that circumvent the irreversible non equilibrium reactions. Since glycolysis and gluconeogenesis share the same pathway but operate in opposite directions, their activities must be regulated reciprocally. Glucagon is secretedas a response to hyperglycemia and activates both glycogenolysis and gluconeogenesis in the liver, causing the release ofglucose into the blood [28].

Ideas Where the Research Go Next

Carbohydrates are widely distributed in plants and animals; they have important structural and metabolic roles. In plants, glucose is synthesized from carbon dioxide and water by photosynthesis and stored as a starch or used to synthesize the cellulose of the plant walls. Animals can synthesize carbohydrates from amino acids but most are derived ultimately from plants. It is the precursor for the synthesis of all the other carbohydrates in the body, including glycogen for storage; ribose and deoxyribose in nucleic acids; galactose in lactose of milk, in glycolipids, and in combination with protein in glycoproteins and proteoglycans.

Type 1 diabetics must rely on exogenous insulin delivered subcutaneous to control hyperglycemia and ketoacidosis. T2D has a strong genetic component. It results from a combination of insulin resistance and dysfunctional β-cells. Insulin resistance is the decreased ability of target tissues, such as liver, adipose, and muscle, to respond properly to normal or (elevated) circulating concentrations of insulin. Obesity is the most common cause of insulin resistance. However, most people with obesity and insulin resistance do not become diabetic. In the absence of a defect in β-cell function, non-diabetic, obese individuals can compensate for insulin resistance with elevated levels of insulin. Available treatments for diabetes moderate the hyperglycemia but fail to completely normalize metabolism. The long-standing elevation of blood glucose is associated with the chronic complications of diabetes including premature atherosclerosis (macrovascular) as well as retinopathy, and neuropathy (micro vascularity) [29]. Gene expression and suppression persist for up to 6 days in the endothelium after the hyperglycemic episode in vitro. Here is the importance of novel GPR agonists which currently are underway in an effort to improve GPR signaling in tissues and its metabolic benefits in patients with diabetes [30,31].

Other epigenetic mechanisms such as microRNAs (miR) can regulate gene expression post-transcriptionally, directly exert their effects in signal pathways, and reach other cells when included in extracellular vesicles called ‘exosomes’ [32]. miR-941, miR-208b, miR-197, and miR223 have been found to have diagnostic value in predicting CV events or CV death [33]. miR-126-5p has been associated inversely with the complexity of CAD with low serum levels in multi-vessel disease and high SYNTAX scores in patients with stable angina [33]. Some epigenetic therapies are underway as potential antithrombotic such as miR-19b for use in patients with unstable angina [34]. And also can increase the apoptosis of macrophages and endothelial cells in atherosclerosis [35].

This review considers the mechanisms, history, controversies, new pharmacological agents, and recent evidence for current guidelines for cardiovascular management in the patient with diabetes mellitus to support evidence-based care in the patient with diabetes mellitus and heart disease outside of the acute care setting [36]. The goal of this review is to provide an update on the diagnosis and management of DKD based on a comprehensive review of the medical literature [37]. Diabetes mellitus has been associated with increased fracture risk by several groups. The Nurses’ Health Study followed 109,983 women aged 34–59 years old with biennial questionnaires for over 20 years and monitored the occurrence of hip fractures. They found that the risk of hip fracture in women with T1DM was six fold higher compared with those without diabetes [38]. The Health Improvement Network (THIN) study used longitudinal electronic medical record data in the United Kingdom (UK) to evaluate incident fractures in men and women with T1DM from age 0 to 89 years old, across a median of 4.7 years of follow up. They found that the risk of incident fracture of any type increased in both sexes and in all age groups compared to those without diabetes. When stratified by age, women with T1DM ages 40–49 had the highest risk for fracture at any site 82% higher than women without diabetes after multivariate adjustment. Men aged 60–69 with T1DM also had double the risk of fracture at any site compared to men without diabetes in the same age group [39].

Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure [40-42]. Given inadequate levels of insulin and increased insulin resistance, hyperglycemia results. The incretins are important gut mediators of insulin release, and in the case of GLP-1, of glucagon suppression. Although GIP activity is impaired in those with type 2 DM, GLP1 insulin tropic effects are preserved and thus GLP-1 represents a

potentially beneficial therapeutic option. However, like GIP; GLP-1 is rapidly inactivated by DPP-IV in vivo. Two therapeutic approaches to this problem have been developed: GLP-1 analogues with increased half-lives, and DPPIV inhibitors, which prevent the breakdown of endogenous GLP1 as well as GIP. Both classes of agents have shown promise, with potential not only to normalize fasting and postprandial glucose levels but also to improve beta-cell functioning and mass. Studies are ongoing on the role of mitochondrial dysfunction in the development of insulin resistance and etiology of type 2 DM. Also very important is adipose tissue, as endocrine organ hypothesis (secretion of various adipocytokines, i.e., leptin, TNFalpha, resistin, and adiponectin implicated in insulin resistance and possibly beta-cell dysfunction).

Major Advances and Discoveries

The goal of insulin therapy in type 1 diabetes is to maintain blood glucose as close to normal as possible and to avoid wide swings in glucose. The use of home blood glucose monitors facilitates frequent self-monitoring and treatment with insulin. The goal in treating type 2 diabetes is to maintain blood glucose within normal limits and to prevent the development of long-term complications. Weight reduction, exercise, and dietary modification decrease insulin resistance and correct hyperglycemia in some patients with type 2 diabetes. However, most patients require pharmacological intervention with oral glucose-lowering agents. As the disease progresses, β-cell function declines and insulin therapy is often needed to achieve satisfactory glucose levels. Insulin is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds. It is synthesized as a precursor (pro-insulin) that undergoes proteolytic cleavage to form insulin and C-peptide, both of which are secreted by the β-cells of the pancreas. Because insulin undergoes significant hepatic and renal extraction, plasma insulin levels may not accurately reflect insulin production. Thus, the measurement of C-peptide provides a better index of insulin levels]. Insulin secretion is regulated by blood glucose levels, certain amino acids, other hormones, and autonomic mediators. Secretion is most often triggered by increased blood glucose, which is taken up by the glucose transporter into β-cells of the pancreas [42].

Because insulin is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. Therefore, it is generally administered by subcutaneous injection. This method of administration may be more convenient for some patients, eliminating multiple daily injections of insulin. The pump is programmed to deliver a basal rate of insulin. In addition, it allows the patient to deliver a bolus of insulin to cover mealtime carbohydrate and compensate tor higher blood glucose [43]. Therapeutic recommendations are based on the relative contribution of beta cell insufficiency that the individual patients have specific etiologic cause for their diabetes should always be considered, especially when the patient does not have a family history of type 2 diabetes or does not have any evidence of central obesity or insulin resistance. Such patients should be evaluated for other types of diabetes such as LADA or MODY. Patients with LADA should be prescribed insulin when the disease is diagnosed and treated as patients with type 1 diabetes. It is also important to note that many patients with type 2 diabetes mellitus have a progressive loss of beta cell function and will require additional therapeutic interventions with time [45].

Current Debate

Epidemiologic studies such as those demonstrating higher concordance rates for disease in monozygotic vs dizygotic twins, have convincingly established a genetic basis for type 1 diabetes. More recently, genome-wide association studies have identified multiple genetic susceptibility loci for type 1 diabetes, as well as for type 2 diabetes. More than 30 susceptibility loci for type 1 diabetes are now known. Of these, the most important loci for type 1 diabetes are now known. Of these, the most important locus is the HLA gene cluster on chromosome 6p21, which according to some estimates contributes as much as 50% of the genetic susceptibility to type-1 Diabetes. Several non-HLA genes also confer susceptibility to type 1 diabetes. The first disease-associated non-MHC gene to be identified was insulin, with variable number of tandem Repeats (VNTRs) in the promoter region being associated with disease susceptibility.

