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Type 1 Diabetes Mellitus: a century of approach
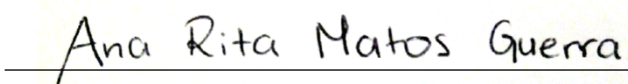
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Type 1Diabetes Mellitus: a century of approach

Dissertation of candidacy for Master's Degree in Medicine by Instituto de Ciências Biomédicas Abel Salazar - University of Porto

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"Aqueles que passam por nós não vão sós,
deixam um pouco de si e levam um pouco de nós."

– Antoine de Saint-Exupéry

Resumo

Diabetes Mellitus tipo 1, é um problema de saúde pública que afeta mais de meio milhão de indivíduos em todo o mundo, segundo dados de 2015 da International Diabetes Federation (IDF).

Estando as doenças endócrino-metabólicas no âmago da atenção, pelo menos na última década, é importante reconhecer todo o caminho evolutivo, desde técnicas de diagnóstico, tratamento e gestão do doente, até então desenvolvidas e identificar todo o espaço para progressão que é ainda possível percorrer.

O reconhecimento da Diabetes enquanto patologia não é recente, contudo, recentemente o progresso do conhecimento da doença e do seu tratamento, tem sido exponencial e cada vez mais rápido. Apesar da longa história, o conhecimento em relação a otimização terapêutica, a prevenção e fatores modificadores da doença estão longe de ser satisfatórios. Estudos recentes visam na tentativa de reconhecer os fatores de risco da doença e o seu mecanismo. Com isto, perceber se há caminho para trabalhar na prevenção e/ou atrasar o aparecimento da patologia.

A introdução de novas terapêuticas mais eficazes tem sido intensificada especialmente desde o início do século XXI. Estas têm como objetivo melhorar a qualidade de vida destes doentes que sofrem de uma patologia crónica, estando a cura longe de ser uma realidade. Ouvimos já falar em pâncreas artificial e novas terapêuticas celulares, que são a antítese perfeita do que estava disponível não há muito tempo atrás.

O objetivo da revisão é fazer uma abordagem histórica da gestão dos doentes com Diabetes Mellitus 1, tendo por base as evidências e informação disponíveis na literatura, em artigos de revisão, trabalhos de investigação e livros disponíveis considerados essenciais e relacionados com os objetivos propostos.

Abstract

Type 1 Diabetes Mellitus is a public health problem that affects more than half a million individuals worldwide, according to 2015 data from the International Diabetes Federation (IDF).

With endocrine-metabolic diseases at the heart of care, at least in the last decade, it is important to recognize the whole evolutionary path, from diagnostic techniques to treatment and management until now developed. As well as identify all the room for progression that is still possible to go through.

The recognition of Diabetes as a pathology is not recent, however, in the past few years the knowledge about the disease and its treatment have been exponential and increasingly faster. Despite the long history, knowledge regarding therapeutic optimization, prevention and disease modifying factors are far from satisfactory. Recent studies are aimed at recognizing the risk factors of the disease and its mechanism, in order to observe if efforts made in prevention to extend disease free period is walking in a valid direction.

The introduction of more effective therapies has been intensified especially since the beginning of the 21st century. These are intended to improve the quality of life of these patients suffering from a chronic pathology, being the cure far from a reality. We have heard of artificial pancreas and new cellular therapies, which are the perfect antithesis of what was available not so long ago.

The aim of this review is to take a historical approach to the management of patients with Type 1 Diabetes Mellitus, based on the evidence and information available in the literature, review articles, research papers and books considered essential and related to the proposed objectives.

Abbreviations

A.D.= Anno Domini
ADA= American Diabetes Association
B.C.= Before Christ
CGM= Continuous Glucose Monitoring
CSII= Continuous Subcutaneous Insulin Infusion
DCCT= Diabetes Control and Complications Trial
DKA= Diabetic Ketoacidosis
Fiasp= Fast acting insulin aspart
FSL= Freestyle Libre
IA= Insulin autoantibodies
ICA= Islet cell autoantibodies
IDF= International Diabetes Federation
GAD= Glutamic Acid Decarboxylase
GDM= Gestational Diabetes Mellitus
HbA1c= Glycated hemoglobine
MDI= Multiple Doses of Insulin
SMBG= Self-monitoring of Blood Glucose
T1D= Type 1 Diabetes
T2D= Type 2 Diabetes

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1. Introduction

Diabetes has a long history reaching back into antiquity. However, during that period, due to poor knowledge of anatomy, pathophysiology and lack of diagnostic tools, the disease remained really mystifying to physicians.[1]

Nowadays, it is recognized as an emerging global epidemic, representing one of the leading causes of morbidity and mortality worldwide, being considered the epidemy of the 21st century.[2]

