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Influence of Cinnamic Acid, Methyldopa and Ethanol on the readings of Three Glucometers Currently Used in Iraq

Esraa Ghazy[1*], Ayat K. Abdulellah[1], Hayder R. Fadhil[1&3], Farah Hashim[1], Mohammed Alawami[2], Zainab Emad[1]

[1]Department of pharmacy, Al-Rasheed University College, Baghdad, Iraq.
[2]Cavendish Laboratory, University of Cambridge, CB3 0HE, Cambridge, United Kingdom.
[3] National Center for Drug Control and Research, Department of technical affairs, ministry of Iraqi Health, Baghdad, Iraq.
Email: The_pharmacist_e@yahoo.com
*****Corresponding Author

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ABSTRACT

Background: Dibetes mellitus represents a major public health concern carrying a high rate of morbidity and mortality. Its complications are highly prevalent and might be inevitable in certain circumstances, and the proper monitoring of patients might be the only weapon to minimize these complications. Self-monitoring with a glucometer is the most widely used method for such an issue. The accuracy of these devices has been always a subject of huge debate. The current study aimed to investigate any potential interfering effect of cinnamic acid, methyldopa and ethanol on the measurement of blood glucose estimated by certain glucometers; Accu-chekinstant, Rossmax HS-200 and Oncall plus.

Method:A total of 8ml of blood from a non-fasting participant was drawn after collecting consent, which was then collected in the lithium-heparin tube and centrifuged to isolate blood plasma, divided into 2 groups each spiked with interferants (methyldopa, cinnamic acid). For ethanol, the procedure is different, a participant's finger was sprayed with 70% ethanol, before the alcohol dries, we lance the finger and test the level of interference by comparing the reading to the baseline. The obtained results were statistically evaluated using Paired T-test.

Results: The presence of cinnamic acid resulted in a significant increase in glucometer readings compared to the baseline reading. The presence of topical 70% ethanol also result in a significant difference in glucometer readings compared to the baseline reading. The presence of methyldopa resulted in a significant decrease in Accu-chek instant compared to the baseline reading but not for Oncall plus or Rossmax HS-200.

Conclusion : all three glucometers were significantly affected by cinnamic acid and topical ethanol 70%, while only the Accu-chek instant was affected by methyldopa.

Keywords: Glucometer, Cinnamic Acid, Methyldopa, Ethanol

INTRODUCTION

Diabetes has become a major public health concern in the 21st century, and its prevalence has been described as an epidemic in many countries, including Iraq, where it has increased from 5% in 1978 to 19% in 2012 [1,2]. Oxidative stress has been linked to diabetes, and it can result from either increased production of free radicals, reduced antioxidant defense, or both [3]. Blood glucose levels in diabetic patients are commonly measured using glucometers since there are no ideal medications available for maintaining blood sugar levels at the same level as that of healthy individuals [3]

The main components of a glucometer are a detector and enzymatic reactions, where the enzyme portion of the glucose meter is often packaged in a dehydrated form in a disposable strip or reaction cuvette. When the glucose in the patient's blood sample rehydrates and interacts with the enzymes, a product that can be detected is created. Some glucometers produce hydrogen peroxide or an intermediary that can interact with a dye to alter color, while others use enzymes to create a biosensor that produces an electron that the meter detects. Glucose oxidase, glucose dehydrogenase, and hexokinase are the three most commonly used enzymatic reactions in current glucose meters [4].

