Journal of Diabetes Mellitus, 2021, 11, 221-233
https://www.scirp.org/journal/jdm
ISSN Online: 2160-5858
ISSN Print: 2160-5831

100 Years of Glucose Monitoring in Diabetes Management

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How to cite this paper: Raza, S.I., Raza, S.A., Kazmi, M., Saad, M. and Hussain, I. (2021) 100 Years of Glucose Monitoring in Diabetes Management. *Journal of Diabetes Mellitus*, **11**, 221-233.
https://doi.org/10.4236/jdm.2021.115019

Received: September 22, 2021
Accepted: November 13, 2021
Published: November 16, 2021

Abstract

Glucose monitoring and diabetes management go hand in hand. Evolution of glucose monitoring and diagnostic tools was a necessary step in better diagnosis and management of diabetes. With time we have seen improvements in terms of accuracy, time and sample collection. Some of the greatest initial advancements in this field were brought forward by the work of scientists who are sometimes not credited for the extraordinary work they have done. The first sample to be used in terms of glucose detection was urine, after which came blood and interstitial fluid. Development of newer methods of glucose monitoring range from urine sampling to usage of interstitial fluid, with each method being unique in terms of utility.

Keywords

Diabetes Management, Glycemic Control, HbA1c Testing, Standard Glucose Values, Glucose Testing

1. Introduction

Diabetes can be found in archives of history as early as 1500 BC, in ancient Egyptian documents. It was described as disease where people lose weight and urinate more often. Glucose monitoring refers to the study of glucose levels and fluctuation in the body. This determines the diagnosis, progression and treatment goals of diabetes.

Diabetes is a chronic disease, needs a standardized way of monitoring its control and optimizing prevention of its complication. Blood Glucose monitoring and reading play a pivotal role in objectively looking at Diabetes control and

prevention of complication related to Diabetes.

Managing diabetes has many aspects, including Psychosocial-Behavioral changes, Diet, lifestyle modification, Exercise, medication and as well as adherence to a drug regime. Glycemic variations away from the baseline values can lead to short-term problems like hypoglycemia, hyperglycemia, diabetic ketoacidosis or dysglycemia in the long run can lead to a known complication involving multiple organs.

Diabetes can be classified into 2 broad categories, type 1 and type 2 diabetes. Type 1 diabetes is culmination of autoimmune effects on pancreas while type 2 diabetes is more centered around metabolic dysfunction including insulin resistance and relative Insulin deficiency. Generally, people with type 2 diabetes are more likely to be unaware of their condition and as estimated by The Centers for Disease Control and Prevention (CDC) nearly 25 percent [1] of the diabetics in America are unaware of their condition. Delay in Diagnosing and duration of being unaware of the condition leads to people having more symptoms at diagnosis and possibility of baseline complications related to diabetes.

2. Evolution of Methods of Diabetes Diagnosis and Glucose Monitoring

2.1. Urine Testing

2.1.1. History

Glucose detection in urine was one of the initial methods of diagnosing diabetes. Evidence of glycosuria was noted by physicians in 600 BC, when ants were attracted to patient's urine. By 1670 the disease got a full name, diabetes mellitus, which means "like honey" due to the sweet taste of urine. In 1674, an English doctor named Thomas Willis described diabetic urine as "wonderfully sweet as if it were imbued with honey or sugar" [2].

(**Figure 1**)

It was in 1776, Matthew Dobson, an English doctor discovers that the urine of such patients has higher levels of sugar. According to an article that the journal Medical Observations and Enquiries published he documented that urine of people with diabetes could have a sweet taste. It was then that distinction of Normal urine, which does not have glucose in it, was made with glycosuria (continuing glucose) and hence a key indicator in the diagnosis of diabetes. Although, it was not clearly known at that time that Glycosuria may also be seen in kidney diseases. He also notices that blood serum tastes sweet due to the high sugar levels. Initially, the diagnostic technique used was tasting the urine, which now thankfully, have evolved into more accurate and less distasteful methods of urine testing.