Recognizing that hyperglycemia is the hallmark of the disease was the turning point for uncovering the so far incomprehensible disease. Furthermore, the discovery of the hormone responsible for glycemic control: insulin. In the current days, the knowledge is wider, and insulin is identified as an anabolic hormone (composed of 51 - amino acids and divided into two peptide chains), and a key regulator of glucose, protein and adipose homeostasis.[3,4] Insulin is synthesized as proinsulin, then processed and secreted by pancreatic β-cells (Langerhans islets) into the portal circulation through the hepatic vein; thereafter the liver extracts a substantial fraction before entering the systemic circulation.[5] In healthy individuals, insulin production follows a basic pattern where basal levels are secreted during fasting periods, and prandial increases are associated with food ingestion.[6] It is essential in the regulation of carbohydrate metabolism, acting to increase the transport of glucose from the blood into muscle and adipose tissue after meals, and to regulate the rate of hepatic glucose production when fasting. Continuous basal insulin secretion from the pancreatic β-cells is needed to regulate the production of glucose from the liver with more prolonged fasting, such as during the overnight period.[6]

When the body cannot produce enough insulin or cannot use it properly, the result is high blood glucose levels. [4,7] According to the American Diabetes Association (ADA), diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[8]

Even though the classification of diabetes is important and has inference for the treatment strategies, it is not straight forward and many patients do not easily fit into a single class especially younger adults.[9] The classical grouping of diabetes as presented by ADA in 1997 as type 1 (T1D), type 2 (T2D), other types, and gestational diabetes mellitus (GDM) is still the most recognized classification.[9]

T1D counts for 5-10% of all patients , and despite being diagnosed at any age, it is more common in childhood.[8,10] Presentation peaks occur between 5–7 years old and at or near puberty.[10]

Presently, T1D is describe as an immune-mediated disease, resulting from pancreas β-cells destruction through T-cell mediated inflammatory response (insulitis), as well as a humoral (B-cell) response, leading to partial, or in most cases, absolute insulin deficiency.[8,9,11] When approximately 90% of pancreatic β-cells are destroyed it becomes clinically symptomatic.[11] However it is not possible to predict it as destruction happens at a variable rate in each individual.[11]

In the past, it was considered a disorder affecting children and adolescents, but this perception has changed over the past decade. For that, age at symptomatic onset is no longer a narrow factor.[10] The knowledge that the disease etiology is multifactorial is not enough, since the specific roles for genetic susceptibility, environmental factors and their part in the immunologic dysregulation underlying T1D remain unclear.[11,12]

The presence of autoantibodies which include islet cell autoantibodies (ICA), insulin autoantibodies (IA), glutamic acid decarboxylase autoantibodies (GAD65) and autoantibodies to the tyrosine phosphatases (IA-2 and IA-2β), are the key to understanding its pathogenesis.[8,9] T1D has a strong genetic association with two chromosomal regions.[12] These are the HLA class II at the short arm of chromosome 6 and the insulin gene region at chromosome 11.[12] HLA- DR3 and HLA-DR4 are involved primarily in the genetic predisposition of T1D.[12] The insulin gene region on chromosome 11 is the second most important.[12]

With genetics explaining only 30-40% of T1D total risk , environmental risk factors in early life have been proposed as possible influences.[9,13] The hypothesis is that it may result in β-cell function progressive loss that is manifested clinically by hyperglycemia.[14] The mechanism remains controversial, but recent evidence supports the causative effect of viral infections in diabetes, such as enterovirus, rotavirus, herpes virus, cytomegalovirus, and others.[9] The descriptive model is based on a process of molecular mimicry, as these pathogens have tropism to human pancreatic islets. Herewith, the components of microorganisms are taken as self-molecules and are not attacked by the T lymphocytes.[15] With the marked reduction on T cell proliferative response in T1D patients and the recruitment of cytotoxic T cells that induce the β-cells (specifically of islets) destruction ,it results in the absence of insulin production.[12] Other environmental factors such as low vitamin D levels, prenatal exposure to contaminants, early introduction of cow's

milk, improved hygiene and living conditions (with decreased childhood infections leading to increased autoimmune diseases) began to be described in the literature, but this was not proven to be causative. [9,12] Insulin resistance in early childhood (due to obesity or increased height growth velocity) causing pancreatic stress was also not well substantiated by literature.[9,12]

The number of people whit T1D is increasing and the reasons for this are still unclear but may result from changes in environmental factors as viral infections.[7]

Common symptoms are polyuria, polydipsia, enuresis, lack of energy, extreme tiredness, sudden weight loss, slow-healing wound and recurrent infections.[14] However, the onset of type 1 diabetes can develop suddenly and may be more variable in adults. On the other hand, they may not present with the classic symptoms seen in children.[9,14] One-third of children diagnosed with T1D present with diabetic ketoacidosis (DKA).[9,14]

DKA has a wide range of symptoms, from mild to severe hyperglycemia, acidosis, dehydration, and coma.[14] This increases the childhood mortality associated with diabetes by 50% .[10] In addition to this condition, there are other long term morbidities of this disease, such as microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications (hypertension, attainment of large blood vessels leading to coronary disease, brain disease and lower limb arterial disease).[16] Glycemic control is fundamental to diabetes management in order to decrease the occurrence of these events.[5]

Incidence of T1D is increasing at a frighteningly fast pace. The disease and its complications bring substantial economic loss to patients and their families, to health systems and to national economies through direct medical costs and loss of work and wages.[17] This paper has the purpose to compile the evolution of the diagnosis, monitoring and treatment of T1D. In a disease that will be highly prevalent in the near future, it is important to identify the path further to be discovered with the ambition of enhancing the quality of life of these patients as much as possible.

