Diabetes Mellitus: Pathological and Clinical Findings

Blas Gil-Extremera1*, Pilar Jimenez-Lopez2 and Elisabet Garcia-Peñalver1

1Department of Medicine, University of Granada, Spain

Abstract

The term diabetes mellitus includes a group of metabolic disorders characterized by hyperglycemia with secondary damage to multiple organ systems. The way to improve this crucial situation is to find better drugs for an early treatment of the disease. The clinical trials, so far, are the best procedure to offer more efficient treatments to the increasing diabetic populations. This paper is an update revision about one of the most important diseases worldwide. We analyzed some historical and pathological aspects of the disease, mainly clinic, and diagnostic, and treatment aspects useful in the clinical practice. We also report information about several clinical trials in which our research group has been participating since about two decades; eight of them are listed in this work.

Introduction

The term “diabetes” comes from the Greek and means “to pass through” or “running throw” referring to polyuria so characteristic during the last stages of the disease. It was first used by the Greek physician Aretus the Cappadocian during the 2nd century B.C. The term “mellitus” comes from the Latin and means sweetened like honey, referring to the sweet taste of urine because of the presence of glucose. Claudius Galenus (3rd century) considered diabetes as a kidney disease. Celsus, in the 1st century of our era, established from his personal experience the “painless polyuria with dangerous emaciation”. Diabetes symptoms were described in Egyptian and Indian manuscripts. Previously, the description was found in the Ebers papyrus.

The word diabetes was first recorded in 1425. In 1675, the Greek word mellitus (like honey) was added to reflect the sweet smell and taste of the patient's urine. Diabetes insipidus, an unrelated and rare disorder, is usually caused by hormone deficiency.

In 1675 Thomas Willis (1621-1675) found in the patients the sweetness of the urine, and William Cullen (1710-1790) proposed the term “mellitus”. In addition, diabetes mellitus (DM) has been recognized since antiquity. Avicenna (980 B.C), Paracelsus (1491-1541), Thomas Willis (1621-1675) and Dobson (1725-1784) described in different periods of the history set milestones in the knowledge of the disease. In 1776 Matthew Dobson confirmed again that the sweet taste comes from an excess of a kind of sugar in the urine and blood.

The majority of historians accept the papyrus form of 1862 close to the ruins of Luxor, the ancient sacred city of Thebes. The well-known document, a roll of papyrus by two meters long and thirty centimeters large, is a vast compendium with the totality of the richness of knowledge at the pharaohs era like at current texts of medicine. The physician-priest recommended, as treatment, fatty of calf, beer, leaf of mint, hippopotamus's blood and offering sacrifice to gods.

The antiquity of this document is about 3500 years; it was acquired and analyzed by the German Egyptologist George M. Ebers (1837-1898). It is currently kept in good conditions at the library of the University of Leipzig. The first description of diabetes appeared in this papyrus where polyuria was described.

In 1859, Claude Bernard (1813-1878) determined blood glucose by hyperglycemia as the fundamental sign; the hereditary character of the disease was postulated by R. Morton (1637-1698) in his text Phthisiologia (1689). Bernard published studies on the pancreas, the mode of action of curare, the development of hyperglycemia following puncture of the fourth ventricle, the role of the liver in carbohydrate metabolism, the discovery of the vasomotor nervous system, and the discovery of the storage form of sugar in the liver, which he named "glycogen". Morton noted the hereditary character of diabetes.

Another historical event was made by Paul Langerhans (1847-1888), who described the pancreatic islets; Oskar Minkowski (1858-1931) removed for the first time the pancreas of a dog, which demonstrated that pancreas is able to produce the substance lacking and being responsible for the disease. Frederick Madison Allen (1879-1964), with a uniqueness criterium, considered diabetes as a hereditary disorder of carbohydrate metabolism resulting in insufficient production of insulin. The results of the work by the German internist Oskar Minkowski and Joseph von Mering (1894-1908) of removing the pancreas led to the conclusion that the cause of diabetes resides in the lack of internal secretion of the Langerhans islets placed in the pancreas. In 1875 Charles-Joseph Bouchard (1837-1915) described two types of the disease:

*Corresponding authors: Blas Gil-Extremera, Department of Medicine, Avda. Investigación, nº 11, 18016. University of Granada, Spain, Tel: +34.958.249081/+34.958.244054/+34.958.241545; E-mail: blasgil@ugr.es

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the classic form (type 1 DM) normally found in young and slim people (juvenile diabetes), and another type (type 2 DM) present in obese adult people [1,2].