During the Middle Ages, doctors established the technique known as uroscopy "visual inspection of urine in a specially shaped flask called a matula", which they used as standard way of diagnosing and treatment of disorders of hormonal imbalance. The first method to measure glucose levels in the body was seen in

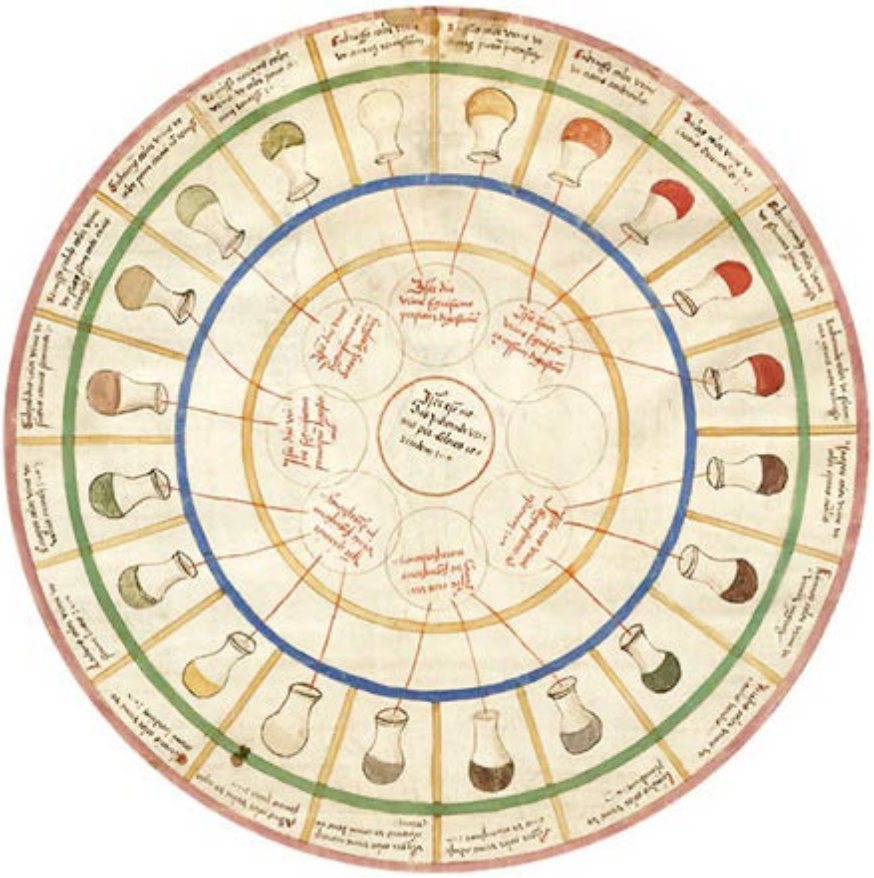

Figure 1. Source: https://www.ediblegeography.com/urine-flavour-wheels/
Urine wheel from Epiphanie Medicorum, Ullrich Pinder (1506), via Oscillator.

the form of urine flavor wheels. Specific flow charts were developed for this method, that included various parameters including sight, smell, and taste of urine. These parameters were compared to those on the chart to estimate values. It was much later that these tests evolved into more efficacious and accurate tests in reference to detecting sugar in urine. The first clinical test for sugar in urine was developed in 1841 by Karl Trommer, which involved subjecting a urine sample to acid hydrolysis [3].

Although step forward but still these methods showed poor and inaccurate results.

It was in the late 1930's that we saw the introduction of urine tests to detect glucose in urine, which worked on the principle of benedicts test. Benedict's reagent was mixed with the urine sample in a test tube and placed over a Bunsen burner. Dr. Walter Ames Compton, who was an American medical doctor and pharmacy researcher joined Miles Laboratories and in 1941 Miles laboratory, under the directions of Dr. Walter Ames, introduced the effervescent tablet Clinitest® [3] [4] [5].

Clinitest utilized cupric sulfate, sodium hydroxide, and citric acid mixed with a bit of carbonate to make it fizz. Procedure of testing included to have urine samples dropped over the tablets and the color of the results could be used to

give a quantitative measure of sugar in urine. The color changes range from (0.5% glucose) to orange (2% glucose) [6]. In 1946, Alfred Free helped Ames Division of Miles Laboratories to set up a biochemistry division and partnered up with Helen Murray. This collaboration resulted in improvement and accuracy of clinitest as well as development of a new technique for the diagnosis of diabetes. Partnership also lead to the formulation of Acetest®, which worked on the principle of using nitroprusside to detect ketones in urine. This became a very important tool in detection of Diabetic Ketoacidosis and later on understanding pathophysiology of diabetes and identification of Insulin deficiency in patient with type 1 Diabetes.

