Chapter 5

Clinical Trials on Diabetes Mellitus

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Additional information is available at the end of the chapter

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1. Introduction

Today in the clinical practice Diabetes Mellitus (DM) has supplanted syphilis and tuberculosis as the big masquerade. Now, from the professional view, many physicians are involved in hard challenges, 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 many others and important clinical questions. Diabetes mellitus, the most common endocrine disorder, is characterized by several metabolic abnormalities and numerous 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 the discovery of insulin in 1921 by Banting and Best, and McLeod, it has been employed in the treatment of DM [1]. 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.

Insulin was obtained from a bovine source; and particularly porcine insulin differs only from the human insulin in one aminoacid. Later in the clinical practice, biosynthetic and semi-synthetic human insulin were introduced, having a structure identical to the native human insulin, and, for that circumstance without antigenic power. The semi-synthetic insulin comes from laboratory transpeptidation of porcine insulin (exchange of alanine by threonine of aminoacid B_{30}), while biosynthetic insulin is obtained by means of genetic recombination process from bacterias (*Escherichia coli*) or yeasts. Today, biosynthetic insulin is the most frequently used in some countries.

On the other hand, insulin is a polypeptide hormone synthesized in the beta cells of the islets of Langerhans of the endocrine pancreas, and it is necessary for normal metabolization of glucose by most cells of the body. In diabetic persons the capacity of body cells to use glucose is inhibited, thereby increasing blood sugar levels (hyperglycemia). When high levels of glucose are present in the blood, the excess must be excreted in the urine (glycosuria). The symptoms derived from the disease are increased urinary volume, thirst, itching, hunger, weight loss, and weakness; in medical expression the classical findings are well known: polyuria, polydipsia, polyphagia, slimming, and asthenia [2, 3].

Diabetes 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/1.73m^2 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, management of hypertension (salt reduction intake adequate diet, exercise and antihypertensive drugs) has become the most important intervention control all modalities of chronic kidney disease (CKD). The role of hypertension in renal disease is crucial. The aged world population is increasing. The ageing is the most common risk factor for the development of hypertension and diabetes, as well as CKD [4].

2. Historical evocation

Diabetes was known some millenniums before the Christian era, and it was in India where the disease was more deeply studied during the ancient age. The first data come from the *Ayurveda,* texts concerning medicine writings (sankrit texts). The word *Ayurveda* means knowledge or "science life"; it has profound roots on the philosophy and Hinduistic spirituality; it was developed between years 3000 and 500 b.C. on the valley rivers of the Indian civilization. Its knowledge was transmitted orally from generation to generation through the verses known as *vedas*. At that time some documents showed detailed information about unquenchable thirst –polydipsia-in the diabetic patients, increased urine –polyuria-, and sugar in urine –glycosuria-. Instead of sweetened and viscous consistency of the urine, they described other symptoms such as halitosis, digestive and respiratory disorders, somnolence, tuberculosis, and furunculosis. The autochthonous black ants indirectly helped to detect this pathology. The physicians observed how ants and flies congregated around the urine being attracted by its taste. Based on that circumstance, it was called honey urine. Also, they pointed out that diabetes were more frequent in obese people, usually taking rice and sweeten food.

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 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

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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. Celsus in the 1st century of our era established from his personal experience the "painless polyuria with dangerous emaciation". Areteus of Capadocia (century II), a Greek physician named the disease *diabetes;* in greek, *diabainein* means "to pass through", or "running throw" which is in relation to severe diuresis favourable to final outcome; and from Latin, *mellitus* (sweetened with honey). Claudius *Galenus* (3rd century) considered diabetes as a kidney disease. Thomas Willis (1621-1675) in 1675 found in the patients the sweetness of the urine, and William Cullen (1710-1790) proposed the term *mellitus*. The hereditary character of the disease was postulated by R. Morton in his text *Phthisiologia* (1689). Another historical event was made by P. Langerhans (1847-1888) when he described the pancreatic islets. Allen (1914) with an uniqueness criteria considered diabetes as a hereditary disorder of carbohydrate metabolism resulting in insufficient production of insulin. Since the discovery of insulin by Frederick Grant Banting, Charles Herbert Best and John Richard MacLeod, Nobel Prizes of Medicine in 1923, the prognosis of the disease is improving, although the *prevalence* still rises progressively from 5 % at age 20 to older people > 75 years.

The Canadian physiologist Frederick Grant Banting (1891-1941) and the medical student Charles Herbert Best (1899-1978) isolated insulin in Toronto in 1922. At that point, the new era on the treatment of diabetes was started. The results of the work by the German internist Oskar Minkowski (1858-1931) 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's islets placed in the pancreas.

Many researchers have dedicated their efforts to obtain the hormone against diabetes. In 1909, the Belgian Jean de Meyer named *insulin* the substance produced by the islets of Langerhans. Particularly, the internist Georg Ludwig Zülzer (1870-1949) was able to isolate after 1903 an effective compound. Nevertheless, two circumstances led him to abandon his work: a) uncontrollable toxic allergic reactions; and, b) overdose impossible to recognize for the absence of method of blood glucose determination. On July, 1921, the director of the Physiology Institute of Toronto, John James Richard MacLeod (1876-1935) provided to the young physician Frederick Grant Banting with a laboratory and ten dogs, and 21-year-old *student* Charles Herbert Best as his assistant. Banting and Best had been working to obtain insulin from a saline solution of triturated islets of pancreas. The extract was administered to diabetic dogs, by intravenous injection; simultaneously Best carried out continuous determinations of sugar in blood. This work made possible the new measuring methods that need only 0.2 ml of blood instead of 25 ml. After this finding Banting and Best studied better and easier procedures to obtain the hormone from cow fetus of four months. They discovered that the active substance was better extracted with acetone instead of acidulous alcohol. The decisive experiments were carried out between the 7 and 14th August of 1921.