In 1960, diabetes was classified according to its etiology: primary form, (type 1), which is hereditary and due to a lack of insulin production; secondary diabetes (type 2), which is caused by pancreatic diseases, endocrine diseases, drugs, chemical substances, or excess of stress.

In 1922, Frederick Grant Banting (1891-1941), the medical student Charles Herbert Best (1899-1978) and John Richard McLeod (1876 -1935) isolated insulin. The substance was initially named “isletin”[3]. This marked the beginning of a new era in the treatment of diabetes, since insulin was initially used therapeutically. In summary, diabetes is a genetic chronic disease that has, in many cases, the following manifestations: a) metabolic syndrome, hyperglycemia, glycosuria with polyphagia or anorexia, polydypsia, polyuria, and lipid and protein disorders; b) vascular disease with multiorgan involvement affecting mainly the kidneys, retina, heart, and cerebral arteries.

The prognosis of the disease is improving, although the prevalence still rises progressively from 5% at age 20 to older people >75 years.

Epidemiology
DM is considered a serious health problem worldwide, being the most common serious metabolic disorder. Several problems make it hard to know the exact prevalence of diabetes: a) insufficient epidemiological studies, b) difficulty in establishing diagnostic criteria in many cases. c) undiagnosed patients, d) insufficient knowledge about the prevalence of the disease as cause of death, since many diabetic patients who died were not listed on the death certificate as the underlying cause of death [4,5].

In general terms, the global prevalence of diabetes is between 2% and 4% of the population. However, it is increasing in the developed countries, where most of diabetic patients are insulin dependent (75% to 80% of cases). This percentage has been rising in the last decades due to population ageing, higher life expectancy, higher fertility rates in diabetic women, increased intake of refined sugars, increase of obesity, and the development of better diagnostic techniques. In summary, DM is a very serious chronic and progressive disease requiring lifelong treatment, with frequent acute complications and a high rate of morbidity and mortality. Vascular complications cause 24% of new cases of end stage renal disease. DM is responsible for the 50% of amputations of lower limbs, and blindness. Diabetic patients represent about 10% of all hospital stays.

Classification of Diabetes
DM is an heterogeneous disease that need to be arranged. Several classifications have been described according to different criteria. In 1961 Fagans and Conn reported the different phases of the disease: pre-diabetes, when it can be predicted because of the hereditary character of the disease; subclinical diabetes, in cases of changes in glucose tolerance; and clinical diabetes, when levels of glucose tolerance test are changed. In this process, β cell depletion occurs. However, DM is classified according to the pathogenic process leading to hyperglycemia, as opposed to earlier criteria like the age of onset or the type of therapy. The two previous categories of DM are called type 1 and type 2. Both cases are preceded by a phase of abnormal glucose homeostasis and the pathogenic processes evolution. Type 1 DM is related to complete or almost total insulin deficiency. Conversely, type 2 DM is a complete group of disorders with some degree of insulin resistance, decreased insulin secretion, and increased glucose production. Although type 1 DM appears mainly before the age of 30, an autoimmune β cell destructive process can develop the disease at any age. We must remain that between 5 and 10% of subjects who develop DM after the age of 30 present type 1 DM. In the other hand, type 2 DM appears more frequently with increasing age; however, it is currently observed in children and mainly in obese adolescents.

DM type 1 was also called insulin-dependent or juvenile diabetes. At present, classification of DM type 1 is divided into DM type1 A (autoimmune DM type1), and DM type1 B (idiopathic DM type1). About 1 out of 10 diabetic patients has DM type 1A. In Spain, approximately 10 new cases per 100 000 inhabitants are diagnosed each year. Although many of these cases are children between 10 and 12 years old, and half of the cases diagnosed are patients of older than 15 years.

Immune and inflammatory diseases cause selective destruction of the β -cells of the pancreas mediated by activated lymphocytic T cells. After the asymptomatic phase of diabetes, insulin secretion decreases, and hyperglycemia and DM symptoms appear: polyurea, polydypsia, polyphagia, loss of weight, and tendency to ketosis when treatment with exogenous insulin is not established [6].

Etiopathogenesis
The detailed causes of diabetes are not yet well-established. There are several processes of different etiopathogenic origin that lead to the same complications of diabetes. A number of factors have been identified as increasing the chances of developing the disease: a) pancreatic, congenital, traumatic, neoplastic and inflammatory diseases, as well as steatosis, which lead to the total or partial destruction of the pancreas; b) hormonal diseases: pheochromocytoma, primary hyperaldosterism, and somatostatinomas; excess of insulin, Cushing syndrome, acromegaly, giantism, and glucagonoma. c) several drugs such as corticosteroids, anovulatory agents, thiazides, analgesics, and beta blockers able to elevate glucose concentrations in blood [7].