2. Methods

A bibliographic search was performed in MEDLINE, through the PubMed search engine, with the combination of the following keywords: type 1 diabetes, diagnose, monitorization, treatment, insulin-pumps and new treatments. The selection comprises the time period between 1970 and January 2019. Articles in Portuguese or English were incorporated. It includes original articles, review articles and grey literature. The selection was made through the abstract reading , excluding those that did not fall within the ambit of this review. Inclusion criteria were based on the fact that the articles report the pathology history , not integrating the criteria those who were too specific to an approach (for example mechanism of action of a drug, and diagnostic techniques)

In addition, information from the official website of the Diabetes Museum in Munich was used, with authors prior authorization. Also, international standards and books considered relevant to the topic were consulted.

3. T1D: Now… and then?

The term Diabetes was introduced into medical nomenclature by Aretaeus, 2nd century A.D., and arises from the Greek verb *diabaino*, which means "I pass through", being Diabetes the condition that makes fluids run through.[1,18,19] The term Mellitus was only introduced in the 17th century by Thomas Willis, due to the sweetness of the urine in those patients.[1]

The history of diabetes starts way back in the past, when first signs of the disease description were found in ancient Egypt Papyrus, called Ebers Papyrus, written around 1552 B.C.[18-20] By the time, there was no name for the disease, only the description of a pathology extensively marked by excessive urination.[4] Many years passed until the middle ages when Paracelsus described it as a hormonal disorder.[4] But, it was in 1788, that Thomas Crawley first discovered the link between the pancreas and diabetes, a very important turning point for the fast development of what we now know about this pathology.[19]

Over the years, there have been many advances and discoveries, but it took around one hundred years (1869) for Paul Langerhans to describe the insulin-producing cells in the pancreas tissues and its implication on the disease.[4,19]

The next major anatomical and physiological findings that have changed the view of the disease happened just over the past decade. A substantial growth, particularly with regard to disease prediction and heterogeneity, pancreatic pathology, and epidemiology, helping patients with T1D to manage the challenge of lifelong insulin administration.[10]

4. Monitorization

4.1. From glycosuria to glycemia

In ancient times, the description of a honey-sweet urine would allow the diagnose. Between 476 and 1000 A.D, there were contracted people called "water testers" who diagnosed the disease by tasting the urine.[19]

The first test to detect sugar in the urine was created in 1791 by Johann Peter Frank, a German physician.[19]

John Rollo, a military surgeon, was the first to publish a book about diabetes based in clinical cases of the military hospital, named *Cases of the Diabetes Mellitus* (1797).[21] Rollo intensively worked with Matthew Dobson, and together they first questioned if this high sugar levels could be present in the blood too.[19,22] Despite that, it was not until the early 19th century that glucose was identified as the sugar present in blood. This association was supported in 1838, when George Rees isolated blood serum sugar of a diabetic patient.[20] Despite being an important finding once it changed the perspective of the disease, the mechanism by which sugar excess happened was still unknown, [19]

Unfortunately, the accurate concept had to be delayed since it was on a time where the correct blood sampling was still far to be known.[18]

Further advances were postponed until 1845 when some researchers could process the blood and calculate sugar weight using copper reduction and gravimetric measurement.[18,20]

However, all required measurement equipment at that time, such as the colorimeter (Fig.1) and polarimeter (Fig.2), required high amounts of blood and urine respectively. Thus, being a disadvantage in the sequenced measurement of glucose.[18] Regardless continuous improvements in reducing sample volume, and improving stability and precision, manual blood sugar estimations in the laboratory were still limited and mainly confined to diagnosis and critical care management, rather than available for monitoring purposes.[20]

Hyperglycemia is the hallmark of the diabetic state, and all the developments from this point focused on the blood glucose value accuracy .[23]

4.2. Ketonuria and the discovery of blood ketones

Urine ketone testing (ketonuria) appeared before fast blood glucose determination and became an important part of T1D monitoring.[23] Ketones are organic compounds that result when body fat is broken down for energy. High levels can be toxic and dangerous for the patient.[3] Current recommendations are that ketones should be checked for if blood sugar is repeatedly over 250 mg/dl for no apparent reason.[15,24] Measuring can be done by urine ketone strips or blood ketones meters.[23] However, ketonemia is more sensitive and clinically useful compared to ketonuria since the results are in real time.[20]

4.3. 1964- The turning point. Glucometers evolution.

