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A Portable Laser Urine Glucose Meter – a Preliminary Investigation

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

The most common method of detection/monitoring Diabetic Meletus (DM) is to draw capillary blood and measure pre-prandial or post- prandial glucose level. In addition, HbA1c is often done to measure glycated red blood cell (RBC) to monitor glucose level in blood over a certain period time (about 2 – 3 months). In any case, drawing blood is the only procedure to measure glucose in circulating fluid, blood. It is minimally invasive procedure and with some level of pain and discomfort. Yet, it is indeed an ordeal process of sharp needle pricking the tissue for repeated monitoring, particularly for those who have been diagnosed with Type 1DM and have to maintain strict control, The minor discomfort becomes an issue for old persons, infants and juvenile (of Type 1DM). If there could be a procedure and reliable technique to measure and monitor glucose in urine, the whole population of DM, will heave a sigh of relief. Also, if glucose level in urine, for borderline cases could be identified, this will be a major step for mass screening, more importantly for poor villagers of many Asian and African countries. The purpose of this research is to device a portable laser spectrometer for monitoring glucose concentration in urine. It is a preliminary study, done as a proof of concept, to explore the possibilities of reliable, alternative for DM detection technique.

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Keywords: Glucose concentration in urine; laser spectrometer; fluorescence; early detection of DM.

1. INTRODUCTION

Diabetes mellitus (DM) is considered to be one of the most common chronic diseases – sometimes called “mother of all diseases”- for the simple reason it is the starting point for a range of heart conditions and renal failures. It debilitates and cuts down the productivity of the individuals and the nation at large. According to the World Health Organization (WHO), approximately 8.9% of the world population (463 million) have diabetes mellitus (DM) in the world in 2020. It was only 415 million (about 8.3% of world population) 2015; this figure is expected to enhance to 592 million by 2035 with a maximum increase in the Middle East and North Africa. Saudi Arabia, according to a new report, has been ranked among the top 10 countries in the world with highest number of diabetic people, as 16% of Saudi adult population is suffering from this disease [1].

Among them, 90% of them were classified as a Type 2 Diabetes Mellitus (T2DM). Insulin resistance is the main reason of T2DM, which arises mostly as a result of over-weight and lack of exercise. The other 10% was reported as a Type 1 Diabetes Mellitus (T1DM) due to inherited insulin deficiency. The growing incidence of DM has gained the attention of the health ministry of Saudi Arabia. Serious steps have been taken by the ministry to reduce diabetes prevalence through focusing on preventative care. Mass screening is considered one of the government’s efforts to control the mortality and morbidity associated with the DM.

In spite of the long-term research, treatment or cure for diabetes has not been developed yet; all the measures that have been done so far were to reduce or retard the gravity of the disease; reversion to normalcy is possible only in rare cases

Hence, managing the life-impeding conditions of DM is essential for its control. By repeated glucose monitoring, the conditions of diabetes can be better controlled by managing the episodes of hypo- or hyper glycaemia and thus, optimizing patient treatment strategies.

The most common method of detection/monitoring DM is drawing capillary blood and measuring pre-prandial or post-prandial glucose level. In addition, (HbA1C) is used to measure glycated hemoglobin which reflects the glucose level in blood over a certain period time (about 2 – 3 months).

As of today, drawing blood is the only procedure to measure glucose in circulating fluid, blood; it is minimally invasive procedure with some level of pain and discomfort in addition to the risk of infection. Yet, the sharp needle pricking, for repeated monitoring is indeed an ordeal for, many particularly, those who have been diagnosed with DM. This minor discomfort becomes an emotional issue for old persons, infants and juvenile (who suffer from T1DM) who have to have periodic dose of insulin injection and glucose monitoring, almost every day.

Hence, a non-invasive, reliable, and low-cost procedure to monitor glucose level is needed, that encourages more frequent testing; such method would help better and tighter control of the glucose level. In addition, it could offer a sigh of relief to the whole population of T2DM and T1DM.

Another important aspect of prevention of DM is, mass screening of DM particularly, in low-resource countries. If glucose level in urine, even for borderline cases, could be established in proportion to the plasma glucose, this will be a major step for mass screening, more importantly for poor villagers of many Asian and African countries, where other tests are not available.