It required a lot apparatuses and procedural skills to detect and measure blood glucose, Alfred and Helen relentlessly worked to make it more convenient and glucose-sensitive. Their efforts lead to urine test strips which were first launched in 1956 [7]. This time researchers used a double sequential enzymatic reaction: glucose oxidase and peroxidase. Urine test strips were of two types, qualitative and semi-quantitative. The Qualitative test strips only tell about a positive or negative test result, whereas, a semi-quantitative also gives us a general idea about quantity of substance present in urine.

Contribution of Miles, Alfred and Helen did not stop here, they went onto develop strips that could be used in the identification of more than one substance in the urine. This was developed by using a water-impervious barrier between the two test strips to prevent mixing. Uristix®, released in 1957, combined tests for glucose and protein [5]. This journey continued and various test strips were later produced that combined reagents for ketones, blood, bilirubin, urobilinogen, protein, nitrite, urinary leukocytes, and pH. The procedure of urine testing was to ask the patient to urinate in a container after which a test strip was dipped into the urine. The changes in color of strips were compared to a color chart, which determined the concentration of various substances.

2.1.2. Evolution

Over time various body fluids have been used to determine sugar levels and diagnose diabetes, the first of these was urine. This is a rather noninvasive and cheaper method compared to testing of blood. Urine analysis is helpful for patients with anxiety caused by needles and for when healthcare professionals cannot access a vein for blood test. Urine testing is less accurate compared to blood tests. Urine test strips to detect glucose can provide some false positive results due to the presence of traces of strong oxidizing agents from disinfectants and intake of substances like vitamin C, aspirin, iron supplements, levodopa and tetracycline-type antibiotics. In the past making test strips was very labor intensive. Researchers cut the filter paper, dipped it into reagent solutions, and dried the paper in ovens [5]. Limitations to this procedure include that it cannot detect hypoglycemia, therefore, puts patients at a risk.

2.1.3. Standard Values

Knowing standard values of different sugar tests help us differentiate healthy

from diseased individuals and also provide basis of monitoring. Uroscopy showed a positive or negative result based on comparison of multiple factors with that on the urine flavor chart.

Benedicts test and clinitest were two very similar procedures with clinitest being more accurate, faster and convenient as it could be performed at the office of the physician. Test values for both the tests ranged from a value of 0% to 2%.

- Blue: 0% (no) sugar in urine
- Green: 0.1% - 0.5% sugar in urine
- Yellow: 0.5% to 1% sugar in urine
- Orange: 1% to 1.5% sugar in urine
- Red: 1.5% to 2% sugar in urine
- Brick red: more than 2% sugar [8]

Acetest showed a positive result through purple lavender discoloration of the tablets indicating presence of acetone/acetoacetate (ketones) darker the color greater the concentration of ketones.

The semi-quantitative urine test strips show positive results, through various colors on the test strip, corresponding to different concentrations. These colors can be matched to 1+, 2+, 3+ and 4+ symbols on the chart, which represent increasing glucose concentration; which can also be estimated as milligrams per deciliter. Automated readers of test strips are also present which provide results using units from international system of units. The normal urine glucose levels are said to be around 0 to 0.8 mmol/L or and any value higher represents an underlying health disease. 25 mg/dl of glucose in urine is normal [9] [10] [11] [12].

2.1.4. Utility

These urine tests lead to giving armamentarium in hand of physicians to combat three most important parameters of Diabetes management, which are measurement of glucose, ketones and proteins in urine. When a person has diabetes and has relative or absolute insulinopenia, the glucose in the blood cannot reach the body cells which leads to the body utilizing energy in the form of stored fat. When the body uses a large number of fat stores as a source of energy, considerable amount of ketones are released into the blood which are cleared through the kidney and added to the urine. The ketones in the blood cause its acidification and that leads to Diabetes ketoacidosis. Diabetes is associated with nephropathy and a key diagnostic factor of diabetic nephropathy is protein in urine.