The upheaval of diabetes diagnosis and monitorization happened in 1964 when an American company developed a visually read strip method for rapid estimation of blood glucose, named Dextrostix.[18,25] This was an advantage especially for health units with limited access to laboratories.[25] The simple method (a large blood drop from the ear lobe or finger, printed on the strip) and the easy results reading (a color chart with a range between 40 and 200 mg/100ml) motivated its fast implementation on the market. Blood sugar tests would be expected to yield more diabetic patients than sugar urine tests, which implied laboratory evaluation.[25] At this time, measurement of 150 mg/100mL or more would prove the diagnose of diabetes.[25] The development in 1970 of an instrument, Reflectance Meter (Fig.3), that provided the patient electronically self-monitoring blood sugar level was an advantage.[26] However, by this time, the device weight was 1.2 kg (mainly due to its casing and lead-acid rechargeable batteries)[20] not allowing the portable transport, and for that, being only used in the context of clinical practice.[18]

For many years, numerous companies worked to provide better and more comfortable devices.[18] The active phase in the meters evolution occurred in the 1980s, with the devices becoming easier to use, smaller in size, with more variation in design, and often with software memory to store and retrieve results. Reagent strips were also changing to accept smaller volumes of blood, and some were barcoded for autocalibration and quality assurance.[20] As the size reduced, the quality and efficiency got better, and in 1984 the first digital devices entered the market.[18] The ability of data storage was integrated by 1987 providing important information to caregivers. (Fig.4) [18]

By the mid-1980s, the patient's capillary glucose replaced the urine tests as the gold standard method for daily monitoring and diagnosis.[15] The correlation between urine and plasma glucose has shown to be inconsistent. Consequently, blood became the preferred sample, more easily collected by fingertip capillary puncture, which reflects 'real time' blood glucose concentrations.[20] This provides patient self-monitoring of blood glucose (SMBG) as a powerful tool to health caregivers and patients to assess the effectiveness and safety of glycemic control management plan.[15] SMBG allows patients to evaluate their individual response to therapy and to assess whether glycemic targets are being achieved, or not.[15] Monitoring glycemic status is considered essential in diabetes control, as the results are used to gauge therapy efficacy and permit treatment adjustments .[23]

New blood glucose meters no longer need the amount of blood that previous models did.[18] Between 1991 and 2000 glucose became one of the most frequently measured analytes in clinical units, primary care and patients homes. This was possible through the availability of systems based on dry-reagent test strips with visually read end-points and/or simple-to-use reflectance meters and biosensors.[20] In current days, many devices are fully automated and equipped with a bolus calculator that allows the patient to know how much insulin to administer both for ingested carbohydrates and for glycemic control.[27]

4.4. Continuous Glucose Monitor and Flash Glucose Monitor Introduction

Diabetes approach evolution and sophistication had an important role in increasing patient safety and commodity with upgrades such as the ability to download graphics to the computer, connect to mobile phone applications, and automate adjustments in insulin dose according to the carbohydrate portions.[28] Continuous glucose monitoring (CGM) systems, appeared in the late 1990s as an electrochemical device that, via a small glucose-oxidase covered electrode inserted into the subcutaneous tissue, determines interstitial glucose concentrations. (Fig.5)[20,29] The measurements are continuously transferred to a receiver device, which processes the incoming data and reports a new glucose value. A difference between CGM and capillary glucose values should be expected, since the CGM is sensing in the interstitial tissue with a time-delay.[29]

These devices are not only useful for monitorization but for treatment too, as some insulin pumps are integrated with CGM systems, which permits detection of

fluctuations in response to meals, insulin injections, hypoglycemic episodes and exercise throughout the day.[20] Hereupon CGM also has an important role in assessing the treatment effectiveness and safety .[15] However, the recent introduction of flash glucose monitoring devices, Freestyle Libre (FSL), which do not require any calibration with daily capillary glucose testing, came to ease monitorization in patients for whom frequent finger prick tests are necessary.[28] The system function with wireless scanning of a transmitter connected with a sensor filament, which is inserted 5 mm under the skin for accurate measurement of glucose in the interstitial fluid.[30] However, in order to take full advantage of the system both the caregiver and the patient with diabetes must proceed to the careful interpretation of the data generated by the FSL.[30] As for disadvantages the majority of devices do not communicate with any pump.[27] Having diabetes still implies a complex management of the disease, but the hope of a future pragmatic approach may help patients to improve glucose control and reduce mortality and vascular complications.