Pathological Findings
The histological changes in DM are not pathognomonic and are relatively common in the disease. Findings are mainly found in the Langerhans islets and vascular system. Insulitis is an inflammatory infiltration of the islets of Langerhans mainly found in young patients with recent onset of type 1 diabetes (<1 year). Less frequent changes are: fatty pancreatic atrophy related to age
and time of evolution of the disease, and vacuolation of pancreatic β-cells. There are two types of changes that can occur in the vascular system: atheromatous changes in the great vessels that are usually serious and appear early, and microvascular lesions with thickening of the basement membrane caused by glycoprotein deposits and PAS positive substances. These alterations define diabetic microangiopathy that is typical of the disease and affects almost the entire body.

Today in the clinical practice DM has supplanted syphilis and tuberculosis as the big masquerade. Now, from the professional point of view, many physicians are involved in hard challenges, and controversies concerning diabetic patients: insulin resistance, management of the disease, diabetic pregnant women, carbohydrate disorders, diabetic foot, diabetes and surgery, pharmacological aspects, psychological and sociological problems, new modalities of treatment, and other important clinical questions. DM, which is the most common endocrine disorder, is characterized by several metabolic abnormalities and many long-term complications affecting mostly the kidneys, peripheral nerves, blood vessels, organ vision, and central nervous system; also, we must not forget that it is the main cause of morbidity and mortality in the Western and developed countries.

Since Banting, Best, and McLeod discovered the insulin in 1921, it has been used in the treatment of DM. By the time, the manufacturing process of insulin has improved, becoming free of impurities or associated to hormonal products (glucagon, polypeptide pancreatic, proinsulin) until obtaining purified insulin.

DM affects an estimate of 366 million people worldwide, with type 2 diabetes mellitus (T2DM) accounting for more than 90% of the cases. Renal insufficiency is a common comorbidity condition in T2DM patients with chronic kidney disease (CKD) defined as kidney damage or an estimated glomerular filtration rate (eGFR) < 60 mL/min, for > 3 months.

The kidney is both the origin and victim of elevated blood pressure. Hypertension is a pathogenic factor that contributes to the deterioration of kidney function. Therefore, the management of hypertension (reduction of salt intake, adequate diet, exercise, and antihypertensive drugs) has become the most important intervention to control all types of chronic kidney disease (CKD).

The role of hypertension in the renal disease is crucial. Population ageing is increasing, and it is the most common risk factor in the development of hypertension and diabetes, as well as in CKD [8-10].

**Clinical Pattern**

Semiological signs of DM vary and have some relation with the etiopathology and physiopathology of diabetes, although it is not yet clear. Type 1 diabetes or insulin-dependent diabetes appears in childhood or youth. It is characterized by sudden onset of symptoms during weeks or months; sometimes it appears as a ketoacidotic coma. Acute manifestations of the disease are the results of a maintained hyperglycemia that lead to loss of free water and glucose in the urine, and when levels of blood glucose levels are above 180mg/dl (renal threshold of glucose) (Table 1).

The volume of urine (diuresis) can be 3-5 L/day, mainly during the night (nocturia). Polyphagia is caused by the loss of glucose in the urine, and the difficulty of glucose to penetrate into cells, leading to a situation of excessive hunger despite the presence of hyperglycemia. Weight loss is due to the decrease of muscle mass and amino acids are derived to form glucose molecules. Asthenia is caused by the muscle mass decrease that can lead to vertigo, weakness, all due to the loss of potassium and protein catabolism. Other less frequent transient signs are blurred vision, impaired consciousness that can lead to coma, parenthesis, as well as gastrointestinal, cardiovascular, genitourinary, and osteoarticular disorders. Good glycemic control among patients with type 2 DM reduces the risk of microvascular complications. It is well-known that many antihyperglycemic drugs are licensed for treatment, but questions concerning the long-term cardiovascular safety of these agents have been postulated [11,12].

**Physical Examination in Diabetic Patients**

In addition to a complete physical examination, special attention should be given to several important aspects such as weight, retinal and foot examination, peripheral pulses, insulin injection site, blood pressure (>130/80mmHg is considered hypertension in diabetic individuals), examination of the lower extremities to seek evidence for peripheral neuropathy.