2.2. Blood Testing

2.2.1. History

Although, increased glucose level in blood were identified but actual commercial measurement did not start till 1960's. Glucose monitoring is done through components of the blood, which include whole blood, plasma and capillary blood. First blood glucose test strip, Dextrostix, was made in 1964 by The Ames Company (a division of Miles Laboratory—eventually acquired by Bayer). This required large drop of blood to be placed on strip and after 60 seconds wait it

would generate a color, it was then compared to a chart on the bottle. These color chart comparisons would give a semi-quantitative assessment of blood glucose. These strips utilized the glucose oxidase-peroxidase system which was developed in 1965 and was a more reliable diagnostic tool.

Further refinement came in 1970 by Ames when they introduced the first glucose monitoring device Ames Reflectance Meter® (ARM), invented by Anton Clemens. This enabled self-monitoring of glucose. This came as a leap managing Diabetes by measuring blood glucose and self-assessment of control. Over years, further improvements in these devices are seen in the form of optically read test strips, electrochemical strips, being able to test capillary blood from areas other than the fingertips and continuous glucose monitoring devices.

In 1970, another tool for managing and diagnosing Diabetes was introduced, known as Glycated hemoglobin (A1c) test [13]. The HbA1C measurement reflects blood sugar over a period of months rather than a single point in time.

This blood test has great utility of not only diagnosing diabetes but can also be used as a tool in its management [14]. Benefit of HbA1c is not limited to giving you an average blood glucose of previous 3 months but also does not require any fasting prior to test and can be obtained at any time of the day. Test results are not altered by acute factors like stress and exercise. HbA1c is a stable sample material, therefore, only a single sample is required and there is extremely low intra-individual variability (CV < 1%) [15].

In 1922, the Oral Glucose Tolerance Test (OGTT) was first introduced [16]. This test helps us study how the body responds to glucose. It is also used as a gold standard screening test to screen type 2 diabetes as well as gestational diabetes. For this test the subject has to fast for a time duration of about 8 - 12 hours overnight. At the test lab the patient would be provided with a bottle of liquid, containing 75 grams of glucose, that he/she would have to drink within 5 minutes. After this blood samples would be taken every 2 hours (every hour when screening for gestational Diabetes). Elevated blood glucose would be considered as a clear indication of diabetes.

2.2.2. Evolution

Glucometers are easy to use devices used to measure blood sugar level, they are fast and require only a small amount of blood. A small "prick and blood test" is currently used to monitor blood sugar levels. However, pain associated with the finger prick is one of the biggest limitations of this method. The method is invasive and continuous monitoring is not possible. Moreover, pricking too often can be tiresome. It might be frightening for some patients and it makes patients less likely to control blood glucose levels. Another weakness of this method is the insufficient sampling frequency. Glucometer readings come with a degree of inaccuracy. The most accurate way of measuring blood glucose level is through a biochemical analyzer. Usage of biochemical analyzer for measurement of blood glucose from serum is considered the gold standard of accuracy [17]. This level of accuracy can be obtained on glucometers by replacing whole blood with blood

serum or plasma for testing. The conversion of blood to blood serum or plasma can be done through centrifugation. Even though a biochemical analyzer has more accurate results but it's not practical to use this machine to continuously monitor blood glucose level due to the expense, pain associated with withdrawal of blood and larger quantity of blood needed as compared to a glucometer.

2.2.3. Standard Values

Glucometers use capillary blood and some reference values for monitoring. Various blood tests are used for glucose monitoring [18], the main tests and there diagnostic blood sugar values are given below:

Diagnosis A1C (percent) Fasting plasma glucose (FPG)

Values in milligrams per deciliter, or mg/dL Oral glucose tolerance test (OGTT)

At 2 hours after drinking 75 grams of glucose

Values in milligrams per deciliter, or mg/dL Random plasma glucose test (RPG)

Values in milligrams per deciliter, or mg/dL

Normal below 5.7 99 or below 139 or below 200

Prediabetes 5.7 to 6.4 100 to 125 140 to 199

Diabetes 6.5 or above 126 or above 200 or above 200 or above

Classification and diagnosis of diabetes adapted from recomendation of American Diabetes Association and European Association for the Study of Diabetes (EASD).

Normal blood sugar values for a healthy individual are between 70 and 130 mg/dL depending upon the time of the day and time since last meal. A normal blood glucose level for a healthy adult who has not eaten for at least 8 hours prior to test is less than 100 mg/dL and two hours after eating is less than 140 mg/dL [19]. Low blood sugar levels indicate hypoglycemia. For many people, a fasting blood sugar of 70 milligrams per deciliter (mg/dL), or 3.9 millimoles per liter (mmol/L), or below should serve as an alert for hypoglycemia [20].