A blood glucose meter is used to measure the amount of glucose in the blood and has been extremely significant in the field of medicine. Due to its portability, quickness, affordability, simplicity of use, and precise and visible

results [5] The current blood glucose meters, however, can only detect glucose levels between 0.6 and 33 mmol/L (10 and 600 mg/L). [6]

Currently, the electrode-type glucose meter, a current mode enzyme sensor, is the most popular portable blood glucose meter. [7] The most prevalent enzymes are glucose dehydrogenase (GDH) and GOx. The two enzymes differ in terms of their glucose affinity and selectivity, stability, and reduction potentials. [8] Recently, two GDH family enzymes, NAD-GDH and flavin adenine (FAD)-GDH, have been developed which are not only extremely specific to glucose but also resistant to oxygen. [9] The accuracy of glucose meters has been reported to be impacted by a variety of factors, including oxygen tension, hematocrit level, ascorbic acid, acetaminophen, and dopamine. [10] Electrochemical techniques used in some glucose meters may be impaired by pH extremes and high concentrations of reducing substances, such as salicylates and ascorbate. [11]

Understanding the chemical basis of the glucose test strip is essential in comprehending how interferants affect glucometer readings. The immobilized glucose oxidase catalyzes the oxidation of β-D-glucose by molecular oxygen, producing gluconic acid and hydrogen peroxide, which is the fundamental principle of the glucose biosensor [12].

$$\text{Glucose} + \text{GOx} - \text{FAD}^{+} \rightarrow \text{gluconic acid} + \text{GOx} - \text{FADH}_2$$

Flavin adenine dinucleotide (FAD) is a necessary redox cofactor for glucose oxidase to function as a catalyst, and as the first electron acceptor, it functions and is converted to FADH2 [13]. Hydrogen peroxide is produced as a result of the cofactor's reaction to oxygen.

$$\text{GOx} - \text{FADH}_2 + \mathbf{O}_2 \rightarrow \text{GOx} - \text{FAD} + \mathbf{H}_2\,\mathbf{O}_2$$

A platinum (Pt) anode is typically used in catalytic hydrogen peroxide oxidation, and the electron flow is easily detected by the electrode, and this electron flow is related to the number of glucose molecules in the blood [14]

The electrochemical sensing of glucose mainly relies on the measurement of oxygen consumption, the measurement of the amount of hydrogen peroxide produced by the enzyme reaction, and the use of a diffusible or immobilized mediator to transfer the electrons from glucose oxidase to the electrode [13]

$$H_2O_2 \rightarrow 2H^{+} + O_2 + 2e$$

The measurement of oxygen consumption, the measurement of the amount of hydrogen peroxide produced by the enzyme reaction, and the use of a diffusible or immobilized mediator to transfer the electrons from the GOx to the electrode are the three main methods for the electrochemical sensing of glucose [13]

Cinnamon has long been known to have anti-diabetic activity, and it has been commonly used among Iraqi diabetic patients to reduce blood glucose levels [15] In vitro studies suggest that cinnamon exerts antidiabetic effects by suppressing gastrointestinal enzymes, modulating insulin response and sensitivity, enhancing glucose uptake, reducing gluconeogenesis, and boosting glycogen synthesis [16]. Cinnamon contains an essential oil in its bark, with cinnamaldehyde being the main component (60-80%). Further minor components include trans-cinnamic acid, o-methoxycinnamaldehyde, eugenol, and monoterpenoids[17] Cinnamon has been demonstrated to have potent antioxidant properties [18], which is essential because insufficient glycemic control-induced hyperglycemia increases the production of reactive oxygen species and damages membranes due to peroxidation of membrane lipids and protein glycation[19] For this reason, targeting oxidative stress is necessary for diabetic patients, and cinnamon is shown to have antioxidant activity, mainly cinnamic acid [20]

Methyldopa is a medication that lowers blood pressure by reducing the levels of certain chemicals in the blood. Methyldopa is considered safe for pregnancy [21] , it has no genotoxic effect [22] and it is used for pregnant women with high blood pressure [23]Methyldopa may improve glucose levels during pregnancy where It was found that the use of methyldopa for gestational hypertension by pregnant women using insulin helped reduce the need for insulin use by 30% [24] There are not enough studies on the effect of using methyldopa on patients with diabetes In addition, the interference of Methyldopa with glucometers has not been investigated yet.

After the COVID-19 pandemic, ethanol use as a sterilizer has increased[25,26]. Studies have shown the interference of some disinfectants, such as hydrogen peroxide, with glucometers. However, the effects of 70% topical ethanol on glucometer readings have not been tested yet.

