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Review

A history of continuous glucose monitors (CGMs) in self-monitoring of diabetes mellitus

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ABSTRACT

Self-monitoring of glucose for individuals afflicted with diabetes mellitus has allowed patients to take control of their disease and thus directly affect the outcomes related to it. It has been almost a century since the first test to monitor one's sugar was developed; that being a urine test. The most well-known and prominent medical device for monitor blood glucose for individuals with diabetes are the finger-prick devices. This itself is an approximately 50 year old technology. More recently has been the introduction of continuous glucose monitors (CGMs) which entered the market place in the last year of the 20th century. As this technology has been further refined and improved, limitations associated with it have decreased. The scope of this review is to present a brief history of CGMs, both with the development of these medical devices and the challenges/limitations that they have shown.

Contents

1. Introduction

In 2014, the global cost of diabetes, calculated in International Dollars, was $825B/year taking into account the cost of treating diabetes mellitus plus managing the disease and its complications [1]. If current trends continue with new diagnoses of diabetes, it is estimated that over 700 million adults worldwide would be affected with diabetes by 2025 [1]. A vast majority of patient with diabetes do end up receiving chronic disease treatment in the form of insulin therapy to help control their blood sugars in conjunction with a blood glucose meter. Without adequate blood sugar control, diabetes can lead to many debilitating and life-threatening

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conditions such as heart disease, stroke, vision loss, kidney disease, amputations, and ultimately death. To prevent these conditions from occurring patients with diabetes are strongly encouraged to also make dietary changes and frequently monitor their blood glucose [2]. To receive the appropriate dose of insulin an accurate measurement of blood glucose is required, typically with a finger-prick glucose meter. However, patients continue to struggle with the pain associated with finger-pricks prior to injecting insulin. With the introduction and advances with continuous glucose monitors (CGMs) the less than ideal compliance of self-monitoring of this disease may be coming to an end.

2. History of diabetes management

Dating as far back as 1552 B.C., the existence of diabetes and its symptoms were reported, with the earliest documentation found on a 3rd Dynasty Egyptian papyrus by a physician named Hesy-Ra [3]. He reported symptoms his patients presented with, such as frequent urination. The very first way of studying diabetes mellitus was through examination of the urine. There were several chemical tests developed with various reagents, primarily indicating if there was any sort of sugar present in the urine. Unfortunately, a diagnosis of diabetes through the analysis of the urine often meant that death was rapidly approaching. If there was sugar present in the urine, the only intervention known at the time was changing one's diet, which was often too late to alter the course of their disease [3].

In the early part of the 20th century, a physician by the name of Dr. Frederick Allen counseled patients to maintain a low calorie diet, which allowed for patients with diabetes to extend their lives for about a year or so [4]. It was not until 1921 when a young Canadian surgeon by the name of Frederick Banting and his assistant, Charles Best, maintained a diabetic dog's survival by injecting it with canine pancreas extracts. James Collip further purified the extract for ultimate use in humans [5]. In 1923, Eli Lilly and Company began the commercial production of what is known today as "insulin" [3]. As this medical breakthrough of pancreas extract began to spread across the nation, there still was a need to measure a patient's blood glucose value prior to the injection of "insulin." Without having an accurate measurement of the patient's level of sugar, injecting insulin could pose more of a risk to the patient rather than a benefit by inducing hypoglycemia.

By 1925, home testing for sugar in the urine was introduced which involved the process of eight drops of the patient's urine to be mixed in a test tube with 6 cc of Benedict's solution, all components of which were dispensed by a physician at the time. The instructions required that the test tube be placed in boiling water for several minutes and depending on the color change observed, the patient would know their sugar level (Fig. 1). Green represented light sugar in the urine, yellow represented moderate sugar, and red/orange presented heavy sugar [3].

In 1946, Alfred Free joined Miles Laboratories to set up their biochemistry division, a company best known for "Alka-Seltzer." The executives of Miles Laboratories' wished to join the prescription drug business with their new biochemistry division and were optimistic on finding the "wonder drug." With Free's background with a Ph.D. in biochemistry from Western Reserve University and additional research experience at the Cleveland Clinic, he assembled a research team that included his future wife Helen Free (Murray), a quality control chemist. Alfred Free understood the current home method of analyzing urine for sugar and knew there was room for advancement because it was nonspecific, detecting all forms of sugar, not just glucose. Helen Free felt that this limitation would cause some hesitation by doctors to use this system, and she concluded this field of study had the potential to be a niché for Miles Laboratories [6].

The research of diabetes continued to expand by refining insulin and the monitoring system. By the late 1940′s, Helen Free developed the "dip-and-read" urine test known as Clinistix, which was capable of monitoring urine glucose levels virtually instantaneously. Free's team was able to embed the reagents on a filter paper strip comprising the first test specific for glucose, with release in 1956. This advancement used a double sequential enzymatic reaction via glucose oxidase, peroxidase, and orthotolidine. In this reaction, glucose oxidase catalyzed the oxidation of glucose to gluconic acid while also converting oxygen to hydrogen peroxide. With a peroxidase, the hydrogen peroxide was used for the oxidation of ortho-toluidine into a deep blue chromogen which was the visual indicator of glucose level (Fig. 2) [7].

Alterations were made to this extensive process and in 1964 another test came to market by the name of Combur-Test, made by Boehringer Mannheim. This test was sensitive towards glucose, protein, pH of urine, and even extended to include ketones later in the product known as Ketostix/Ketodiastix [8]. Although the urine "dipstix" tests on the market were painless and low cost, some glaring limitations existed such as the inconvenience due to requirement of urine and the test in itself appeared "dirty" and/or having poor hygiene [8]. Additionally, it was a challenge to evaluate the readings of blood glucose and draw conclusions since the levels were what was being excreted versus the level present in the blood. Being unable to detect hypoglycemia, the patient's renal threshold and other substances found in the urine were other variables that had the potential to alter the readings at the time. With all these limitations in mind, researchers continued to pursue other alternative options to monitor glucose [8].

Concurrently, oral drugs to help lower blood glucose were beginning to be introduced into the market [3]. As patients became more conscientious of the benefits of measuring glucose levels, home testing popularity was on the rise, continuing to increase the demand for devices to come to the market. The first test strips for blood glucose were developed in 1964 by Earnest C Adams and was known as Dextrostix from Ames-Miles Laboratories. It was the first ever dry-reagent blood sugar test-strip. It used the same glucose oxidase/peroxidase reaction as the Clinistix (Fig. 2) but with an addition of an outer semipermeable membrane. This semipermeable membrane was capable of trapping red blood cells but

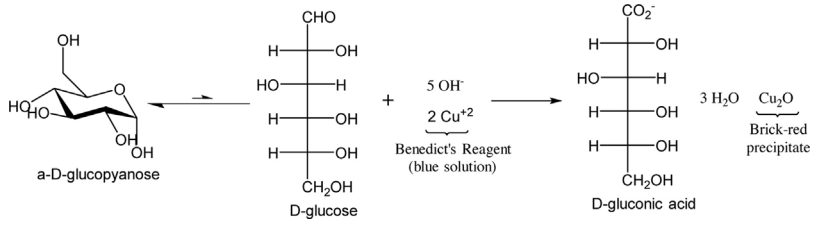

Fig. 1. Chemistry of the Benedict's solution for urine glucose testing.

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