After the first and successful achievements, MacLeod decided to interrupt any other investigation and focus on the insulin project: purification, control and manufacturing. The chemist James Bertram Collip (1892-1965) was able to obtain huge amounts of insulin and to success

to its standardization. The latter is of capital importance because overdose can produce muscle spasm due to hypoglycemia.

Since the end of the 19th century, researchers have found the relationship between the pancreas and the metabolic disease –diabetes-. Some of them pointed out that the clinical problems are produced by the lack of a hormonal substance secreted by the endocrine pancreas or Langerhan's islets, although the German Oskar Minkowski (1858-1931) and others investigators failed to isolate this hormone. Edward Albert Sharpey-Schafer (1850-1935) coined the word "insulin"; he considered that insulin controls the hydrocarbonate metabolism and that the absence of insulin will be followed by hyperglycemia and an increase of glucose in urine. After that conclusion, pancreatic extract was given to diabetic patients; but unfortunately, this attempt was unsuccessful because the hormone was destroyed by the proteolytic enzymes. Also, the technical procedures for blood and urine glucose determinations available were rudimentary and with little accuracy. After numerous attempts, researchers obtained more purified insulin to be used in the clinical practice. Insulin was used for the first time in 1922 in a 14-year-old diabetic boy, who presented good results; it was the first publication concerning the efficacy of insulin in humans and was published in the prestigious journal *Canadian Medical Association Journal*.

One year later, in 1923, the Medicine Nobel Prize was awarded to Banting and MacLeod for his crucial medical milestone. In 1926, Jakob Abel found the synthesis of insulin; this finding was published in the *Proceedings of the National Academy of Sciences*, Washington, with the article entitled *Crystalline insulin*. After that, the era of insulin was started.

As it is well known, there are two modalities of the disease: insulin dependent diabetes mellitus or IDDM (type I) found in young people requiring daily insulin injection; although most cases of IDDM appear before age 20, the disease can develop late in life. In these patients, the necessary insulin is not secreted by the pancreas and hence must be managed by parenteral way. On the other hand, Type II, non-insulin dependent diabetes mellitus (NIDDM), adult onset diabetes, can be controlled by strict dietary restriction of carbohydrates, oral hypoglycemic agents (blood-sugar-lowering) and also insulin in some particular patients. The situation coming from sluggish pancreatic insulin secretion and concomitant tissue resistance to secreted insulin worsens insulin secretion by the beta cells. Anyway, despite the previous classification as juvenile or adult diabetes, either type can be observed at any age; however, NIDDM is the most common clinical presentation found in up to 90 percent of all forms of diabetes. The risk factors predisponing to type 2 diabetes are pointed out in table 1.

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 [table 2]. 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. Nowadays, the goals of therapy with insulin or oral agents for varied circumstances is frequently hazardous [5]. This particular point explains the urgent necessity to find better drugs (more effective and well tolerated). The way to reach this goal is, undoubtedly, the *clinical investigation*; in others words, *clinical trials* [6].

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Family antecedents of diabetes (parents)
Obesity (Body Mass Index BMI >25 kg/m^2
Sedentarism
Race/ethnicity
Previously identified impaired fasting glucose (IFG), or impaired glucose tolerance (IGT)
Gravid diabetes mellitus (GDM)
HDL cholesterol < 35 mg/dl and/or triglyceride level > 250 mg/dl
Previous vascular disease
Acanthosis nigricans or polycistic ovary syndrome

Table 1. Risk factors predisposing to type 2 diabetes mellitus.

1. Symptoms of diabetes –polyuria, polyphagia, polydipsia, slimming or asthenia- plus random blood glucose level 200 mg/dl. Or
2. Fasting plasma glucose > 126 mg/ dl. Or
3. Two-hour plasma glucose (200 mg/dl) during an oral glucose tolerance test.
1) Random is considered at any time since the last meal
2) Fasting is defined as no food intake for previous 12 hours
3) Two-hours plasma glucose > 200 mg/dl during glucose tolerance test

Table 2. Clinical and laboratory criteria for diagnosis of diabetes mellitus

In 1912, two Boston researchers, F. G Benedict and Elliot P. Joslin, founder of the Joslin Diabetes Center –Boston-iniciated extensive metabolic balance studies in diabetic patients whose circulating blood glucose levels were high; they intended to control the disease by an strict dietary restriction of carbohydrates. And now, more than a century after the creation of the former institution, it continues the tradition of excellence recognized everywhere as a diabetes research, treatment, and teaching center. It is focused to improve the lives of persons with diabetes today and in the future. We now know that the excreted sugar coming from exogenous and endogenous proteins is converted in our body by the liver into glucose. But, in spite of the hard investigations, nowadays diabetes remains a difficult clinical problem mostly in the Western and developed countries.

3. Personal overview

Based on this controversial clinical status and related to our conventional duty since March 1990, our group in Granada (Spain) has created a *Hypertension and Lipid Unit*, and during the large *interim* period (twenty four years) until now, we have carried out a huge work by

participating in several international clinical studies –more than one hundred fifty-focused mostly on hypertension and diabetes, but also on lipid disorders and ischemic heart disease; many of them are well recognized everywhere by prestigious publications using acronyms titles for an easier identification of them: SYST-EUR, HYVET, CONVINCE, VALUE, ONTARGET, TRANSCEND, TECOS, STABILITY, SAVOR, ODISSEY, OMNEON, LIXILAN, as well as other works in process and others scheduled to start in the near future.