A few studies have been made in this line, in which urine, sweat, and breath etc. were used as alternative samples for non-invasive glucose detection using different techniques [2-8]. In all these, the blood plasma glucose level (bgl) had been the most reliable gold standard. In a study of 2011 [1- 3] such a good correlation has been observed with 2080 subjects of varying level of insulin intolerance.

Optical techniques for monitoring glucose level have also been tried for four decades [9,10]. More recently, a great emphasis has been given to develop optical novel non-invasive procedure to provide point- of- care sample information using other accessible biological fluids, such as sweat. The results obtained have proven the potential of measuring the glucose concentration of biological body fluids using the optical methods, such as Infra-red spectroscopy, Raman Spectroscopy, with reasonable correlation with

blood measurements [4-13]. Such correlation between the blood & urine measurements has been verified in a preliminary work done by us on 20 subjects with varying levels of insulin intolerance using Laser induced Fluorescence spectroscopy. To the best of our knowledge this is the only systematic quantitative study of urine glucose level (ugl) employing portable laser spectrometer.

2. MATERIAL AND METHODS

The sample was prepared as below: 5 ml of Benedict reagent chemical was mixed with 0. 5ml of urine (from subjects of different level of DM); it was heated to boil; shaken gently for even mixing and then allowed to stand till room temperature was reached. Note that the urine samples were collected from persons of known blood glucose level (bgl) as measured by Hb A1c

The fluorescence spectra were recorded in a laser spectrometer explained below. (Fig. 1 is the schematic of laser spectrometer). A violet diode laser (405 nm 10 mw operated with 6 v battery) beam was allowed to fall on the sample to produce laser induced fluorescence (LIF) from the sample. The LIF signal was collected by an optical fiber and fed to (grating- CCD) spectrometer. The output of the spectrometer was processed by an A-D convertor and a custom-built software. The final result was read on a laptop (as shown in this paper) or a digital meter very similar to the conventional blood glucose-meter (not shown). The whole instrument could be made portable, compact with the dimension of 15 cm x 12 cm x 5cm and weight of 500 gm. It can be interfaced with the mobile, as and when required through a custom-built app. In the following only the LIF of different samples are shown one blow another to visualize the sensitivity of the technique.