High blood sugar levels indicate hyperglycemia. Hyperglycemia is blood glucose greater than 125 mg/dL (milligrams per deciliter) while fasting [21] and levels greater than 11.0 mmol/L (200 mg/dl) 2 hours after meals [18].

2.2.4. Utility

Currently, we have various blood glucose tests that help us identify blood glucose levels at a single point in time. These tests include fasting plasma glucose test and random plasma glucose test. Fasting plasma glucose test requires patients to fast for 8 hours prior to the test, but excludes moderate consumption of water. While, random plasma glucose test is similar to the fasting plasma glucose tests but this test is used when symptoms of diabetes are present and healthcare professionals do not want to wait till the patient has fasted.

Gestational Diabetes, which like type 2 diabetes, reflects insulin resistance with decreased insulin secretion during pregnancy when placenta is producing hormones. These hormones lead to exposing pregnant females to the two defects mentioned above. Patient without underlying pathology, can compensate in-

creased insulin requirement but in patients with gestational diabetes unable to do so. Two diagnostic tests which are pivotal in diagnosing Gestational diabetes include oral glucose tolerance test and Glycohemoglobin A1C [22] [23].

2.3. Serum Glycohemoglobin A1c (hbA1c)

2.3.1. History

HbA1c was discovered in 1960 and wasn't implemented in clinical practice up till 1977 [24]. The methods used during that time to use HbA1c as a laboratory diagnostic marker lacked precision and there were no calibrators or material with assayed values for quality control purposes. The discovery of Glycated hemoglobin has been one of the greatest advancements in laboratory medicine. In the 1990's it was realized that test results were not comparable from one laboratory to another and one country to another ,therefore, during this period efforts to standardize hbA1c methods and diagnostic tools were made [25].

2.3.2. Standard Values

In most labs, the normal range for hemoglobin A1C is 4% to 5.9%. 6.5% is termed as the cut off value for diabetes but values below this do not rule out diabetes.

In well-controlled diabetic patients, hemoglobin A1C levels are less than 7.0%.

In poorly controlled diabetes, its level is 8.0% or above.

2.3.3. Utility

The formation of sugar-hemoglobin linkage occurs when blood sugar levels are higher than normal and is often indicative of diabetes. HbA1c is of particular interest as it is easy to detect. The test is limited to taking a 3 month average as the lifespan of a red blood cell is 4 months.

Commonly used HbA1c analytic techniques include immunoassay, ion-exchange high-performance liquid chromatography (HPLC), boronate affinity HPLC, and enzymatic assays. HbA1c is an accurate diagnostic marker for the detection of diabetes and pre-diabetes. A three month average of blood sugar levels is presented and it correlates well with adherence and effectiveness of drug regime as well as risk of long term complications of diabetes.

2.4. Interstitial Fluid

2.4.1. History

The latest method of monitoring blood glucose levels is through the interstitial fluid. Continuous glucose monitoring devices and flash glucose monitoring devices are examples of such devices. The first device for reading blood glucose levels continuously was a professional CGM that was approved by the FDA in June 1999 [26]. There is innate time delay when checking interstitial fluid, especially after eating or if you're exercising. This delay is due to rapid change in capillary blood glucose, and attaining new level of Glucose while glucose freely diffuses from capillaries into interstitial fluid.

The existence of a patient-specific time delay which might vary from a few to up to 20 minutes must be taken into consideration when a patient is to use a CGM sensor [27]. The delay is due to the time taken by glucose to travel from the blood vessel wall to the interstitial space and then to the CGM sensors. However, because interstitial glucose levels are not identical to blood glucose levels, continuous monitoring devices (CGMs) must be calibrated with a blood glucose reading from time to time. Continuous glucose monitoring devices measure your blood glucose throughout the day and continuously send information to your display screen, therefore, they can be used to set an alarm for hypoglycemia as well as hyperglycemia.

Flash monitoring devices only send input to display screens when scanned [28]. Most, Flash glucose monitoring devices have standard factory set calibrations and therefore do not require individualized calibrations through blood tests.