### Table 1: Drugs associated with hyperglycemia

- **Non-steroid anti-inflammatories (NSAIDS):** Glucocorticoids, Febuxostat.
- **Psychoactives:** Phenytoin, Duloxetine.
- **Anti-infectives:** Antiretrovirals, Fluoroquinolones, Interferon &thabendazole, Pyrazinamide.
- **Antineoplastics:** Asparaginase, cabazitaxel, decitabine, fribuline, temsirolimus, vorinostat.
- **Immunosuppressives:** Cyproterone, Tacrolimus, Mycophenolic acid, cyclosporine.
- **Cardiovascular drugs:** Thiazide diuretics, beta-adrenergic blocking agents, furosemide, clonidine, nifedipine, statins, epoprostenol, adrenaline.
- **Bronchodilators:** Salbutamol, terbutaline, salmeterol, teofilin, oral contraceptives, octeotide, acetazolamide.
of peripheral neuropathy, calluses, superficial fungal infections, nail disease, ankle reflexes, teeth and gums examination, head, eyes, ears, nose, throat, thyroid, respiratory and cardiovascular system, abdomen (liver, spleen), and lymph nodes (neck, armpits, and groins).

**Acute and Chronic Complications of Diabetes**

Until the discovery of insulin, the major cause of death in diabetic patients was the acute metabolic imbalance due to diabetic coma that sometimes caused 40% of the deaths. Fortunately, therapeutic advances are able to prevent and treat, with some success, the serious metabolic complications of the disease. Sometimes, aged diabetic patients can present hyperosmolar nonketotic coma characterized by severe hyperglycemia, plasmatic hyperosmolarity, and dehydration that can lead to renal insufficiency, with involvement of the central nervous system.

It's well established that DM is a serious health problem in the worldwide population and the most frequent metabolic disease, but, it is hard to know its real incidence in the general population. There are several causes to hold up the adequate epidemiological knowledge: a) limited number of studies and difficulty in comparing them; b) in many patients, diagnosis of DM is not established, mainly in older people with very poor symptoms because of the absence of the conventional common disorders such as polyuria, polydipsia, polyphagia, weight loss, and asthenia; c) Sometimes, the diagnosis of diabetes is not reported in the death certificate.

The prevalence of the disease in the European countries varies between 2% and 19.5% per 100,000 inhabitants/year; but the incidence of diabetes increases with age and other factors such as more expectancy life, obesity, increase of glucose intake, and a better and earlier detection of the disease. Another important feature of the disease is its chronic and progressive character, needing treatment for life, and the acute and chronic complications that lead to high morbidity and mortality rates. Unfortunately, the current trend towards the increasing incidence worldwide is a reality. With this preface, diabetes will be a leading cause of clinical problems for the foreseeable future.

We must not forget that DM includes a group of common metabolic disorders characterized by the presence of hyperglycemia usually followed by glycosuria. There are a number of types of diabetes related to a complex interaction between genetic factors, environmental influence and lifestyle of patients. The consequences of the metabolic deregulation secondary to this disorder lead to changes in different organ systems and affect the health and future of many patients. For example, this disease is the leading cause of end-stage renal disease, lower extremity amputations, adult blindness, and chronic heart failure. The therapeutic procedures are aimed at controlling diabetes; that is glycemic index < 100 mg/dl, negative glycosuria and glycated hemoglobin < 6%.

**Acute Metabolic Complications**

Patients with diabetes are susceptible to four acute metabolic complications: hypoglycemia, ketoacidosis, hyperosmolar acidosis and lactic acidosis. All of them can result in coma. The first two are complications of IDDM, while the other two are usually developed in the setting of NIDDM. In the clinical practice, it is crucial to distinguish between diabetic coma (caused by ketoacidosis, hyperosmolar coma, lactic acidosis) and the coma in diabetic patients (caused by stroke, acute heart failure, or hepatic dysfunction).

Unfortunately, a lot of patients present comatose situations despite the treatments available, which are generally caused by incorrect dose administration, or missed dose of medication. This is a relevant point to consider other possibilities like clinical trials.

**Diabetic Ketoacidosis**

Diabetic ketoacidosis is frequently caused by cessation of insulin administration, but it may result from physical (infection, surgery, trauma) or emotional stress despite of being under continued insulin therapy. Several complications can be present in diabetic ketoacidosis: erosive gastritis or acute gastric dilatation manifested by pain, vomiting of blood, weight loss, cerebral edema with or without neurological signs or coma, elevated potassium serum (cardiac arrest), myocardial infarction, respiratory distress syndrome, or thrombotic events.

**Hyperosmolar Coma**

This type of acute diabetes complication is usually due to NIDDM. It is characterized by a profound dehydration resulting from a sustained hyperglycemic diuresis under circumstances in which the patient is unable to drink enough water to keep up normal urinary excretion of detritus. This situation usually occurs in elderly patients often living alone or in a nursing home. They develop stroke or bacterial infection that worsens adequate water intake. Hyperosmolar coma can also be caused by peritoneal dialysis or hemodialysis, or the use of osmotic agents such as mannitol and urea. Clinically, these patients show extreme hyperglycemia, hyperosmolality and central nervous system disorders (seizure activity, transient stroke, hemiplegia, or clouded sensorium and coma). Pneumonia, gram-negative sepsis or other infections are also very common. Bleeding probably caused by disseminated intravascular coagulation, acute pancreatitis and widespread thrombosis is usually found at necropsy.