Our participation in clinical trials about diabetes represents a big and continual effort in the most relevant clinical research of this important and crucial area. We believe and hope that the abstract's information (clinical and pedagogical) contained in this article will be suitable to many physicians (practitioners, internists, cardiologists, endocrinologists), chemists, nurses and others health professionals. Unfortunately, nowadays the knowledge concerning clinical trials and it relevance for research and health is very poor not only for physicians but also for the general population. We would like that the present book and particularly this chapter will offer some attractive and available information for a better knowledge of diabetes mellitus and current medical challenges.

From this particular contribution we present to the reader a conventional design of clinical trials commonly used everywhere. *Sensu lato*, the primary objective is to provide better benefits to diabetic patients by the new non commercialized drugs (phases II, III of clinical trials) matched to ordinary ones or placebo. To reach the aim of this research it is mandatory to have a huge financial support coming from pharmaceutical companies, with the indispensable contribution of investigators, patients, data managers, physicians, auxiliary staff, technical support, computer experts, nurses, etc. In summary, the following twenty items represents a schematic example common in many clinical trials in which we participated.

4. Conventional clinical trial design

A clinical trial is intended to produce credible results answering the questions raised about a drug or treatment without exposing patients to unnecessary risks.

It thus requires rigorous scientific methodology:

- In choosing the options in the methodology (study design, protocol, development, calculation of sample size, statistical analysis) which are the subject of another work in this collection.
- In conducting the trial: this is the objective of the rules of Good Clinical Practice (in research): use of procedures that leave little room for improvisation, validated techniques, suitable working methods, qualified staff, a paper trail documenting all steps, data that can be verified post hoc, which are the subject of this book.

A clinical trial is a project which involves different tasks and the final quality of its conclusions depends on the wakest link in the chain of events. Therefore, it is important to make a major effort in ensuring the quality of each area of interest involved, i.e. quality of documents,

medical products, monitoring, follow-up of adverse events, and the computerized data processing. In addition, the quality of trial should be "auditable" at all times, and hence the need for quality in archieving all documents [table3].

	Screening	**Run-in**	**Randomization**	**Randomized**	**Post-trial**
	V1	**V2**	**V3**	**Treatment**	
	W-3	**W-2**	**Day 1**	**Phase**	
				V4….	
				Day 6	
Screening period					
Single-blind placebo run-in		X	X		
Double-blind Treatment period			X	X	
TRIAL PROCEDURES					
Obtain informed consent. Inclusion/exclusion criteria	X				
Medical history	X				
Weight	X	X	X	X	
Physical examination					
12-lead electrocardiogram (ECG)			X	X	
Adverse event monitoring		X	X	X	
Vital signs (pulse, rate and blood pressure (measured duplicate)	X	X	X	X	
INSTRUCTIONS/ COUNSELING					
Diet and exercise					
Dispense glucose meter					
Introduction on dose recording					
OTHER MONITORING TEST					
CENTRAL LABORATORY TESTS					
Hematology	X	X	X	X	

	Screening	Run-in	Randomization	Randomized	Post-trial
	V1	V2	V3	Treatment	
	W-3	W-2	Day 1	Phase	
				V4….	
				Day 6	
Chemistry panel	X	X	X		
Lipid Panel					
Fasting plasma Glucose (FPG)	X	X	X	X	
Hemoglobin A1c (A1c)	X	X	X		
Urinalysis	X				
STUDY MEDICATION					
Dispense single-blind		X	X		
Placebo medication	X				
Medication compliance	X	X	X		

V1: visit 1; V2: visit 2, W-3: week 3; W-2: week 2; FPG: fasting plasma glucose.

Table 3. Conventional Model of Trial Flowchart

1.	**PRINCIPLES**	
	1.1.	Declaration of principle
	1.2.	Organization charts
	1.3.	Definitions of function
	1.4.	Writing, management and revising procedures
	1.5.	Principles of planning studies
2.	**DOCUMENTS**	
	2.1.	Investigator's brochure
	2.2.	Protocol* (standard plan, approved cycle, amendments)
	2.3.	Case report forms* (standard pages, approval channel)
	2.4.	Operations manual
	2.5.	Study report
3.	**PROTECTION OF PERSONS***	
	3.1.	Submission of project to a committee
	3.2.	Writing the documents to obtain consent

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4.	**MONITORING***	
	4.1.	Initial visit(s)
	4.2.	Meeting to set up project
	4.3.	Intermediate visits
	4.4.	Final visit
	4.5.	Phone contacts
5.	**SERIOUS ADVERSE EVENTS**	
	5.1.	Definition of serious adverse events*
	5.2.	Collection, documentation of cases and follow-up
	5.3.	Reporting*
	5.4.	Causal relationship
	5.5.	Corrective measures
	5.6.	Crisis management
6.	**THE STUDY DRUG**	
	6.1.	Obtaining a standard drug (reference therapy)
	6.2.	Double-blind methodology
	6.3.	Jury of resemblance
	6.4.	Packaging*
	6.5.	Randomization list*
	6.6.	Labelling*
	6.7.	Release of finished product (pharmaceutical and for use)*
	6.8.	Dispatch – Reception*
	6.9.	Expiry date*
	6.10.	Drug accountability
	6.11.	Dispensing
	6.12.	Destruction
7.	**DATA**	
	7.1.	Progression cycle of CRFs
	7.2.	Deferred correction of data*
	7.3.	Coding
	7.4.	Computer entry of data
	7.5.	Test to validate data
	7.6.	Comprising a data base
	7.7.	Safeguards and protection