2.4.2. Evolution

Usage of continuous glucose monitors saves us from the pain and hassle of having to prick our fingers multiple times a day. Apart from its convenience, continuous glucose monitoring devices have allowed us to study glucose variability in time and range. We can now understand and detect various blood sugar trends, allowing us to understand the effect of diet and exercise on our body. Continuous glucose monitoring devices come with hypoglycemia and hyperglycemia alerts, minimizing the occurrence and negative impact of both events. Limitations and disadvantages of such devices include there relatively high prices compared to glucometers, delay in reading of glucose trends and the need of calibration by twice-daily finger sticks tests. Continuous glucose monitoring normally requires the use of electrodes that are inserted into the skin at various sites, which is painful or could lead to skin irritations. Flash glucose monitoring devices are similar to continuous glucose monitoring devices but are comparatively cheaper, do not require calibration and show "more information" on the glucose trend. The limitation to these devices is that they only show values when sensors are scanned and for that reason they cannot be used for hypo and hyper alarms. Neither of both devices is preferred over the other, both come with their own advantages and disadvantages.

2.4.3. Standard Values

Devices like continuous glucose monitors and flash glucose monitors, utilizing interstitial fluid, give values showing blood glucose levels through calibration of interstitial fluid values with blood glucose values. Although rapidly becoming popular but still long term studies required before this to become standard of care.

2.4.4. Utility

These CGM/Flash Monitoring devices have given new meaning to blood glucose and hence given opportunity for better evaluation of "glycemic variations" and

concept of "time and range". These not only keep the fluctuation to a minimum, but now there is scientific data to support that they may play a role in macro-vasculature and microvasculature complication of Diabetes. Newer Technologies like artificial pancreas/close loop insulin pumps utilize these and function only after integration between a glucose monitoring device and an insulin injecting device. Insulin delivery is intricately managed by constant feedback from these continues glucose monitoring devices. BMJ in 2018 published data that the artificial pancreas is "efficacious and safe" for people with type 1 diabetes to use [29]. The Medtronic MiniMed 670G system is the first FDA hybrid closed loop system which was approved on September 28, 2016 [30].

2.5. Newer Innovations

The future of glucose monitoring includes methods that are less invasive and more accurate, using various body fluids including tears and saliva. A team of researchers affiliated with UNIST has recently introduced a new biosensing contact lens capable of detecting glucose levels in diabetes. The devices will use tears to monitor glucose levels and the two major uses of these devices would be continuous glucose monitoring and treatment of diabetic retinopathy. Despite wide investigations of smart contact lenses for diagnostic applications, there has been no report on electrically controlled drug delivery in combination with real-time biometric analysis. The devices have not yet been tested on human patients but would be a breakthrough in the future; providing a pain free method towards managing diabetes [31].

Researchers at The Hong Kong Polytechnic University, have been working on a new ultra-sensitive transistor-based biosensor for detection of glucose in saliva. This sensor works on the principle of glucose oxidase enzymes, where these enzymes oxidize glucose producing an electrical current and this signal is later converted into a value reflecting glucose levels in the body [32].

2.5.1. Evolution

In regard to current methods, Bio-sensing Contact Lenses and saliva glucose biosensors could be eliminated limitations associated with the current methods of testing. Bio-sensing contact lenses can be used as a non-invasive method for continuous glucose monitoring. Through this method compliance could be improved as the individual can replace it every day and as they are transparent they would not make the individual self-conscious.

Saliva biosensor is a high-performance flexible glucose biosensor, which is sensitive to specifically detect trace amount of glucose level in human saliva, making it highly accurate. These devices are low in cost and could be used as a portable non-invasive glucose level meter for home use. It is convenient for people who face difficulty extracting blood samples such as infants, the elderly and hemophiliacs. The devices demonstrate a good linear response in a wide glucose level range.

2.5.2. Standard Values

Biosensors can be used to determine glucose in tears and saliva. With an increase in blood glucose concentration an increase in glucose concentration in tears and saliva is also seen.