Aim

The current study aimed to investigate any potential interfering effect of cinnamic acid, methyldopa and ethanol on the measurement of blood glucose estimated by certain glucometers; Accu-chekinstant, Rossmax HS-200 and Oncall plus

MATERIALS AND METHODS

Interfering substance preparation

Cinnamic acid is dissolved in ethyl alcohol (since it is slightly soluble in water) in the following concentrations: 0.06, 1 and 5 mg/dL, no heat was required;the cinnamic acid solution wasrefrigerated for multiple use cases. Methyldopa is dissolved in distilled water to prepare a stock solution (100mg in 100 ml) then prepare the desired concentrations with serial dilution; the methyldopa solution was made and used for spiking immediately

Main experiment

A total of 4ml of blood from a non-fasting participant was drawn after collecting consent (discussed in the ethics section), which was then collected in lithium-heparin tube to be centrifuged and to isolate blood plasma, about 495 micro milliliter of plasma was placed in disposable tubes to be spiked with 5 micro milliliters of interference of various concentrations (discussed in interference table). For ethanol, the procedure is different, a participant's finger is sprayed with 70% ethanol, before the alcohol dries, we lance the finger and test the level of interference by comparing the reading to the baseline.

Eight milliliters of blood were taken from each of the sixteen participants—six were assigned to the methyldopa and cinnamic acid experiment, and the remaining ten were assigned to the topical ethanol experiment.

Materials and concentration

Table 1: substances used as interference for glucometers: cinnamic acid, topical ethanol 70% and methyldopa.With the corresponding concentrations for cinnamic acid and methyldopa, the specified concentrations were chosen to represent different levels: low, normal and overdose for each substance.

Interference	Group	No. of aliquots	Concentrations	References
Topical ethanol (70%)	healthy	*	N/A	18
Cinnamic acid	healthy	3	0.06,1, 5 ml/dL	20
methyldopa	healthy	3	5,20,50 ml/dL	21

Ethics

In the beginning, we searched for volunteers by making posters for volunteering to do the experiment, and the publication was near the experimental work center (research laboratory) inside the university. Every volunteer who came was free to agree or refuse after we asked some questions.

The volunteers were between the ages of 19 and 23, all healthy, last meal was recorded. We made sure of the availability of tools for physical health and safety from chronic diseases. Blood was drawn with the help of a trained supervisor. We also informed the volunteer of the availability of treatment in the event of an emergency after drawing a blood sample from them.

Storage and cleaning process

All graduated cylinders used for storage were thoroughly cleaned before use, cinnamic acid solution is refrigerated for multiple use cases, methyldopa solution is kept in a dark, cool place away from light since it is photosensitive and immediately discolors, topical ethanol is kept at room temperature. Blood samples were incinerated according to protocol.

Statistical analysis

Paired T-test was used for this study to indicate the changes in level of interference, program used was Jamovi. error bars were reported as standard deviation (SD).

Paired SamplesT-Test

Table 2: paired sample T-test and P-value for all glucometers and interreferences

			statistic	df	p
RossMax	MethyldopaConc.(mg\dl)	Student'st	5.79	3.00	0.010
Accu-CheckIn.		Student'st	5.26	3.00	0.013
OncallPlus		Student'st	11.21	3.00	0.002

			statistic	df	p
RossMax	Cinnamic acid Conc.(mg\dl)	Student'st	45.7	3.00	<0.001
Accu-CheckIn.		Student'st	45.0	3.00	<0.001
OncallPlus		Student'st	40.3	3.00	<0.01

			statistic	df	p
RossMax	Topical Ethanol 70%	Student'st	2.76	9.00	0.022
Accu-CheckIn.		Student'st	2.00	9.00	0.077
OncallPlus		Student'st	1.35	9.00	0.210

RESULTS

Effect of Cinnamic Acid, Topical 70% Ethanol and Methyldopaon Glucometer Readings

1) As shown in the table, the mean reading of cinnamic acid resulted in a significant decrease in glucometer readings compared to the baseline measurement for all devices.