	7.8.	Computer systems (validation, documentation, use, security)
	7.9.	Statistical analysis
8.	**AUDIT AND INSPECTION**	
	8.1.	Audit of a study site
	8.2.	Audit of a study file
	8.3.	Systems audit
	8.4.	Preparation for inspection
9.	**LABORATORY VALUES**	
	9.1.	List of compulsory test
	9.2.	Quality control of assays
	9.3.	Centralized laboratory
10.	**DEVELOMENT**	
	10.1.	Designing a development plan
	10.2.	Monitoring a development plan
	10.3.	Coordination of a multicenter trial
	10.4.	Termination of a study center's participation
	10.5.	Termination of a trial
	10.6.	Termination of a product development
11.	**REGULATORY AFFAIRS**	
	11.1.	Declaration or request for authorization of a trial*
	11.2.	Relations with the competent authorities
	11.3.	Submission for registration
	11.4.	Insurance*
	11.5.	Import / export of drugs for clinical trials
	11.6.	Periodic reports
12.	**MISCELLANEOUS**	
	12.1.	Monitoring training programs
	12.2.	Trial with no direct individual benefit
	12.3.	Relations with sub-contractors
	12.4.	Corrective measures in case a document is lost
	12.5.	Publication
	12.6.	Abbreviations
	12.7.	Definitions
	12.8.	Archieving*

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The procedures for the most part can be written by referring to the following plan.

1.	**Introduction**
–	Title of procedure and name of company
–	Objetive (summary in a few lines)
–	Other procedures simultaneously involved
–	Personnel involved
–	Date and number of ongoing version with the wording: "replaces previous version of…"
–	Date of application
–	Name of person responsible who approved this version.
2.	**Responsibilities: "Who?"**
–	Status of persons(s) responsible for carrying out each task stipulated in the procedure (by job title and not by name)
–	Status of person responsible for seeing that a procedure was carried out.
3.	**Operations**
–	What?
	Definition of the task
	Where does the operation begin and end?
–	Where?
	In-house or on-site; parent company or subsidiary?
–	When?
	Start: "as soon as…" (receipt of a document…)
	End: minimum, maximum duration
	Chronological flow-chart of events
–	How?
	Systematic description of steps and methods to be used (equipment, personnel, documents)
	Options, or variations planned (specify circumstances)
	Unplanned: How and whom to refer to?
4.	**Verification of tasks performed**
–	One or more checklist (dated and signed)
–	Model and circulation of report or written note
–	Distribution list
–	Measures to be taken when a check reveals non-compliance
5.	**History**
–	Dates of validity of different versions and a very succinct presentation of the reasons for the revision (one or two lines per version)

CORE PROTOCOL	
1.	Objectives and hypotheses
–	Primary
–	Secondary

2.	Study Endpoints: Primary, Key secondary endpoints.
3.	Evidence of a personally signed and dated informed consent document indicating that the patient has been well informed about all aspects of the study.
4.	Subject/patients:
	4.1. Inclusion Criteria. Subject eligibility should be reviewed and documented by an appropriate qualified scientific study team before inclusion in the trial.
	4.2. Exclusion Criteria.
5.	Trial Design and Duration
6.	Pre-randomization visit.
	6.1. Randomization visit. Following completion of the run-in period, subjects will be randomized for active drug and in some cases for placebo. The goal for blood glucose, glycated 6.2. hemoglobin or other biological parameters has been established by any protocol submitted for investigation. For example, group 1 (drugs), group 2 (drugs or placebo).
7.	Trial Visits. General information. Informed Consent
8.	Follow-up of subjects.
9.	Drug supplies.
	These items include formulation and packaging, preparation and dispensing, administration, doses adjustments, drug storage, and accountability.
10.	Study Procedures.
	The specific procedures, including laboratory test to be performed at all study visits. Blood draw must be taken in the morning before 12.00 p.m.; ECG, and others parameters, and, in some cases, X-Ray, or other diagnostic imaging procedures. It must be taken in the same day in order to offer more facilities to patients.
11.	Data Collection.
	The case report forms to be used are designed to collect an appropriate amount of data necessary for the study.
12.	Administrative and Regulatory Details.
13.	Analysis of the End-point.
14.	Quality Control.
15.	Committees.
	The Coordinating Office and investigators will follow the principles of *Good Clinical Practice*. According with law, the trial information will be recorded in all electronic or papers forms and keep it during 10-15 years after the end of the study.
.	The Committee structure is very similar from one trial to another. The members of the committees will be detailed at the end of the publication, and also an appendix for acknowledgments will be provided
	On the other side, the members of the Data Monitoring Committee are not investigators of the trial. A National Coordinator for each country is desirable. The Steering Committee is responsible for agreeing the protocol, any change to the protocol and for the general running of the trial. The monitoring and statistical Committee (Data Monitoring Committee) will be responsible for quality control of the data, monitoring recruitment and other important aspects of the investigation.
16.	Data analysis / Statistical Methods. Steering Committee, Scientific Committee.
17.	Ethical aspects.
	Ethical conduct of the study.

	Subject information and consent.
	Subject recruitment.
18.	Definition of the end of trial.
19.	Periodical audit.
	During the study frequent external audit to the data and investigators will be done.

5. Diabetes mellitus a medical challenge

Type 2 Diabetes Mellitus (DM) accounts for more than 90% of all diabetes. This disorder is a worldwide epidemic affecting an estimate of 366 million adults aged 20-79 years, according to data from 2011. The prevalence of this metabolic disorder in adult population is expected to go from 8.3% to an estimate of 9.9% by 2030, resulting in an increase in the number of people with diabetes worldwide up to 552 million.