**Lactic Acidosis**

It is a serious clinical finding that may be caused by an increase in endogenous lactic acid, which is the final step of carbohydrate metabolism, producing profound effects on the respiratory, cardiac, and nervous systems. The pH of blood drops suddenly and is accompanied by an increase in respiratory ventilation (Adolph Kussmaul, 1822-1902), depression of cardiac contractility, pulmonary edema, and altered central nervous system function manifested with headache, lethargy, stupor, and in such patients even coma. The prognosis is very bad and most of the patients die soon. Lactic acidosis is a less frequent but very serious complication, which includes tachypnea, dehydration, abdominal pain, and coma.
Late Complications

Diabetic patients are susceptible to develop several complications responsible for morbidity and early mortality; some of them do not present problems, whereas others develop early complications, usually after the appearance of hyperglycemic symptoms developed between 15 and 20 years after the onset of the disease. The clinical findings showed the following circulatory abnormalities: atherosclerosis, coronary artery disease, stroke, heart failure, peripheral vascular disease, and left ventricular failure. Chronic complications of DM are those caused by microangiopathy, involving retina, kidneys, myocardium, and cutaneous tissue; macroangiopathy, which involves the coronary arteries, cerebral arteries, and lower extremities; neuropathy, central and peripheral nervous system, autonomic system, and other complications such as cataract, osteopathic disease, and Dupuytren disease.

Microvascular Complications

Retinopathy, proliferative, non proliferative, neuropathy, mononeuropathy, and nephropathy.

Macrovascular Complications

Coronary artery disease, peripheral vascular disease, and stroke.

Others

Infections, skin problems, genitourinary (sexual dysfunction), cataracts, psychological disorders, glaucoma, and circulatory changes.

We recognize hypertension and DM as common disorders, but there is much evidence to suggest that the two conditions occur together more frequently than by chance. Development of hypertension greatly worsens the prognosis of diabetic patients. Raised blood pressure accelerates the progression of diabetic nephropathy, and possibly retinopathy, while the damaging cardiovascular effects of the two disorders are at least additional. There are a number of reasons why hypertension and diabetes may be associated, and these are discussed in this paper.

Life expectancy is reduced in diabetic patients, both insulin-dependent (IDDM) and noninsulin dependent (NIDDM) patients, and the leading cause of death are cardiovascular complications.

The excess mortality cannot be explained by the diabetic state "per se". Based on the Whitehall study of more than 17,000 civil servants followed for 15 years, RJ Jarrett and MJ Shipley suggested that diabetes and cardiovascular disease may not be causally linked at all but might rather share a common, possibly genetic antecedent. Among the known risk factors for cardiovascular disease in diabetes, hypertension has attracted much interest. The prevalence of hypertension is increased in diabetic patients (IDDM and NIDDM), and hypertension is known to be a powerful risk factor for cardiovascular disease in diabetes, insulin treated or not. It's well known that hypertension has also a consistent relation to coronary heart disease and other risk factors which are not only found by the presence of proteinuria. Furthermore, from the clinical point of view, to get a suitable control of the disease (blood glucose, glycated hemoglobin, lipids profile, body weight, and quality of life) it is crucial to ensure successful outcomes. We must realize that subjects with asymptomatic, undiagnosed diabetes not unusually develop serious complications. Despite the absence of fasting hyperglycemia large-scale screening with glucose tolerance test should be established in many cases [13,14].

Diagnosis

It is well known that DM I is the most common endocrine disorder characterized by metabolic abnormalities, long-term complications involving the kidneys, eyes, nerves, and blood vessels. The disease is not homogeneous and several different diabetic syndromes have been found.

In the clinical practice, the diagnosis of symptomatic diabetes is not difficult since the patients present signs and symptoms related to polyuria and hyperglycemia; in this case diagnosis is unequivocally clear; when the patient has no symptoms but fasting plasma glucose levels are persistently elevated, the diagnosis must be established. In some asymptomatic patients who, for one reason or another, should be clinically considered as potential diabetic persons although presenting normal glucose blood levels, oral glucose tolerance test must be done. The oral glucose tolerance test (OGTT) should be performed using a load containing the equivalent of 75 grams anhydrous glucose dissolved in 300 ml of water; it must be avoid as a control of diabetic patients. The current criteria for the diagnosis of DM pointed out that Fasting Plasma Glucose (FPG) is the most reliable and convenient test for identifying DM in asymptomatic subjects. The normal glucose values are between 60-100 mg/dL. Values above 120 mg/dL, when confirmed, are usually diagnosed as overt diabetes. When a random plasma glucose concentration (≥ 200 mg/dL) is accompanied by classic symptoms of DM (polyuria, polydipsia, polyphagia, and weight lost), the diagnosis can be established (Table 2).