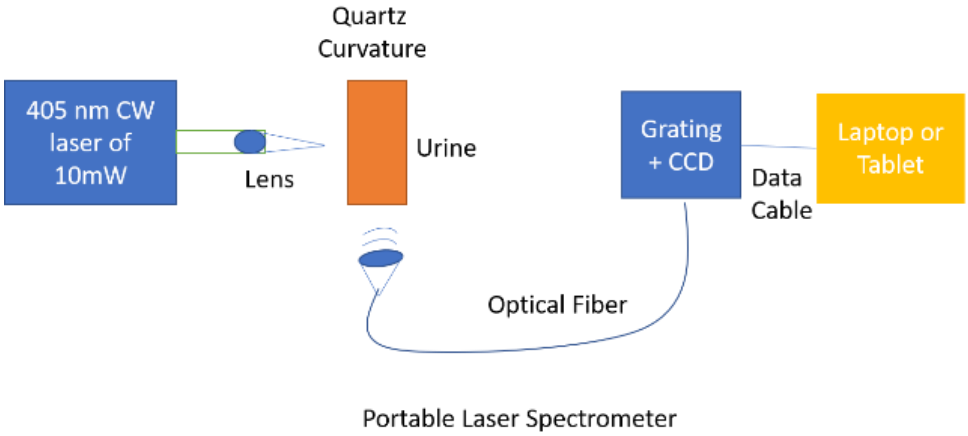

Fig. 1. The schematic of laser spectrometer

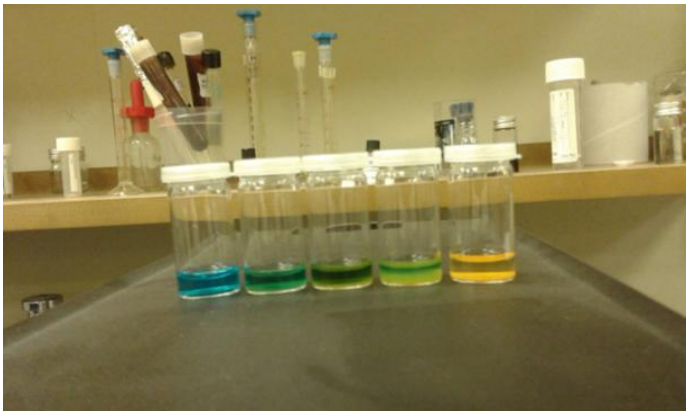

Fig. 2. Changes in the color of the samples

3. RESULTS AND DISCUSSION

Fig. 2 represents the changes in the color of the samples of Benedict reagents treated with the urine. It gives a qualitative view of changes in the coloration.

All the other figures given below may be regarded as the quantitative measurements of LIF as a function of different level of urine glucose level (ugl).

Fig. 3 gives the LIF of chemical *without any addition of urine;* it is the back-ground signal. This has a peak at 460nm and a band width, Half width half maximum (HWHM) of 50 nm with an intensity of 20 in arbitrary units.

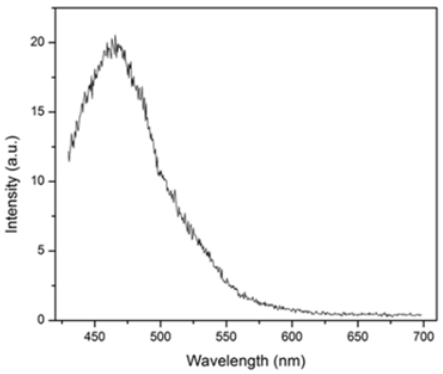

Fig. 3. LIF of chemical without any addition of urine

In contrast, the Fig. 4 gives the LIF of the sample treated with urine of Non diabetic patient of bgl = 5.0; Note the increase in intensity from 20 to 220 at 465nm and a weak shoulder at 525 nm with an intensity of 70. Note the spectral width (HWHM)=70nm. All these should be compared with the spectral features of sample of patients of higher level of bgl.

Fig. 5 given below is the LIF of the sample treated with urine of pre - diabetic patient of bgl = 6.5. Note the decrease in intensity from 220 to 110 at 465nm and a weak shoulder at 525 nm with an intensity of 60; The spectral width (HWHM)=90nm

The Fig. 6 gives the LIF of the sample treated with urine of diabetic patient of bgl = 8; Note the peak at 550nm which has become prominent to the level of 100 and the peak at 465 has gone down (with the intensity of 20 only) HWFM has become again 60nm; note the remarkable red shift of the spectrum.