Unfortunately, many people are unaware that they have diabetes. The figures reveal that over six million Americans are undiagnosed. The proportion is very similar in other Western countries. The disease is commonly discovered when the typical symptoms, previously mentioned, are developed and high blood sugar levels are found, defined as a daytime level greater than 200 milligrams per deciliter or a fasting level greater than 120 milligrams per deciliter. In some cases oral glucose tolerance test is required for undiagnosed people.

The relationship between glycemia and the risk of microvascular disease has been well-established. The results of the *Diabetes Control and Complications Trial* (DCCT), the *United Kingdom Prospective Diabetes Study* (UKPDS) [7], and the *Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation* (ADVANCE) *Trial* [8], demonstrated that patients with DM treated to lower glycemic targets have reduced rates of microvascular complications (e.g., retinopathy and nephropathy). However, results of more recent trials including ADVANCE, the *Action to Control Cardiovascular Risk in Diabetes* (ACCORD), and *Veterans Affairs Diabetes Trial* (VADT) [9] aimed for an A1c <6.0, and ADVANCE aimed for an A1c<6.5%. These and other data have more recently led to a movement away from blanket prescriptive targets for A1C (e.g. <6.5% or <7%) and to the growing consensus among diabetes experts that glycemic targets and glucose-lowering therapies should be individualized. Age, weight, and comorbidities such as established cardiovascular disease, and kidney or liver disease are among the patient's factors that should be considered by physicians, nurses, family, and others. Diet, exercise, and education remain the main stay of treatment for diabetic patients in order to avoid serious complications [10]. In addition, there are several classes of oral antihyperglycemic agents (AHA) available for use as monotherapy or as combination therapy, including the dipeptidylpeptidase (DPP-4) inhibitor class, which is administered either once or twice daily [11, 12, 13].

In general, medication adherence in chronic diseases, such as diabetes may be low, ranging from 36% to 93%. Side effects associated with oral antihyperglycemic agents therapies, including hypoglycemia, (sulfonylureas, meglitinides, insulin), weight gain, (sulfonylureas, meglitinides, insulin, hypersensitivity reactions, thiazolidinediones) and gastrointestinal

intolerance, nausea, vomiting (metformin, alpha-glucosidase inhibitors) are common patient-reported reasons for poor medication adherence. Many studies have demonstrated that adherence to antihyperglycemic agents therapy is related to the number of pills prescribed: several studies have reported that, when patients were prescribed multiple drugs to treat diabetes, adherence significantly decreased, with reductions ranging from 15% to 54%. A prospective study showed a mean adherence of 79% for a triple-daily regimen, 65% for a twice-daily regimen, and 38% for a thrice-daily regimen. Some data from osteoporosis therapies indicate that, compared to a once-daily regimen, a once-weekly treatment can increase medication adherence and compliance. Therefore, a once-weekly oral AHA therapy might improve treatment adherence in many patients with these metabolic disorders.

6. Epidemiology and social relevance of diabetes

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

The prevalence 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 early detection of the disease. Another important feature of the disease is it chronic and progressive character that need treatment for life, acute and chronic complications, and high morbidity and mortality rate. 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 is 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 dysregulation 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; in other words, glycemic < 100 mg/dl, negative glycosuria and glycated hemoglobin < 6%.

All patients must be put on an appropriate diet personally designed to help them to reach and maintain normal body weight and to restrict their intake of carbohydrates and fats. They must be encouraged to exercise daily (at least 30 minutes walking), which improves the movement of glucose into muscle cells and blunts the rise in blood glucose that follows carbohydrate

ingestion. In all cases, the objective of diabetes treatment is to keep the level of blood sugar within normal values (90-100 mg/dl) as well as to reduce metabolic complications, such as diabetic ketoacidosis, hypoglycemia, hyperosmolar coma, or lactic acidosis, and late complications such as circulatory abnormalities, nephropathy, neuropathy, foot ulcers, frequent infections, and retinopathy (retinal changes leading to blindness).

Recent researches into the area of treatment include pancreas transplantation and implantable mechanical insulin infusion system, new medication, as oral hypoglycemic agents, different modalities of insulin, and recent monoclonal antibodies given by intradermal injection way.

From another point of view, it's well known that some clinical trials have demonstrated how angiotensin – converting enzyme (ACE) inhibitors decrease mortality for stroke, myocardial infarction, and other heart problems in patients with cardiovascular disease or high risk diabetes. Nevertheless, up to 20% of patients –mostly women-are unable to tolerate captopril, enalapril, ramipril or others ACE drugs mainly due to persistent and improductive cough, or even other side effects such as hypotension, renal dysfunction or angioneurotic edema, according to our personal experience [14, 15]. *The Action in Diabetes and Vascular Disease: preterAx and DiamicroN Controlled Evaluation* (ADVANCE) Trial, using perindopril combined with gliclazide was designed to assess outcome of macrovascular and microvascular disease on diabetic patients [15]. Ramipril did not affect heart failure events in low-risk patients according to the findings reported in the DREAM Study [16]. It's possible to believe that when the absolute risk of heart failure is low, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are not able to reduce the incidence of heart failure. Myocardial infarction rate was lower in TRASCEND study compared to HOPE trial. It is possibly due to that patients included in the TRASCEND study were at lower risk compared with those admitted in HOPE (Heart Outcomes Prevention Evaluation) Study Ongoing Trial [17]; the population of women was about 40% in the TRASCEND study while only 2% was reported in ONTARGET trial, and other previous studies of ACE inhibitors.