If abnormal blood glucose values are found, the patient is diagnosed as having impaired glucose tolerance or diabetes. It must be established without any doubt that normal glucose tolerance test means that diabetes is not present. Some evidence pointed out

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<th>Prediabetes</th>
<th>Diabetes</th>
<th>Gestational diabetes</th>
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<tr>
<td>Fasting</td>
<td>100-125 mg/dL</td>
<td>≥126 mg/dL</td>
<td>&gt;92 mg/dL</td>
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<td>After 1 hour</td>
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<td>140-199 mg/dL</td>
<td>≥200 mg/dL</td>
<td>&gt;153 mg/dL</td>
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that the conventional oral glucose tolerance tests over diagnosed diabetes, probably related to a variety of circumstances, mostly stressful, that can cause abnormal response in the patient. The operating mechanism is probably related to epinephrine discharge. Epinephrine blocks insulin secretion stimulates glucagon release, activates glycogen breakdown, and impairs insulin action in tissues, so that hepatic glucose production is increased. Epinephrine elevations in blood lead to elevation of plasma glucose in normal subjects. The hyperglycemic action is due to a transient increase in hepatic glucose output as well as a reduction in the rate of glucose disposal.

On the other hand, the American Diabetes Association (ADA) and the World Health Organization (WHO) accepted in 2011 the use of glycated hemoglobin (HbA1c) testing in the diagnosis of diabetes mellitus, when values are above 6.5%. When asymptomatic individuals present slightly higher levels of HbA1c (above 6.5%), general recommendations such as weight loss, physical exercise, and balanced diet are indicated. In these cases a new glycated hemoglobin determination must be indicated three months later; if elevated levels persist, OGTT must be done. The diagnosis of DM has deep implications for an individual from a medical point of view, patient’s quality of life, and financial standpoint. Because it is hard for the individual to accept the disease, the clinician must be unequivocally sure, even the repetition of some tests before making a definite diagnosis of DM would be recommended.

**Treatment**

The management approach of DM includes five measurements: diet and physical exercise, agents, insulin, and new drugs.

**Diet and Physical Exercise**

Type 1 and type 2 diabetic patients must receive education about nutrition and exercise among several other therapeutic recommendations. The exercise suggested for diabetic patients consists of walking on flat surface 5 days a week for 30- 60 minutes.

It is also important for the optimal care of the disease, the self-monitoring of blood glucose levels, insulin administration, control of concomitant illnesses, skin and foot care, avoid hypoglycemic situations by checking blood sugar levels before, during and after physical exercise. For many years, the management of dietary instructions has been difficult for diabetic patients. Medical nutrition for patients must be individualized, taking into account eating habits, lifestyle, ageing, and work activity. Monitoring metabolic parameters, including blood glucose glycated hemoglobin, lipids, blood pressure, and body weight are crucial to ensure successful outcomes. Low-protein diet is related to the improvement of nephropathy. An adequate protein requirement for good nutrition ranges between 1.0 and 1.5 g/kg per day; however, when nephropathy appears, protein ingestion should be limited to 0.8 g/kg daily, or about 10% of calories per day. Also, the role of diet in the management of DM varies according to the phase of the disease. In insulin-dependent diabetes, the composition of the diet is important, but not of critical relevance, since adjustment of insulin dosage can cover wide variation in food intake. In non-insulin dependent patients, more vigorous adherence to diet is required, because the endogenous insulin reserve is precarious.

**Insulin**

The discovery of insulin has represented an important event in the treatment of DM; insulin is required for all patients with IDDM and some with NIDDM. If agents are not used, and NIDDM subjects do not respond to diet regimen, insulin administration is necessary. It is difficult to control the symptoms of the disease with insulin as well as to maintain normal blood glucose levels for 24 hours, even when several injections of regular insulin or insulin pumps are administered. The administration of insulin and treatment procedures varies depending on the physician and the patient (Table 3).