4.5.   HbA1c

Since the 1970s, glycosylated hemoglobin (HbA1c) has been used to monitor the effectiveness of diabetes management.[28] Measurements of glycated proteins became widely available by the early 1980s, as blood and urine glucose and ketone testing could not provide an objective measure of glycemia over an extended period of time.[23]

In 1993, the Diabetes Control and Complications Trial (DCCT) study established treatment goals using HbA1c as an index of mean blood glucose.[31] It is used as a measurement of long term glycemia (90 to 120 days), which translates the risk for chronic complications in diabetes.[23]

More recently, measurement units were internationally standardized, changing from percentage to mmol/mol, and being universally accepted as a standard for monitoring and diagnosis.[28]

ISPAD recommendations for testing HbA1c is at least quarterly a year, and targets of <7% (53 mmol/mol) has been shown to reduce microvascular morbidities.[15,32]

In recent times, time in range (70 – 180mg/dl) and daily glycemic variability are taking more importance as a good control target.[33]

5. Insulin therapy: Understanding insulin from the beginning

In the early 1900s, Frederick Madison Allen and Elliot Joslin were battling in an attempt to treat diabetic patients on a fasting diet and later with heavy caloric restrictions.[4] They advocated a self-management concept on diet, exercise and frequent urine testing in an attempt to keep the urine sugar-free.[20] With that, they were able to demonstrate an improvement in glycosuria and urinary ketones, with a reduction in mortality and an increase in the life expectancy of these patients.[4] By that time, all diabetics were advised to decrease their sugar and dietary starch intake, and those who were obese were advised to lose weight.[34] However, even before they demonstrated significant effects with dietary treatment, John Rollo in 1797 had already described it in his book exclusively dedicated to this pathology. Based on a protein diet showed significant reductions with delayed complications.[21]

If in the past diabetes management was only relying on diet and non-pharmacological therapeutic interventions, the discovery of insulin and its role in the disease has changed the prospect. In T1D patients, β cells are destroyed. For that reason, insulin in circulation is not enough, making its external administration imperative for proper treatment.[4] The discovery of insulin with therapeutic purpose did not happen until 1921-1922, being considered the most significant event in the history of type 1 diabetes.[10] Endogenous insulin was first isolated in July 1921 by Frederick Banting, from the pancreas of dogs, and first named *isletin*.[4] Purification techniques started immediately with the aim of producing insulin on a large scale for therapeutic purposes as it was proved that rapidly lowered glycemia, decreased glycosuria, and ketonuria disappeared, resulting in a significant improvement in overall patient status.[4] This was how in November 1922 the first commercial insulin in the world appeared (Fig. 6), and in 1923 the Medicine Nobel Prize was awarded to Banting.[4] At this point, insulin was obtained from pigs or cows pancreas.[4] Nowadays, insulin is biosynthetically produced by recombinant DNA technology being as close to human insulin as possible.[4]

The benefits of glycemic control and quality of life have been clearly established, with the multiple dose insulin (MDI) administrations (the so called "functional intensive insulin therapy") (Fig.7).[34] Investigations efforts to optimize therapy, in order to extinguish barriers that are user dependent and replicate the normal pancreas production of insulin.[34]

Prolonging insulin action by adding protamine was discovered by H.C. Hagedorn in 1930. In Toronto, Scott and Fisher extended insulin action further by

adding zinc, which led to the introduction of longer-acting animal insulins in the market.[4,34] The isophane insulins could be mixed with regular insulins, and it was also found that the pharmacokinetics of slow insulins depended on the proportion of zinc.[4,34] The first recombinant DNA human insulin was obtained by David Goeddel in 1978, by utilizing and combining the insulin A- and B- chains expressed in Escherichia coli. This enabled the commercialization of rDNA insulin in 1982, Humulin R® (rapid) and Humulin N® (NPH, intermediate-acting), were marketed.[4,32]

There are a number of alternatives designed to improve the patient's quality of life. An example is Exubera®, the first inhaled insulin, that was developed by Sanofi-Aventis in 2006. However, because the inhaler device was bulky to use and did not add physiologic benefit over rapid-short acting insulin analogs it was taken off the market in 2008.[4]

Despite substantial advances in the treatment of type 1 diabetes, maintaining good glycemic control without hypoglycemia remains a challenge for patients at all ages and for healthcare providers.[35] This was possible by modifying the site of amino acids in the insulin, changing the pharmacokinetics and leading to faster absorption, the earlier peak of action, and shorter duration of action. Lispro, the first short-acting insulin analog, was approved in 1996.[4,34] Following that, aspart insulin and glulisine entered the marked in 2000 and 2004 respectively.[4] Recently, in 2017 a faster acting insulin has been announced by pharmaceutical companies.[29] Faster acting insulin aspart (Fiasp®) is a new formulation of insulin aspart with faster glucose lowering effect without increasing the risk of hypoglycemia.[36]

On the other hand, long-acting insulin as glargine was first approved in 2000.[4] The duration of 24 hours and the risk of nocturnal hypoglycemia motived investigators to work on ultralong-acting insulins. Degludec entered the market in 2015 and has the ability to improve basal insulin administration in patients with type 1 diabetes since it provides effective glycemic control and reduces the risk of nocturnal hypoglycemia.[4,10]