2) The mean reading of methyldopa results did not show a significant difference in readings between the Rossmax and Oncall plus devices, but it displayed a noticeable decrease in readings on the Accu-Chek Instant device compared to the baseline measurement.

3) The mean of topical 70% ethanol resulted in a significant decrease in glucometer readings compared to the baseline measurement for all devices.

Table 3: All readings related to the interferences and their differences with the baseline readings were assessed through the mean, which was calculated after three readings for each device and concentration.

Rossmax HS-200 (FAD-GDH enzyme strips)								
Baseline Mean	Cinnamic Acid			Methyldopa			Topical Ethanol	
	Concentra-tion	Mean Reading	Standard Deviation	Concentra-tion	Mean Reading	Standard Deviation	Before Mean	Before Standard deviation
81.6	0.06 mg\dl	78	3	5mg\dl	80.2	1.095445	93.5	19.1847
	1mg\dl	78.6	1.527525	20mg\dl	81.4	1.516575	After Mean	After Standard deviation
	5mg\dl	78.3	1.154700	50mg\dl	82.8	2.863564	81.6	13.4594
Accu-chek instant (FAD-GDH enzyme strips)								
Baseline Mean	Cinnamic Acid			Methyldopa			Topical Ethanol	
	Concentra-tion	Mean Reading	Standard Deviation	Concentra-tion	Mean Reading	Standard Deviation	Before Mean	Before Standard deviation
86	0.06 mg\dl	84	2	5mg\dl	82.2	1.303840	96.6	21.7929
	1mg\dl	83.3	5.7735027	20mg\dl	82.4	1.516575	After Mean	After Standard deviation
	5mg\dl	82.6	1.5275252	50mg\dl	80.6	3.049590	102.4	23.8616
Oncall plus (glucose dehydrogenase enzyme strips)								
Baseline Mean	Cinnamic Acid			Methyldopa			Topical Ethanol	
	Concentra-tion	Mean Reading	Standard Deviation	Concentra-tion	Mean Reading	Standard Deviation	Before Mean	Before Standard deviation
143	0.06 mg\dl	140.6	2.886751	5mg\dl	143.2	3.633180	89.6	25.2595
	1mg\dl	131.6	5.7735027	20mg\dl	141.2	5.263078	After Mean	After Standard deviation
	5mg\dl	135.6	6.1101009	50mg\dl	144	1.870828	80	16.8325

DISCUSSION

The effects of three distinct interferences on the glucometer results, namely cinnamic acid, topical ethanol 70%, and methyldopa, were investigated. Our results revealed that cinnamic acid and topical ethanol 70%significantly affected all three glucometers, while only the Accu-Chek instant was affected by methyldopa.

Cinnamic acid showed high statistical significance, we hypothesize the reason for this result is the antioxidant effect of cinnamic acid [29], since ascorbic acid, a substance which is well-researched about its effect on glucometer readings [30], interferes withreadings through its antioxidant activity[31].

The influence of ascorbic acid is attributed to its competition to the redox indication system. Ascorbic acid is a strong reducing agent that reacts with hydrogen peroxide. With less hydrogen peroxide available to react with the dye on the test strips resulting from ascorbic acid consumption, this will lead to insufficient dye color development, which causes falsely reduced glucose readings.[32]

Topical ethanol showed an interference with glucometer readings, Mahoney et al. experimented with participants where one finger was cleaned was water and soap, the other finger used alcohol-based hand sanitizer, third was coated with cola and air-dried, forth finger was coated with cola and cleaned with alcohol sanitizer, finger sticks used for each individual finger, the experiment showed significant difference in readings with alcohol-based sanitizers.All glucose reading differences resulted by the dilution effect of topical ethanol,

are statistically significant depending on the surface area and so it will be an issue to use topical ethanol as disinfectant.[33]
For methyldopa, the readings were not significantly affected in the Rossmax and Oncall Plus devices, but they were impacted in the Accu-Chek Instant, with readings decreasing.This coincides with another study done in Chinese hospitals by Lv et al. [34]
To summarize,all three glucometers were significantly affected by cinnamic acid and topical ethanol 70%, while only the Accu-chek instant was affected by methyldopa.
For diabetic patients and medical professionals who use glucometers to check blood sugar levels, the study's findings are significant. It emphasizes the necessity of giving medication use careful thought when assessing blood sugar levels and highlights the significance of choosing an accurate and precise glucometer for diabetes management.