These values can be calibrated for diagnostic use. For a healthy individual fasting, tears averaged 3.6 mg/100ml (0.2 mmol/l) and in the diabetic patients it averaged 16.6 mg/100ml (0.92 mmol/l), these numbers can be taken as reference values [33]. Normal glucose levels in saliva are estimated to be 0.5 - 1.00 mg/100ml [34]. In a study published in Journal of Oral and Maxillofacial pathology it was found that patients with serum glucose levels between 100 and 280 mg/dl showed a mean salivary glucose level of 1.002 mg/dl and patients with serum glucose levels between 180 and 440 mg/dl reflected a mean salivary glucose level of 2.31 mg/dl. [35].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] CDC (Centers for Disease Control and Prevention) (2017) Diabetes Growth Rate Steady, Adding to Health Care Burden. https://www.cdc.gov/media/releases/2017/p0718-diabetes-report.html

[2] Sanders, L.J. (2002) From Thebes to Toronto and the 21st Century: An Incredible Journey. *Diabetes Spectrum*, **15**, 56-60. https://doi.org/10.2337/diaspect.15.1.56

[3] Foderaro, L.W. (1990, October 14) W. A. Compton 79. A Doctor Who Rose To Head Miles Labs. New York Times. https://www.nytimes.com/1990/10/14/obituaries/w-a-compton-79-a-doctor-who-rose-to-head-miles-labs.html

[4] Martin, D.F. and Reiger, B.A. (2013) Kamlet Laboratories and Clinitest: Idea to Product. *Technology & Innovation*, **15**, 81-86. https://doi.org/10.3727/194982413X13608676060691

[5] American Chemical Society (2010) The Development of Diagnostic Test Strips. National Historic Chemical Landmarks Program, American Chemical Society, Washington DC.

[6] Youngson, R.M. (2005) Collins Dictionary of Medicine. Collins. https://medical-dictionary.thefreedictionary.com/clinitest

[7] Comer, J.P. (1956) Semiquantitative Specific Test Paper for Glucose in Urine. *Analytical Chemistry*, **28**, 1748-1750. https://doi.org/10.1021/ac60119a030

[8] Aryal, S. (2019, August 15) Benedict's Test—Principle, Composition, Preparation, Procedure and Result Interpretation. https://microbiologyinfo.com/benedicts-test-principle-composition-preparation-procedure-and-result-interpretation/

[9] American Diabetes Association (2020) 6. Glycemic Targets: *Standards of Medical Care in Diabetes*—2020. *Diabetes Care*, **43**, S66-S76. https://doi.org/10.2337/dc20-S006

[10] Riley, R.S. and McPherson, R.A. (2017) Basic Examination of Urine. In: McPherson,

R.A. and Pincus, M.R., Eds., *Henry's Clinical Diagnosis and Management by Laboratory Methods*, 23rd Edition, Elsevier, St Louis, Chap 28, 445-479.

[11] Sacks, D.B. (2018) Carbohydrates. In: Rifai, N., Ed., *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*, 6th Edition, Elsevier, St Louis, Chap 33, 709-730.

[12] Cowart, S.L. and Stachura, M.E. (1990) Chapter 139: Glucosuria. In: Walker, H.K., Hall, W.D. and Hurst, J.W., Eds., *Clinical Methods*: *The History*, *Physical*, *and Laboratory Examinations*, 3rd Edition, Butterworths, Boston, 653.

[13] Gillery, P. (2012) A History of HbA_{1c} through *Clinical Chemistry and Laboratory Medicine*. *Clinical Chemistry and Laboratory Medicine*, **51**, 65-74. https://doi.org/10.1515/cclm-2012-0548

[14] https://medlineplus.gov/diabetes.html#summary

[15] Schnell, O., Benjamin Crocker, J. and Weng, J. (2017) Impact of HbA1c Testing at Point of Care on Diabetes Management. *Journal of Diabetes Science and Technology*, **11**, 611-617. https://doi.org/10.1177/1932296816678263

[16] Jagannathan, R., Neves, J.S., Dorcely, B., Chung, S.T., Tamura, K., Rhee, M. and Bergman, M. (2020) The Oral Glucose Tolerance Test: 100 Years Later. *Diabetes, Metabolic Syndrome and Obesity*: *Targets and Therapy*, **13**, 3787-3805. https://doi.org/10.2147/DMSO.S246062

[17] Le Huong, T., Harris, N.S., Estilong, A.J., Olson, A. and Rice, M.J. (2013) Blood Glucose Measurement in the Intensive Care Unit: What Is the Best Method? *Journal of Diabetes Science and Technology*, **7**, 489-499. https://doi.org/10.1177/193229681300700226

[18] Mathew, T.K. and Tadi, P. (2021) Blood Glucose Monitoring. StatPearls Publishing; Treasure Island.