There are three methods for the use of insulin: a) conventional insulin therapy, b) multiple subcutaneous injections (MSI), and c)

| Table 3: Types of insulin usually employed in the clinical practice |
|------------------|-------------|-------------|-------------|
| Mode of action   | Route      | Start       | Peak        | Duration    |
| Fast             | I.V        | <1min       | 1-3min.     | 5 min.      |
|                  | I.M        | 5 min.      | 30-60min.   | 60-90min.   |
|                  | S.C.       | 20-60min.   | 1-3hr.      | 6-8hr.      |
| Rapid analog of insulin | S.C. | 5-15min. | 30-90min. | 4-6hr. |
| Intermediate     | NPH        | S.C.        | 2-4hr.      | 4-8hr.      | 12-20hr.   |
|                  | NPL        | S.C.        | 15 min.     | 4-8hr.      | 12-20hr.   |
|                  | Gargine    | S.C.        | 3-4hr.      | (-)         | 20-24hr.   |
|                  | Detemir    | S.C.        | 2-4hr.      | (-)         | 12-20hr.   |

I.V= intravenous; I.M= intramuscular; S.C= subcutaneous; NPH= Neutral Protamine Hagedorn; NPL= insulin lispro protamine;
The aim of this study was to investigate the quality of life of patients by providing easier routes and modes of administration of the medications.

Conventional insulin therapy involves the administration of one or two injections a day of intermediate-acting insulin, such as zinc-insulin (lente insulin) or isophaneprotamin insulin (NPH insulin) with or without addition of small amounts of regular insulin. The multiple subcutaneous injections technique must commonly involve the administration of intermediate-or long-acting insulin in the evening as a single dose together with a regular insulin dose before each meal.

Continuous subcutaneous insulin infusion is related to the use of a small battery-driven pump that delivers insulin subcutaneously into the abdominal wall. Unfortunately, the danger of hypoglycemia is real, mostly during the night in patients who maintain blood glucose levels consistently below 100 mg/dL. In some cases mortality occurs due to severe hypoglycemia [15,16].

**Agents**

Diabetic patients (NIDDM) that are unable to be controlled with diet and changes in their lifestyle, could respond to sulfonylureas, whose mechanism of action is different from other oral agents. The use of these drugs is easy and safe. Metformin, abiguanide useful for NIDDM patients, may be prescribed as monotherapy in obese diabetics but it is usually added as an adjunctive agent in patients whose disease is not controlled after administration of maximal doses of sulfonylureas. The primary action of metformin is thought to be the inhibition of hepatic gluconeogenesis; it also may increase glucose disposal in muscle and adipose tissue. It is important to note that metformin does not cause hypoglycemia. The possibility to produce lactic acidosis is low; in order to avoid this serious complication, the drug should not be given to patients with renal insufficiency. It has been demonstrated that Metformin reduces some complications related to DM and mortality. It should be interrupted in cases of nausea, vomiting, diarrhea, or intercurrent illness.

Thiazolidine derivatives are used for the treatment of type 2 DM. Pioglitazone reduces blood glucose by increasing the peripheral utilization of it. Free fatty acids and triglycerides also reduce insulin resistance in fat tissue, muscle, and liver, by binding to nuclear receptor PPARg (gamma receptor activated by the proliferative lissome). We must remember that some drugs or substances such as acetylsalicylic acid, amphetamine, clofibrate, alcohol, marijuana, propranolol, and oxytetracycline can produce hypoglycemia [17-22].

**New Drugs and Modalities of Treatment**

The main purpose of clinical trials is a) to search and develop new and more efficient drugs to treat the disease, b) also, to find a better tolerance and greater effectiveness and safety of the drugs in order to ensure a better control of diabetes mellitus, and c) to improve the quality of life of patients by providing easier routes and modes of administration of the medications.

The investigation of new drugs or new modalities of treatment (Anti-Interleukin-18 Monoclonal Antibody, Albiglutide + Insulin Glargine, Insulin Lispro + Insulin Glargine, Insulin Glargine/Lixisenatide Fixed Ratio Combination, Insulin Glargine Alone, Lixisenatide Alone on Top of Metformin, Albiglutide alone, Canagliflozin, Sitagliptin, and Sotagliflozin as adjunct therapy) are aimed at finding a better metabolic control and increasing patient’s comfort such as weekly dosages.

**Incretins and Glycosurics**

Gastric inhibitory popypeptide (GIP) and glucagon-like-peptide-1 (GLP-1) analog are gastrointestinal hormones of posprandial release implicated in carbohydrate metabolism. GLP-1 stimulates insulin secretion, inhibits glucagon secretion, delays gastric emptying, and contributes to feeling of satiety. This agent inhibits dipeptidyl peptidase (DPP-4) to stop incretin hydrolization, increasing his level, leading to stimulation and insulin release by the pancreatic cells and reducing glucagon secretion. So far, agents such as linagliptine, saxagliptine, sitagliptine, and vildagliptine are used in the clinical practice [23-36].