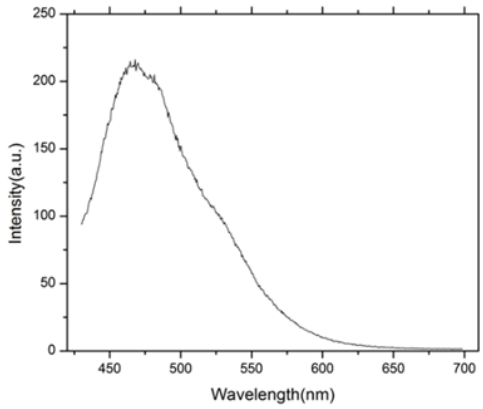

Fig. 4. LIF of the sample treated with urine of Non diabetic patient

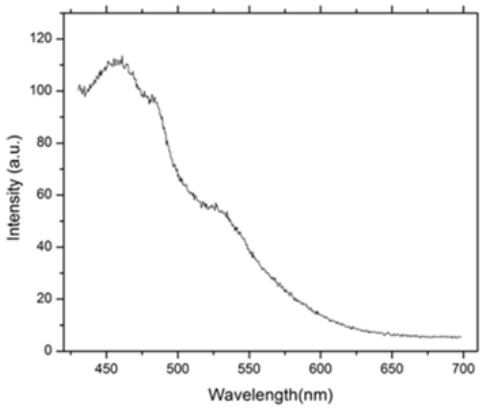

Fig. 5. LIF of the sample treated with urine of pre - diabetic patient

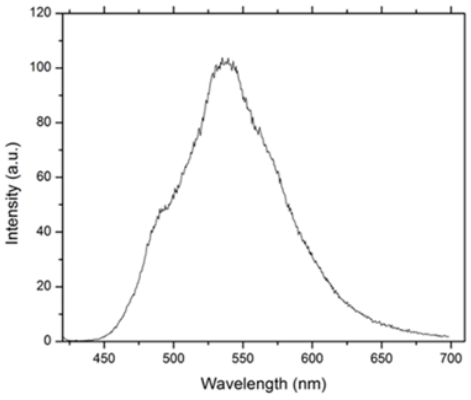

Fig. 6. LIF of the sample treated with urine of diabetic patient of bgl =6

Fig. 7. gives the LIF of the sample ample treated with urine of diabetic patient of bgl =11; the peak at 550nm has become 60 only with the intensity of 15 at 465 nm

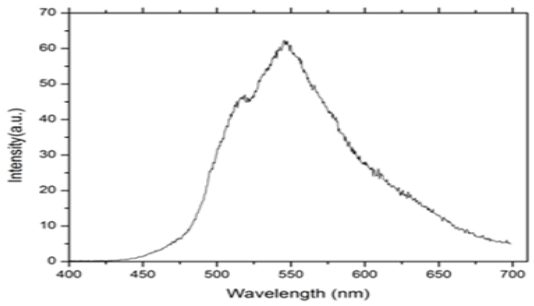

Fig. 7. LIF of the sample ample treated with urine of diabetic patient of bgl =11

Fig. 8 given below is the LIF of the sample treated with urine of diabetic patient of blood glucose level= 13.5; the 465 nm peak has almost disappeared with an intensity of only 3. Note the shift in the peak from 550 to to 575 nm and the intensity is at 35 only even at 550nm !! :

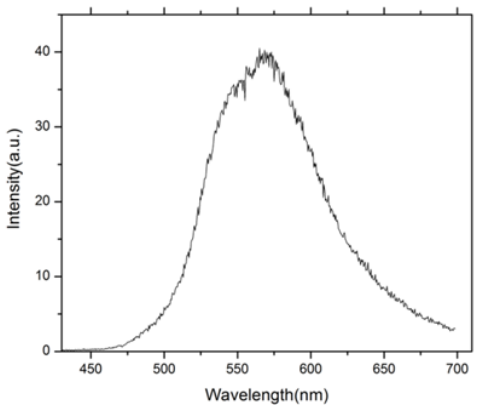

Fig. 8. LIF of the sample treated with urine of diabetic patient of blood glucose level 13.5

There are two major changes in these LIFS (laser induced fluorescence spectra): firstly, reduction in intensity and secondly, shifts in the wavelengths as glucose level in urine increases.

Fig. 9 shows 5-fold decrease in intensity as blood glucose level changes 2.5 times (from 5.5 to 13.5)

In order to quantify precisely the changes of color we may adopt ratio fluorometry (capable of showing high sensitivity) wherein the ratio of intensities is measured at two different wavelengths. In this case, R1 = I_{550}/I_{465} , ratio of intensities at 550 and 465 nm had been chosen which shows (Fig. 10) dramatic non- linear increase in the ratio parameter R1 with the increase in the glucose excreted into urine.

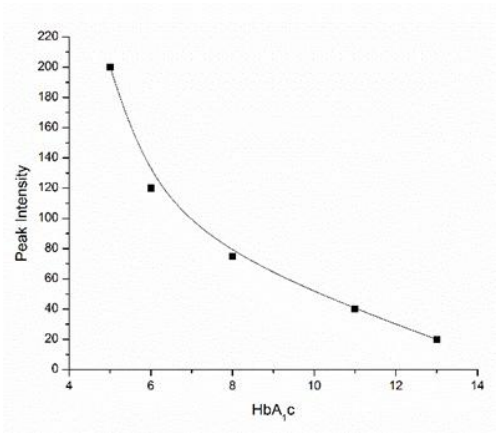

Fig. 9. Note 5-fold decrease in intensity as glucose level increases in urine

3.1 Discussion

There are two ways of disease management of DM: first is the prevention; second is the constant monitoring. This is very much true for most of the chronic but not life -threating disease like DM. With this objective, a portable quantitatively reliable urine glucose monitor had been designed and tested.