It is also important to realize, according to numerous clinical experiences and data from TRASCEND study, that telmisartan (angiotensin-receptor blockers) could be regarded as a potential treatment for patients with vascular disease or high-risk diabetes when the patients are unable to tolerate antihypertensive drugs as ACE inhibitors.

Concerning hypertension and based on data from many large-scale clinical trials, international guidelines recommend two drugs with subsequent complementary mechanisms of action to control BP in most patients, with initial combination therapy when Systolic Blood Pressure (SBP) is 150 mmHg or Diastolic Blood Pressure (DBP) is > 100 mmHg above target [18, 19]. These guidelines also favour the use of a fixed dose combination for the clinical practice [20].

From the clinical point of view, it is significant to understand the strong pathophysiological relationship between diabetes and hypertension. The latter is predicted to rise dramatically with a number of cases expected to reach 1560 million worldwide by 2025 [21]. Unfortunately, this is coupled with low rates of BP control (target <130/80 mmHg), despite the increased use of antihypertensive treatment. It must be emphasized an early and sustained BP control in order to reduce the long-term burden associated with this condition. To address challenges

for now and the future, some international guidelines recommend early treatment with agents that have complementary mechanism of action. These combinations have benefits related to compliance, efficacy and safety for the patients.

The difficulty in getting good metabolic and clinical control of BP in many patients, may result in the development of acute clinical disorders or chronic complications. Physicians must keep in mind when the patient develops acute confusional states or coma; these events could be due to DM *per se*, or other pathologies developed in those patients, such as hepatic failure, renal disease, stroke, respiratory distress, poisoning or drug overdose; the distinction between coma secondary to inadequate level of insulin, and non diabetic disease is crucial for the prognosis of the patients.

7. Acute metabolic complications

Patients with diabetes are susceptible to four acute metabolic complications: hypoglycemia, ketoacidosis, hyperosmolar and lactic acidosis. All of them can result in coma. The two first are complications of IDDM, while the other two are usually developed in the setting of NIDDM. These clinical situations must be considered completely different from severe disorders that occur not related to DM *per se* such as stroke, acute heart failure, hepatic dysfunction, in others words: *coma* in *diabetic patients* is completely different for *diabetic coma*.

Unfortunately, a lot of patients developed coma situations despite the treatments available, generally caused by incorrect dose, or medication missed dose. This is the relevant point to consider other possibilities, and the way is clinical trial.

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

Hyperosmolar coma. This modality of acute diabetes complication is usually due to NIDDM. It is characterized by a profound dehydration resulting from a sustained hyperglycemic diuresis by situations in which the patient is unable to drink enough water to keep up normal urinary excretion of detritus. This situation commonly 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, the use of osmotic agents such as manitol and urea. Clinically, 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 others infections are also very common. Bleeding probably caused by disseminated intravascular coagulation, acute pancreatitis and widespread thrombosis is usually found at necropsy.

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Lactic acidosis. It is a serious clinical finding that can occur because of an increase in endogenous lactic acid, the final step of the carbohydrate metabolism. That causes profound effects on the respiratory, cardiac and nervous systems. The blood pH drop 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, or in such patients even coma. The prognosis is very bad and most of the patients die soon.

8. Late complications

Diabetic patients are susceptible to developing several complications responsible for morbidity and early mortality; some of them do not present problems, whereas in others, complications appear early, usually after the appearance of the hyperglycemic symptoms developed between 15 and 20 years after the onset of the disease [table 4]. The clinical findings showed the following circulatory abnormalities: atherosclerosis, coronary artery disease, stroke, heart failure, peripheral vascular disease and left ventricular failure.

Microvascular Complications
Ocular disease
Retinopathy
Proliferative
Nonproliferative
Neuropathy
Mono-and polyneuropathy
Nephropathy
Macrovascular complications
Coronary artery disease
Peripheral vascular disease
Stroke
Others
Infections
Dermatology problems
Genitourinary (sexual dysfunction)
Cataracts
Psychological disorders
Glaucoma

Table 4. Late complications developed in diabetic patients

8.1. Diabetic retinopathy

Is a relevant cause of blindness; however a high number of diabetic patients never lose the vision. When the occlusion of retinal capillaries occurs, it results in a subsequent formation of saccular and fusiform aneurysm and arteriovenous shunt. Hemorrhages into the inner retinal surface are dot-shaped; conversely, bleeding into the superficial larger nerve fiber produces flame-shaped, blot-shaped or linear lesions. Cotton-wool spots can be observed by angiography, and sudden increase of the number of these lesions has an ominous prognostic sign and is the beginning of rapid progress of retinopathy. Hard exudates are common findings and are probably related to leakage of protein and lipids from damaged capillaries. The lesions must be summarized into two categories: *simple* (microaneurysms, dilated veins, hard exudates, arteriovenous shunts, hemorrhage, cotton-wool spots, increased capillary permeability and capillary closure, and dilation) and *proliferative*: new vessels, vitreous hemorrhage, retinitis proliferans (scar) and retinal detachment.

8.2. Renal disease

Despite the worldwide importance of diabetic nephropathy as a cause of mortality and morbidity, many questions still remain about treatment aimed at delaying its harmful effects [22, 23]. So far, there is little scientific evidence to support strict glycemic control at this stage, although common sense dictates that wild swings of control should be avoided. Protein restriction may have a role but the studies to support this have not been forthcoming.