During the last years, our group has participated in several diabetes clinical trials. It is noteworthy to mention some of them:

**A Study to Investigate the Efficacy and Safety of an Anti-Interleukin-18 Monoclonal Antibody in the Treatment of Type 2 Diabetes Mellitus:** The aim of this study was to investigate whether inhibition of IL-18 had any therapeutic benefit in the treatment of T2DM. Preliminary efficacy, safety and tolerability, pharmacokinetics, and pharmacodynamics of the anti-IL-18 monoclonal antibody were assessed.

**Safety and Efficacy of Albiglutide + Insulin Glargine Versus Insulin Lispro + Insulin Glargine Subjects With Type 2 Diabetes Mellitus (Switch Study):** The purpose of this study (Phase IIIb, randomized, open-label, parallel group, active control, multicenter, treat-to-target study of 26 weeks’ treatment duration) was to evaluate the efficacy and safety of once-weekly albiglutide as replacement of prandial insulin in subjects with type 2 diabetes mellitus (T2DM) failing to achieve adequate glycemic control on their current basal bolus insulin regimen (with or without metformin).

**Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects with Type 2 Diabetes Mellitus:** Albiglutide is an analogue of glucagon-like peptide-1 (GLP-1), used to treat type 2 diabetes. This is a double-blind, randomized, medium-term controlled study with placebo for evaluation the effect of albiglutide when it is added to standard hypoglycemic agents to cardiovascular events in DM type 2.

**Efficacy and Safety of Insulin Glargine/Lixisenatide Fixed Ratio Combination Compared to Insulin Glargine Alone and Lixisenatide Alone on Top of Metformin in Patients With T2DM (LixiLan-O):** The primary objective was to compare the insulin glargine/lixisenatide fixed ratio combination to lixisenatide alone and to insulin glargine alone (on top of metformin treatment) in HbA1c change from baseline to week 30; the secondary objective

was to compare the overall efficacy and safety of insulin glargine/lixisenatide fixed ratio combination to insulin glargine alone and to lixisenatide alone (on top of metformin treatment) over a 30 week treatment period in patients with type 2 diabetes.

Albiglutide versus Placebo in Insulin-treated Subjects with New-onset Type 1 Diabetes Mellitus: Purpose: This is a Phase II, randomized, double-blind, parallel group, placebo controlled, multicenter study of 52 weeks duration treatment. The primary objective is to evaluate the efficacy (on endogenous insulin secretion), safety and tolerability of weekly albiglutide (a glucagon-like peptide-1 receptor (GLP-1R) agonist) versus placebo when added to insulin therapy in subjects with new-onset type 1 diabetes mellitus (NOTIDM) and residual insulin production.

A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus (CANVAS-R): It is a Randomized, multicenter, double-blind, parallel, placebo-controlled study. The purpose of this trial was to assess the effect of canagliflozin compared to placebo on progression of albuminuria in participants with Type 2 Diabetes Mellitus receiving standard care but with inadequate glycemic control and at elevated risk of cardiovascular events.

TECOS: A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes After Treatment with Sitagliptin in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control (TECOS Study): The purpose of this clinical trial was to assess the cardiovascular outcome of long-term treatment with sitagliptin used as part of usual care compared to usual care without sitagliptin in participants with type 2 diabetes mellitus (T2DM) having a history of cardiovascular (CV) disease and a hemoglobin A1c (HbA1c) of 6.5% to 8.0%. The primary cardiovascular outcome was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina, after a 3-year follow-up. In summary, among patients with type 2 DM and established cardiovascular disease, adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse complications.

Efficacy, Safety, and Tolerability Study of Sotagliflozin as Adjunct Therapy in Adult Patients With Type 1 Diabetes Mellitus Who Have Inadequate Glycemic Control With Insulin Therapy (inTandem2): Purpose: This Phase 3 study is intended to demonstrate superiority of either Sotagliflozin high dose or low dose versus placebo on glycosylated hemoglobin A1C (A1C) reduction at Week 24 when used as an adjunct in adult patients with type 1 diabetes mellitus (T1D) who have inadequate glycemic control with insulin therapy.

Conclusions

The term diabetes mellitus includes a group of metabolic disorders characterized by hyperglycemia with secondary damage to multiple organ systems such as end-stage renal disease, lower extremities amputations, and adult blindness. The way to improve this crucial situation is to find better drugs for an early treatment of the disease. The clinical trials, is so far, the best procedure to offer more efficient treatments to the increasing diabetic populations.

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References