The principle of urine glucose measurement is the well- known Benedict test. Some sugars such as glucose are reducing agents because they are capable of transferring (electron) to other compounds, a process called reduction. When reducing sugars are mixed with Benedict's reagent and heated, the Copper (II) ions in the Benedict's solution are reduced to Copper (I) ions, which causes the color change. As more and more glucose molecules are found in the Benedict solution more and more Copper (II) ions are reduced to Copper (I) ions . Consequently ,there is a steep increase in the ratio parameter R1, which is a measure of glucose level in urine in comparison to that of normal level. It has been found that for a variation of blood glucose level 6.5 to 13.3 (all in mm/l) there is a corresponding urine glucose level LIF indicator enhancement from 0.9 to 18. Note, as the slope is high, every small variation in glucose level could be quantified. For example, the ratio parameter R1 is 0.3 for normal (<5) but 0.62 (6-6,6)for pre-diabetic and it is 1 for HbA1c =7.

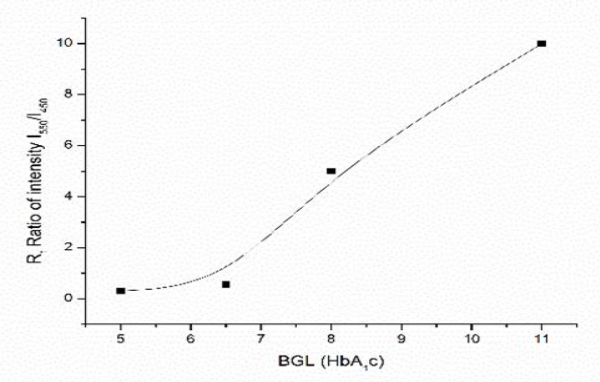

Fig. 10. Dramatic non- linear increase in the ratio parameter R1 with the increase in the glucose excreted into urine

The two -fold increase is sure way of catching pre diabetic subjects and they can be warned to change their lifestyle such as food habits and exercises.

The ratio parameter R1 becomes 1.0 for a HbA1**C** level of 7. which may be indicative of the "cut off" point for uncontrolled level of glucose level in blood; It appears as though, kidney seems to groan under the overload of glucose. It seems to open a" glucose gate" at this critical point after which it throws out most of the glucose left in the blood circulation. This must be taken as a warning signal of emergency measures to salvage kidney and of course cardiovascular system.

The advantage of this kind of laser spectrometer are: it can be a self- testing machine something similar the blood pressure measuring or blood glucose kit. It can be made cheap as the technology involved is very simple and the number of users is very large, almost 15% of the adult population.

4. CONCLUSION

In this preliminary report the design of a portable laser detector had been demonstrated for monitoring glucose level in urine; Here, we have employed laser induced fluorescence with a diode laser at 405 nm**.** The ratio parameter R1, readable on the digital display, is so sensitive

1. That the invention is useful for continual, every day home-monitoring by the patient without any medical personnel assistance.
2. The ratio parameter R1 readable on the digital display is so sensitive in the range of 0.04 to 1 so that pre -diabetic could be identified in mass-screening in the villages.

It is important to note that DM is controllable if not curable; Hence, many DM patients manage to live long healthy life by changing their life style to keep their bgl around 6.5. The whole laser meter can be made compact to the same size and weight of blood- glucometer available in market and made user friendly. For those kind of health -conscious people whose parents are T2DM this device may become the most -sought after boon.

On the other side of the spectrum of people, many villagers do not take up the burden of health check -up because of unavailability of hospitals and clinics in easy reach; morbid fear of needle prick and fasting blood test. This is an unbelievable but real tricky problem in many villages where at least 20 % of populations live in semi literacy and semi poverty in each country. For this segment of the people, the so-called "out -reach programs" will be necessary. For them, such camps with urine sample analysis, will go a long way to reduce the hefty burden of DM in any part of the world.

A caveat is that the results of the paper is the first step- with known cases of known level of blood glucose level. It has to go through many more stages such as single blind and double-blind studies etc. before it could become a clinically viable protocol.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests OR non-financial

interests OR personal relationships that could have appeared to influence the work reported in this paper.

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