5.1. From Multiple dose insulin to Continuous subcutaneous insulin infusion

In addition to the duration of insulin action it was found that it was necessary to improve patients quality of life. Adherence to therapy is crucial 24 hours a day 365 days a year. For that reason, it is easy to understand why any new technology developed for helping patients to cope with the disease should be taken into

consideration.[37] It is a chronic treatment whose mistakes can be fatal. The appearance of insulin pumps to improved preparations and delivery systems started in the 1970s.[4] Continuous subcutaneous insulin infusion (CSII) is closer to physiological needs. Its benefits are recognized both for metabolic effectiveness and quality of life.[38] The major indications for an external pump include persistently elevated HbA1c despite intensive MDI therapy, repeated hypoglycemia, significant glycemic variability, pregnant women, patients with other chronic conditions and small children.[38] Although it is a cost-effective treatment option[39], it requires stronger patient motivation and involvement.[38]   Education regarding matching prandial insulin dosing to carbohydrate intake, premeal glucose levels, and anticipated activity should be considered. Selected individuals who have mastered carbohydrate counting could also be educated on fat and protein gram estimation.[15]

The combined use of CGM and CSII via an external device is the more recent development with a view towards the greatest treatment of T1D.[38] However, multiple daily treatment decisions still must be done by the patient in order to control glycemia. This requires a substantial commitment to reach treatment goals.[40] With that in mind, the use of a sensor that correct hyperglycemia and the low glucose suspend feature was found to be cost effective compared with simple CSII and SMBG (Fig.8). [35]

Now, many meters as SMBG can automatically send glycemia readings to the pump. These are equipped with algorithms for suggesting bolus doses based on user-estimated grams of carbohydrate and glycemia level, with the intention of reducing the probability of human error.[41]

Despite modern insulin pumps, errors of insulin infusion can occur. The most common are pump failure, set blockage, infusion site problems, insulin stability issues, user error or a combination of these. Users are therefore exposed to significant and potentially fatal threats as interruption of insulin infusion, which can result in hyperglycemia and ketoacidosis. Contrarily, the excess of insulin infusion can cause severe hypoglycemia, being possible to discontinue the administration and restart it when the problem is solved.[41] Recent technological progress has been advanced in order to solve some of these problems. The development of insulin patch pumps commits to simplify the technical aspects of treatment and to improve patient comfort. The patch pump incorporates the functions of a conventional insulin pump adding some advantages such as:

eliminating the tubing, being easy to use, requiring simple training and being discreet. (Fig.9) [38,42]

Nevertheless, even with the use of the most advanced treatment tools currently available (CSII and CGM), only a minority of T1D patients manage to maintain near-normal blood glucose levels.[29] This resource is certainly demanding in the sense that it takes time as well as mental capacity to perform the procedures and to make treatment decisions. Accordingly, automation of the insulin dose calculation and administration procedures has been much discussed by patients and caregivers.[29] Research continues toward a fully closed-loop artificial pancreas that integrates CGM and insulin pumps. It includes an algorithm that doses the correct amount of insulin at the right time with the latest ambition of normalizing glucose levels automatically. This will be discussed later in this paper.[39]

6. Progress Benefits

Type 1 diabetes is a chronic disease with considerable phycological and social consequences which represent a burden in health expenditure worldwide. For this reason, a greater disease approach and management, with reduced morbidity and fewer hospital admissions has high socioeconomic benefits.[7,20,29]

With the advances made in the technological field it was possible to lessen comorbidities and mortality. However, they do not disappear, demonstrating that the disease requires close and regular control.[38] All people dealing with diabetes should be aware of the most effective management of the disease, providing the patient and caregivers with the best health workforce possible. This requires a high level of education in managing the condition, as well as access to insulin and monitoring equipment.[7]

The International Diabetes Federation (IDF) works in many places around the globe to provide treatments and services to improve the outcomes for people with diabetes.[7] But despite the progress made for diagnose and treatment of type 1 diabetes, individuals in many parts of the world continue to die because of lack of access to insulin, meters and consumables.[10] These inequalities are proof that progress and evolution in approaching the disease have been and are important in order to always improve the expectancy and quality of life for all patients.[10]

7. Overview of the future: What to expect?

The expectation of improving the care provided to these patients motivates continuous researches in order to find the optimal treatment and approach of diabetes. Many fascinating system extensions and pharmacological improvements are under investigation.[29]

In 2000, a breakthrough protocol was developed for islet transplantation without the use of glucocorticoids for immune suppression, but the promising result did not meet expectations, therefore it remains as an experimental procedure with an ongoing focus on new methods using biomaterials, immune modulation, delivery site, improved vascularization and others.[10] This set the stage for other promising areas, as the use of stem cells as insulin-producing surrogates for β-cells.[10] Immunomodulation using antigen-specific and non-antigen-specific agents has also been on the front line of new and better treatments.[28] Glutamate decarboxylase is one of the examples and has been identified as an antigen-specific immune agent that could reverse the destruction of β-cells, however the efficacy in humans has not yet been proven.[28] In the future, stem cell therapy may prove to be a way of curing diabetes.[28] Although promising there are still not enough advances on these techniques to be put into practice, and further studies are needed.[10]

There has been much pioneering work on whole pancreas and islet cell transplantation, which offers real hope of a cure. The first pancreas transplant in a human was performed by William Kelly, Richard Lillehei and colleagues at the University of Minnesota in 1967.[1,28] Transplantation is currently restricted to those with disabling hypoglycemia or highly erratic glycemic control and is limited by the scarcity of donor tissue and specialist transplant centers as well as problems with transplant rejection and side effects of immunosuppressive drugs.[28]