The mechanism underlying this association is unknown. It is possible that these polymorphisms influence the level of expression of insulin in the thymus, thus affecting the negative selection of insulin-relative T-cells. The association between polymorphism in CTLA4 and PTPN22 and autoimmune thyroiditis was mentioned earlier; not surprisingly, these genes have also been linked with susceptibility to type-1 diabetes. The relationship of type 2 diabetes to altered T-cell selection and regulation is also underscored by the striking prevalence of this disease in individuals with rare germ line defects in genes that code for immune regulators, such as AIRE, mutations of which cause autoimmune polyendocrinopathy syndrome, type 1 (APS, type 1) [46].

Critical illness, in particular severe sepsis, induced insulin resistance and hyperglycemia. Corticosteroids are often used for reversal of fluid-and vasopressor-resistant septic

shock. Such an adjuvant treatment aggravates illness-induced hyperglycemia, even in low-dose steroid regimen [47]. For glucocorticoid-induced hyperglycemia in non-critically ill patients, there is general agreement on treatment, because prolonged hyperglycemia causes cardiovascular and infectious complications [48]. Whether patients in septic shock in the intensive care unit (ICU) with glucocorticoid-induced aggravation of "diabetes of injury" should be treated is controversial. This debate is embedded in the overall controversy about whether to treat critically ill patients with hyperglycemia with insulin, and if so, to what blood glucose levels [49].

Conclusion

Once insulin is secreted into the portal venous system, approximately 50% is removed and degraded by liver. Unextracted insulin enters the systemic circulation where it binds to receptors in target sites. Insulin binding to its receptors stimulates intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signaling molecules, such as insulin receptor substrates (IRS). IRS and other adaptor proteins initiate a complex cascade of phosphorylation and de-phosphorylation reactions, resulting in the widespread metabolic and mitogen effects of insulin. Activation of other insulin receptor signaling pathways induces glycogen synthesis, protein synthesis, lipogenesis, and regulation of various genes in insulin responsive cells.

Glucose homeostasis reflects a balance between hepatic glucose production and peripheral glucose uptake and utilization. Insulin is the important regulator of this metabolic equilibrium, but neural input, metabolic signals, and other hormones (e.g. glucagon) results in integrated control of glucose supply and utilization. In the fasting state, low insulin levels increase glucose production by promoting hepatic gluconeogenesis and glycogenolysis and reduce glucose uptake in insulin-sensitive tissues (skeletal muscle and fat), there by promoting utilization of stored precursors such as amino acids and free fatty acids (lipolysis).Other tissues, most notably the brain, utilize glucose in an insulin-independent fashion [50]. Alcohol and smoking are still taboo for diabetics: Alcohol can cause hypoglycemia, interact with medication, and lead to liver damage. Smoking cigarettes doubles the risk of diabetes. Smoking damages the pancreas, where the insulin is produced. Kicking the smoking habit certainly helps, but don't count on quitting someday to bring your diabetes riskback to normal. The damage you're done to your pancreas apparently remains even after you're quit.

While many of the nutrition rules have changed, the game remains the same: Your diet is important. Healthy eating can prevent complications and. for type II diabetics; reduce your need for insulin [51]. Do you need your morning coffee or tea to keep up with those energetic kids? Don't share that cup with your children! Children who drink one or more cups of coffee or tea each day greatly increased their risk of developing type 1 diabetes. So keep that coffee break for the adults; children have enough on their own b [52]. Too little chromium for either of these reasons can lead to a mild insulin resistance which could turn into diabetes [53]. Chromium acts as insulin's overseer: It makes sure that insulin does a good job moving excess sugar from the bloodstream to the cells. Chromium has to work hard after you eat a lot of simple sugar [54].

Chromium supplements can be good ammunition if you're at risk for developing diabetes. Large supplements of vitamin C may help you sidestep many complications of diabetes. Large doses of vitamin C can distort urinary glucose test results. Vitamin E may make cell walls more physically fit. In fact, a recent study found that people at risk for developing diabetes can clear up to 11 percent more sugar from their blood with the same amount of insulin after regular aerobic exercise [55].

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