CONCLUSION

In conclusion, this study provides evidence that cinnamic acidand methyldopa can cause significant variations in glucometer readings, while topical ethanol 70% did not interfere as much, leading to inaccurate glucose measurements. Healthcare providers should be aware of the potential for interferences and should consider using glucometers that are less susceptible to interference. Further research is needed to identify other substances that may interfere with glucometer measurements and to mitigate the effects of interferences on glucose measurements.

Limitation

This study was conducted on a limited number of participants, this is a limitation that future studies can work on and utilize a larger group of participants and also increases the number of plasma samples by default. We also worked on specific devices for their popularity in Iraq and other devices can be tested in future studies. All substances used were highly pure but results may differ depending on the source of the material and the handling of said materials.

Gaps

In general, there is a lack of paper worked on the accuracy of glucometer in Iraq; the last one was in 2018 in Basra. High levels of misinformation about self-management practices [35] Because of less education for diabetes patients is a problem in Iraq. Consequently, Iraqi people do not trust the glucometer results so 44.3% calibrate with laboratory results and 46.6% of the patients will seek help from family members to use the device, on other hand, only 24% seek help from a doctor. [36].
Iraqi people have various beliefs and different health culture. [37]
For example, they use Cinnamon recipes to reduce glucose levels in the blood, which is 15% more effective compared with placebo. [38].Cinnamon also used in the Middle East and Iran for diabetes Acne, it is also used in Turkey for the same reasons. [39,40]
Methyldopa is an effective drug to decrease the level of blood pressure during pregnancy, in late-stage pregnancy the daily dose may increase. [41]
Gestational diabetes has become more prevalent in the Arab Gulf (5.1-37.7%) which is one of the highest scores in the world and it’s rising up quickly. [42]
For topical ethanol, its use after covid-19 as sterilizer was increased.Studies conducted on different detergents concluded that they can affect the accuracy of glucometer especially with high concentrations to a certain extent. [25] However, there is limited research on ethanol popularity in Iraq and its effect on glucometer accuracy.

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Author contributions

Blood collection, Ahemdsalim mahmood; collection of chemicals, Tiba M. Hameed; statistics and data analysis, Raeddhiaahashim; supervisors, Esraa G. Jaber, Raed dhiaahashim andMaysam hussien; writing and main experiment, Farah hashimkhammas, Zainab EmadAl-Araji, Huthaifahashim, Zahraa hussien, Haneen A. salih, and Hala meqdam;Practical lab work, Ehab khalifa

Declaration

The authors declare no conflict of interest

Key resources table

REAGENT or RESOURCE	SOURCE	IDENTIFIER
GLUCOMETERS		
OnCall plus	ACON laboratories Inc.	SN 103A30595D4
Accu-Chek instant	Roche	REF 09221794078
Rossmax HS200	Tyson Bioresearch Inc.	SN 218P01001800
STRIPS		
OnCall plus blood glucose strips	ACON laboratories Inc.	LOT 1692106
Accu-Chek instant blood glucose strips	Roche	REF 07819382446
Rossmax HS200 blood glucose strips	Tyson Bioresearch Inc.	LOT MPY1277012
CHEMICALS		
Cinnamic acid (>99%)	MERCK labs.	Art.800235
Ethanol absolute (>99%)	AFCO jordan	LOT No. AF1953
OTHER		
APCO Vacuum blood collection tubes, lithium heparin, 4ml	Al Hanoof for medical & lab supplies	REF: FV09009 LOT: 210608

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