[19] Eyth, E., Basit, H. and Smith, C.J. (2021) Glucose Tolerance Test. StatPearls Publishing, Treasure Island.

[20] MayoClicic.org (2020, March 13) Hypoglycemia. https://www.mayoclinic.org/diseases-conditions/hypoglycemia/symptoms-causes/syc-20373685

[21] Clevelandclinic.org (2020, February 12) Hyperglycemia (High Blood Sugar). https://my.clevelandclinic.org/health/diseases/9815-hyperglycemia-high-blood-sugar

[22] American Diabetes Association (2016) 2. Classification and Diagnosis of Diabetes. *Diabetes Care*, **39**, S13-S22. https://doi.org/10.2337/dc16-S005

[23] Reddi Rani, P. and Begum, J. (2016) Screening and Diagnosis of Gestational Diabetes Mellitus, Where Do We Stand. *Journal of Clinical and Diagnostic Research*, **10**, QE01-QE04. https://doi.org/10.7860/JCDR/2016/17588.7689

[24] Garry John, W., Mosca, A., Weykamp, C. and Goodall, I. (2007) HbA1c Standardization: History, Science and Politics. *Clinical Biochemist Reviews*, **28**, 163-168.

[25] John, W.G. (2003) Haemoglobin A1C: Analysis and Standardization. *Clinical Chemistry and Laboratory Medicine*, **41**, 1199-1212. https://doi.org/10.1515/CCLM.2003.184

[26] Nihaal, R., Neha, V. and Kathleen, D. (2020) Monitoring Technologies—Continuous Glucose Monitoring, Mobile Technology, Biomarkers of Glycemic Control. In: Feingold, K.R., Anawalt, B., Boyce, A., Chrousos, G., de Herder, W.W., Dhatariya, K., *et al.*, Eds., *Endotext* [Internet], MDText.com, Inc., South Dartmouth.

[27] Schmelzeisen-Redeker, G., Schoemaker, M., Kirchsteiger, H., Freckmann, G., Heinemann, L. and del Re, L. (2015) Time Delay of CGM Sensors. *Journal of Diabetes Science*

and Technology, **9**, 1006-1015. https://doi.org/10.1177/1932296815590154

[28] Pleus, S., Kamecke, U., Link, M., Haug, C. and Freckmann, G. (2018) Flash Glucose Monitoring: Differences between Intermittently Scanned and Continuously Stored Data. *Journal of Diabetes Science and Technology*, **12**, 397-400. https://doi.org/10.1177/1932296817733095

[29] Bekiari, E., Kitsios, K., Thabit, H., Tauschmann, M., Athanasiadou, E., Karagiannis, T., *et al.* (2018) Artificial Pancreas Treatment for Outpatients with Type 1 Diabetes: Systematic Review and Meta-Analysis. *BMJ*, **361**, Article No. k1310. https://doi.org/10.1136/bmj.k1310

[30] https://www.fda.gov/news-events/press-announcements/fda-approves-first-automated-insulin-delivery-device-type-1-diabetes

[31] Ulsan National Institute of Science and Technology (UNIST) (2018) New Smart Contact Lens for Diabetics Introduced. ScienceDaily. https://www.sciencedaily.com/releases/2018/02/180222090133.htm

[32] Yan, F. (2015, November 2) PolyU Develops Highly Sensitive Biosensor for Measuring Glucose in Saliva. https://www.polyu.edu.hk/archive/media-releases/en/index_id_6159.html

[33] Sen, D.K. and Sarin, G.S. (1980) Tear Glucose Levels in Normal People and in Diabetic Patients. *British Journal of Ophthalmology*, **6**, 693-695. https://doi.org/10.1136/bjo.64.9.693

[34] Gupta, S., Nayak, M.T., Sunitha, J.D., Dawar, G., Sinha, N. and Singh Rallan, N. (2017) Correlation of Salivary Glucose Level with Blood Glucose Level in Diabetes Mellitus. *Journal of Oral and Maxillofacial Pathology*, **21**, 334-339. https://doi.org/10.4103/jomfp.JOMFP_222_15

[35] Gupta, V. and Kaur, A. (2020) Salivary Glucose Levels in Diabetes Mellitus Patients: A Case-Control Study. *Journal of Oral and Maxillofacial Pathology*, **24**, 187. https://doi.org/10.4103/jomfp.JOMFP_15_20