9. Circulatory changes

We recognize hypertension and DM as common disorders, but there is much evidence to suggest that the two occur together more frequently than by chance. Development of hypertension greatly worsens the prognosis of diabetic patients. Raised BP accelerates the progress of diabetic nephropathy, and possibly retinopathy, while the harmful 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 contribution.

Life expectancy is reduced in diabetic patients, both insulin-dependent (IDDM) and non-insulin dependent (NIDDM), and the leading causes 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, Jarrett and 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, the

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clinical significance of hypertension as an important risk factor was recently strongly supported by two independent studies on IDDM patients, demonstrating an improved survival rate in the decade following the introduction of efficient antihypertensive drugs.

Hypertension is a community problem everywhere with hazardous solution. It is the major risk factor for development and progression of the disease in non-diabetic and diabetic chronic kidney disease. About one billion people worldwide have high BP (defined as > 140/90 mmHg), but the number is higher considering the present criteria of >130/80 mmHg, and it is expected to increase up to 1.56 billion patients by 2025. The predicted prevalence of hypertension will increase by 24 per cent in developed countries.

Hypertension control rate, defined as BP level < 130/80 mmHg, is substantially lower in patients with CKD, particularly in those with diabetes and chronic renal failure. This is illustrated by the National Kidney Foundation's (USA) Kidney Early Evaluation Program (KEEP), a US-based health screening program for individuals at a high risk for kidney disease.

Hypertension is the most prevalent cardiovascular disease in the world and a major public health issue. Cardiovascular disease is the leading cause of mortality worldwide and is expected to increase with the general ageing of the world's population. The goal of antihypertensive therapy is to reduce the incidence of blood pressure-related morbid events and cardiovascular mortality.

It is well established that heart is an important target organ in hypertension. Continuous high BP level is associated with myocardial problems, such as left ventricular hypertrophy and increases the burden of coronary artery disease (CAD). These forms of damage may result in congestive heart failure, CAD manifestations, arrhythmias and sudden cardiac death. The event rates of cardiovascular disease in Japan, for example, differ from those in Europe and the United States. Mortality from CAD in the Japanese country is one-third that of the United States, and mortality from cerebrovascular disease is 1.5 times higher in Japan than that reported in the United States. Hypertension is the most common cause of disease and is even more prevalent in the Japanese population than in the Western countries. The percentage of cerebral bleeding is two or three times greater than in Caucasian people from Europe and the United States, and cerebral infarction is mostly caused by lacunar type ischemic stroke owing to hypertensive small vessel disease. The incidence of athero-thrombotic infarction or cardioembolic infarction is currently increasing in Japan, and the dominant pathogenetic factor for stroke is changing from small arterial disease to large arterial disease in Japanese hypertensive patients. These differences may be partly explained by differences in the lifestyle of Japanese and Western populations, which are reflected in body mass index (mean BMI: 23.25 and 28-30 kg/m^2, respectively). However, most of mortality-morbidity trials have been carried out in the Western countries, in which none or only a minority of East Asian patients were included. Owing to the scarcity of large-scale trials in East Asian people, it remains to be determined whether the results from similar clinical trials in Western societies are internationally applicable to East Asian races or the Japanese population, or whether genetic background can cause different pharmacokinetic and pharmacodynamic responses to the same drug.

There is a clear and substantial evidence in juvenile onset IDDM that strict BP control by reducing and maintaining levels under 130/80 mmHg or a mean arterial pressure of 105 mmHg remains the only effective treatment for the physician to try to slow the development of end stage renal failure and the need for renal support. In practical terms, the use of a combination of drugs including diuretics will be often required. The newer classes of drugs such as ACE inhibitor or calcium channel blockers have a clear advantage in their side-effect profile over betablockers in diabetics, because they are safer and better tolerated. The primary goal remains effective in BP control and often beta-blockers may need to be added to the regime to achieve this.

In patients with IDDM aged older than sixty and in diabetics with nephropathy who are non-insulin dependent, there is no definitive scientific evidence that prognosis is improved and that the progression to end stage disease is slowed after antihypertensive treatment. It is reasonable for the physician to assume that aggressive treatment of BP in this group is justified from data of several studies in younger patients. A crucial question remains about the degree of BP reduction required and in particular whether it is necessary or indeed harmful to aggressively reduce systolic BP in this group. Accurate long-term clinical trials with measurement of cardiovascular end points as well as the slowing of GFR decline and reduction of proteinuria need to be carried out. Indeed, it is important to reach normal BP levels especially on the stage of incipient nephropathy in order to obtain better therapeutic results in patients.

Large scale, long-term multicenter studies in both IDDM and NIDDM patients with proteinuria will be required to give a clear answer to the question of whether there is a selective benefit of the ACE inhibitor group over a suitable hypotensive agent such as a calcium channel blockers. So far, there is some evidence that ACE inhibitors used in the evolution of nephropathy or when employed later in combination with diuretics are effective in reducing protein excretion which may be separate from their BP lowering capacities. These data, make them a reasonable choice in the antihypertensive regime of diabetics with nephropathy. This property to reduce proteinuria without reducing BP has not been shown with any other antihypertensive agents and until and unless such evidence is forthcoming, the careful use of ACE inhibitors in combination with diuretics can be recommended in diabetic nephropathy. As many of these patients will have occult or manifest cardiovascular dysfunction, this approach may be beneficial also in improving cardiac performance. Future studies, especially in non insulin-dependent patients should evaluate the potential benefit of reducing morbidity and mortality from cardiovascular disease with the newer antihypertensive drugs, such as ARA II.