At the same time, technological advances have resulted in an artificial implantable pancreas, which does not require any input from the patient in regard to insulin administration or glucose monitoring, taking over glucose control.[40] Artificial pancreas systems are an effective and safe approach for treating patients with T1D.[35] It is also referred as closed loop glucose control which combined an insulin pump and CGM with a control algorithm to deliver insulin in a glucose responsive manner with the possibility to deliver glucagon too.[35,40] Therefore, compared with insulin pumps or sensor augmented pumps, artificial pancreas use can reduce treatment related complications by automatically adjusting the amount of insulin entering the body on the basis of sensor glucose levels. Thereby it will

improve glucose control, reduce the risk of diabetes complications and markedly improve patient quality of life.[29,35]

Compared to the current treatment for diabetes, the artificial pancreas is promising, but it adds challenging safety issues because it combines several components into one system and takes control of the patient, not having an active role in the disease.[40] The major limitations are related to inconsistency in outcome reporting, small sample size, and short follow-up duration of individual trials.[35] Despite the apparent simplicity of the system and the availability of functioning CGMs, insulin pumps, algorithms and computers, there are still challenges to overcome before an automated artificial pancreas becomes a reality for the majority of patients.[29]

At this moment, artificial pancreas systems are available only in a restrict number of patients but are emerging at a rapid pace and quite promising in the effective treatment.[40]

8. Conclusions

For many years, T1D has been in the center of attention of many researchers and physicians. The history reaches 1552 B.C. and today is still on the front line of development. Focusing different points, the changes with an impact on approaching this disease happened in the past century. Today many are the health-related workers who try to provide every day a better quality of life for the patients who live with this chronic, still not curable disease.

All the previously described (both at pathophysiological, approach and therapeutic levels), allowed us to reach the point where we are today. The number of individuals dying due to this pathology is decreasing thanks to all the effort made throughout the years. If at the beginning the attention was centered in understanding and defining this pathology, the focus moved to improve treatment with the beginning of the current century. (Fig. 10)

In a disease that is highly dependent on the will of the patient to improve the treatment, working on options that eliminate or reduce these variables has an important role.

Treatment optimization is still not a reality, but besides that, recent studies are trying to clearly identify risk factors in order to recognize if prevention is a possible way to reduce the number of patients suffering from this disease. Although without valid conclusions because of the lack of studies , they show the important value of continuing investigating and learning about diabetes.

The extensive negative economic impact that diabetes has around the world justifies all the work needed to improve access to health care, to reduce complications and provide a longer life with better quality.

Approaching diabetes is still an unfinished story with many new chapters to be written in the near future.

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Figure 1 Colorimeter.

Used in 1890s for blood glucose measurement. It required 50ml blood to determine the glucose.[18]
Image from: Diabetes Museum Munich

Figure 2 Polarimeter.

Used in the beginning of 1900 for urine glucose measurement.[18]
Image from: Diabetes Museum Munich

Figure 3 Reflectance Meter- 1974.

Costs around 500$ and only needed 20 ul for measurement.[18]
Image from: Diabetes Museum Munich

Figure 4 Glucometer in 1987.
It has the ability of data storage as time and measurement results.[18]
Image from: Diabetes Museum Munich

Figure 5 1994- First portable CGM
Image from: Diabetes Museum Munich

Figure 6 1922- First insulin entering the market
Image from: Diabetes Museum Munich

Figure 7 Insulin pens
In the late 1990s, the so-called insulin pens appeared with the intent of once again facilitate patient life. The insulin cartridge is tightly integrated, so it is possible to unscrew the pen needle only. After the consumption of the pre-filled pen is disposed of.[18]
Image from: Diabetes Museum Munich

Figure 8 Different insulin pumps currently on the market
Image from: Diabetes Museum Munich