Coexisting hypertension and diabetes act as additive risk factors to accelerate vascular complications. The incidence of coronary and cerebral vascular diseases is much higher in hypertensive than in normotensive diabetic patients. Mortality rates in diabetic patients with systolic BP exceeding 160 mmHg is four times higher than that of other diabetic individuals. Whereas antihypertensive therapy has been clearly shown to retard deterioration of renal function and urinary albumin excretion, evidence that pharmacological control of BP reduces overall mortality in the diabetic population without overt nephropathy is strikingly lacking. Thus, current recommendations for drug intervention in diabetics with hypertension rely on data derived from the general hypertensive population. Specific adjustments in drug selection

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and dosage need to be made for drug effects which might be of particular significance in the diabetic patient. Nevertheless, a recent alarming retrospective study from the Joslin Clinic demonstrated that antihypertensive treatment is associated with a marked increase in cardiovascular mortality in diabetic hypertensive patients. The most obvious implication of this finding is the need for large scale prospective studies in diabetic hypertensive individuals to assess the risks and benefits in treating hypertension in this population. Some of the newest strategies for BP control must be examined and compared with these retrospective findings. Until further information becomes available, much attention should be given to careful drug selection, therapy monitoring, and judicious and continuous assessment of coexisting risk factors in the course of treatment of high BP in diabetes.

10. Etiology of chronic diabetes complications

The cause of diabetic complications is still unknown and probably multifactorial. Chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality. Special attention must be given to the metabolic conversion of glucose to sorbitol. This one is implicated in the pathogenesis of neuropathy, retinopathy, aortic disease, nephropathy and lens damage (cataracts). Another mechanism of possible pathogenetic relevance is glycation of proteins. The effect of glycation on hemoglobin is well known; in addition, other proteins are altered by the same mechanism such as plasma albumin, fibrin, collagen, lipoproteins, and low protein. Retinopathy, nephropathy and neuropathy are considered common disorders of microvascular complications; and stroke, gangrene, and myocardial infarction for macrovascular complications [table 4].

11. Can diabetic complications be prevented?

This is an important and fascinating question strongly related with the patient prognosis. Hyperglycemia or other aspects of the abnormal metabolism of diabetes are responsible for the development of complications; additional factors, which maybe genetic, have also a pathogenic influence. The clinical practice shows the mistery; how diabetic patients suffering for decades from poor control are free of late complications; however typical complications can be found at the time of diabetes diagnosis, even in the absence of fasting hyperglycemia. Intensive therapy for all diabetic patients with strict dietary control is essential. The role of the family doctor, specialist and other professionals –nurses, nutritionists, auxiliary persons, etc-, are very important for these particular patients.

12. Miscellaneous findings on diabetes

Because diabetes affects almost every body systems, the patients can develop several symptoms and complications. The chapter of I*nfections* is large. In some cases this finding may not

occur more frequently than in non diabetic population, but it seem to be more severe probably because in diabetic patients leukocyte function is impaired and subsequently accompanied by poor control. Also this population is particularly prone to four unusual infections with strong relationship with diabetes –focus on skin, urinary tract, lungs, and bloodstream. *Malignant external otitis*, usually due to *Pseudomonas aeruginosa* tends to appear in older population and is characterized by severe pain in the ear, fever, and leukocytosis. The facial nerve becomes paralyzed in 50% of the cases, but other crucial nerves can be involved. *Emphysematous cholecystitis* tends to affect diabetic men and diagnosis is established when gas is seen in the gallbladder wall or during non invasive imaging examination.

Hypertriglyceridemia is common in diabetics and is related to overproduction of VLDL (*Very Low Density Lipoprotein*) in the liver and to a defect of metabolization on the peripheral tissues. The latter is due to a deficiency of lipoprotein lipase, an insulin-dependent-enzyme. It is important to know that some patients have high level of lipids profile even when diabetic disease is controlled; probably these cases have a primary familial hyperlipoproteinemia, a circumstance independent of DM. Of course, these patients must be treated for lipids disorder –hypertriglyceridemia and lipids hypercholesterolemia with HMG-CoA reductase inhibitors such as lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, as mode of action that reduces cholesterol synthesis and increases LDL receptors; ezetimibe reduces the absorption of lipids from diet at the intestinal level; and fibric acid derivatives –↓ LPD and tryglyceride, hydrolysis, VLDL synthesis, ↑ LDL catabolism. Patients can also suffer from a variety of skin lesions: necrobiosis lipoidica diabeticorum, candida albicans, vaginal moniliasis, in women, hypertrophy of fat, bullosis diabeticorum, diabetic dermopathy, atrophy of adipose tissue, Dupuytren's contractures, and schleroderma. Additional illnesses such as the prevalence of eating disorders can be seen particularly in young women.

13. Physical examinations of diabetic patients

Either complete physical examination or brief physical examination will be performed at the time points specified in the Time and Events Table.

The complete physical examination will include evaluation of the following organ or body systems:

- Skin (including injection site)
- Head, eyes, ears, nose, and throat
- Thyroid
- Respiratory system
- CV system, BP
- Abdomen (liver, spleen)
- Lymph nodes (neck, axilas, inguinal)

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- Central nervous system
- Extremities

The brief physical examination will include evaluation of the following organ or body systems:

- Skin (including injection site)
- Respiratory system
- CV system
- Abdomen (liver, spleen)
- Central nervous system

14. Conclusions

The term of diabetes mellitus includes a group of some 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 ameliorate this crucial situation is to obtain better drugs for an early treatment of the patients. The clinical trials, is so far, the best procedure to offer more efficient treatments to the increasing diabetic population, thanks to the procedures of clinical trials [24, 25].

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