Figure 9 Insulin Patch Pump
Around 2010,a pump which the catheter tube is eliminated entered the market.
Insulin Patch Pumps use an automatic needle stitch and controls basal rate,
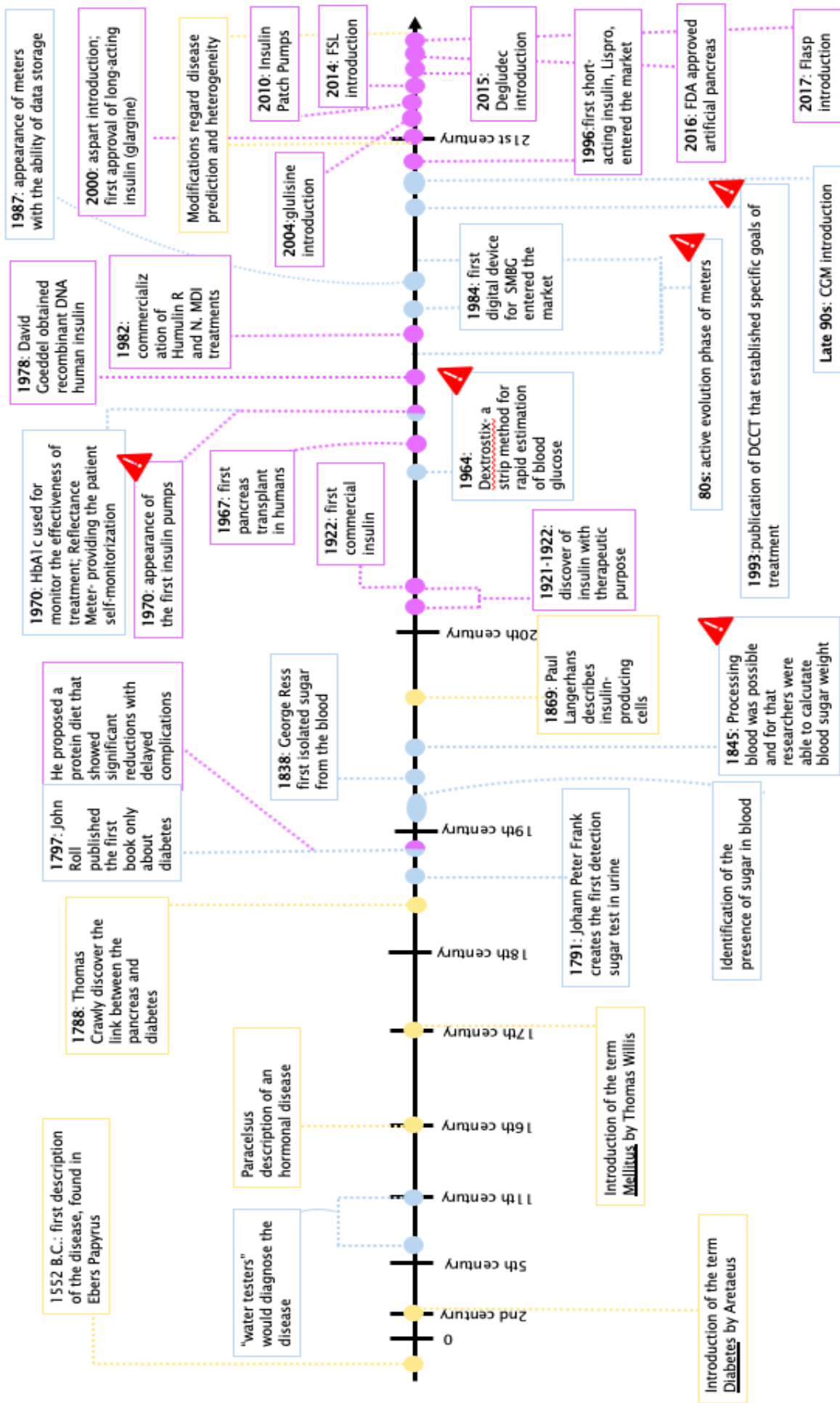delivery corrections and bolus.[18]
Image from: Diabetes Museum Munich

Figure 10 Timeline of T1D history

Legend:
- Definitions and pathophysiological findings
- Diagnosis and Monitorization
- Treatment

1552 B.C.: first description of the disease, found in Ebers Papyrus

"water testers" would diagnose the disease

Introduction of the term Diabetes by Aretaeus

Paracelsus description of an hormonal disease

Introduction of the term Diabetes Mellitus by Thomas Willis

1788: Thomas Crawly discover the link between the pancreas and diabetes

1797: John Roll published the first book only about diabetes

He proposed a protein diet that showed significant reductions with delayed complications

1791: Johann Peter Frank creates the first detection sugar test in urine

1838: George Ress first isolated sugar from the blood

Identification of the presence of sugar in blood

1845: Processing blood was possible and for that researchers were able to calcutate blood sugar weight

1869: Paul Langerhans describes insulin-producing cells

1921-1922: discover of insulin with therapeutic purpose

1922: first commercial insulin

1964: Dextrostix: a strip method for rapid estimation of blood glucose

1967: first pancreas transplant in humans

1970: appearance of the first insulin pumps

1970: HbA1c used for monitor the effectiveness of treatment; Reflectance Meter- providing the patient self-monitorization

1978: David Goeddel obtained recombinant DNA human insulin

1982: commercializ ation of Humulin R and N. MDI treatments

1984: first digital device for SMBG entered the market

80s: active evolution phase of meters

1993:publication of DCCT that established specific goals of treatment

Late 90s: CGM introduction

1987: appearance of meters with the ability of data storage

2000: aspart introduction; first approval of long-acting insulin (glargine)

Modifications regard disease prediction and heterogeneity

2004:glulisine introduction

2010: Insulin Patch Pumps

2014: FSL Introduction

2015: Degludec introduction

1996:first short-acting insulin, Lispro, entered the market

2016: FDA approved artificial pancreas

2017: Flasp introduction

2nd century
5th century
11th century
16th century
17th century
18th century
19th century
20th century
21st century

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