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Keywords

Glucose meter; antioxidant; Parkes' error grid analysis; vitamin-C; *N*-acetylcysteine; glutathione; dihydrolipoate; cysteine; dithiothreitol; points-of-care; glycemic control; falsely-elevated glycemia; glycemic mismanagement; hypoglycemic drug overdoses; COVID-19

Abstract

Owing to their ease of use, glucose meters are frequently used in research and medicine. However, little is known of whether other non-glucose molecules, besides vitamin C, interfere with glucometry. Therefore, we sought to determine whether other antioxidants might behave like vitamin C in causing falsely elevated blood glucose levels, potentially exposing patients to glycemic mismanagement by being administered harmful doses of glucose-lowering drugs. To determine whether various antioxidants can be detected by seven commercial glucose meters, human blood samples were spiked with various antioxidants *ex vivo* and their effect on the glucose results were assessed by Parkes error grid analysis. Several of the glucose meters demonstrated a positive bias in the glucose measurement of blood samples spiked with vitamin C, *N*-acetylcysteine, and glutathione. With the most interference-sensitive glucose meter, non-blood solutions of 1 mmol/L *N*-acetylcysteine, glutathione, cysteine, vitamin C, dihydrolipoate, and dithiothreitol mimicked the results seen on that glucose meter for 0.7, 1.0, 1.2, 2.6, 3.7 and 5.5 mmol/L glucose solutions, respectively. Glucose meter users should be alerted that some of these devices might produce spurious glucose results not only in patients on vitamin C therapy but also in those being administered other antioxidants. As discussed herein, the clinical relevance of the data is immediate in view of the current use of antioxidant therapies for disorders such as the metabolic syndrome, diabetes, cardiovascular diseases, and coronavirus disease 2019.

1. Introduction

Owing to their ease of use, glucose meters are frequently used in medical practice and preclinical research. Vitamin C is known to falsely elevate glucose measurement on certain glucose meters [1–4], for example by reducing pyrroloquinoline quinone (PPQ; methoxatin), a component of some glucose meter test strips [5,6]. Antioxidants other than vitamin C, such as *N*-acetylcysteine (NAC) and reduced glutathione, can also reduce quinones [7]. These antioxidants, like vitamin C, are typically well tolerated by patients and are often administered in high doses both therapeutically and in clinical trials. We therefore questioned whether antioxidants other than vitamin C might also interfere with glucose measurements on glucose meters. To answer this question, we compared glucose results from seven commercially available glucose meters with those from a central laboratory (hexokinase method; Roche C502), for samples spiked with a series of antioxidants at, above, and below expected therapeutic levels.

2. Materials and Methods

2.1. Human blood samples obtained and study protocol

This study was conducted at Lille University Hospital (France). All results were obtained on venous blood samples (collected on heparin tubes [Vacutainer 4 mL, Lithium heparin 68 UI, Becton Dickinson]) by using glucose meters and central laboratory devices. They were acquired within 90 min following patient blood collection. Each blood sample was assessed simultaneously using glucose meters and Cobas C502 [Basel, Switzerland] determinations (used for comparisons) and testing was completed by an ultimate Cobas C502 determination performed in the absence of any drug for comparison with the initial baseline value. Differences of less than 15% between the initial baseline and final glucose values on the Cobas C502 system were required to retain a sample in the study dataset.

Patients were informed of their right to refuse the use of their clinical data and/or residual blood samples for this study (authorization DC-2008-642, French Research Ministry). Two antioxidants (NAC and glutathione) in addition to vitamin C were tested in this study. Homologous groups of blood samples (vitamin C [n = 35], NAC [n = 28], and glutathione [n = 31] groups) were prepared from the authorized residual blood sample bank through non-parametric comparison with the baseline plasma glycemic, and whole blood pH, pO_2, and hematocrit values (Kruskal–Wallis test p-values > 0.05). These initial baseline values (Table 1) were obtained with central laboratory Cobas C502 for glycemia, ABL 800 flex [Radiometer, Copenhagen, Denmark)] for pH and pO_2, and Sysmex XN analyzer [Kobe, Japan] for hematocrit.

Table 1
Range of glucose and other baseline values in the various blood sample groups tested.

Biological parameters	Human blood sample groups		
	Vitamin C (n=35)	NAC (n=28)	Glutathione (n=31)
Baseline glucose (mmol/L)	4.72 ± 0.9 [2.97-6.7]	4.97 ± 2 [2.64-13.2]	4.81 ± 0.85 [3.08-6.49]
pH	7.39 ± 0.06 [7.24-7.56]	7.38 ± 0.05 [7.23-7.47]	7.39 ± 0.06 [7.23-7.54]
pO_2 (mmHg)	110.4 ± 51 [38-200]	120 ± 45 [38.3-209]	119 ± 43 [36.7-195]
Hematocrit (%)	36.74±6.86 [25.6-51.1]	34.25 ± 4.8 [27.3-47.5]	35.5 ± 4.8 [27.2-48.4]

Biological data are expressed as the mean ± SD, with range values indicated within square brackets.

Results obtained from seven different glucose meters for samples with various concentrations of antioxidants (vitamin C, NAC, glutathione) were compared to results obtained for these samples using a central laboratory glucose assay (hexokinase; Roche Cobas C502).
The mid-level concentrations of the antioxidants used in this study were based on the blood concentrations reported in the literature for patients treated with vitamin C [8], NAC [9] or glutathione [10]. The low and high antioxidant concentrations are simply concentrations lower or higher than the mid-level concentrations; they may also correspond to levels in other therapeutic protocols or clinical trials. Blood samples were spiked to antioxidant concentrations of (all

concentrations given in mmol/L); 0.28, 1.13,and 2.84 for the vitamin C samples, 2.58, 12.9, and 64.3 for the NAC samples, and 0.06, 0.30, and 1.5 for the glutathione samples.

The clinical risks of biased results were assessed using the Parkes error grid analysis for type 1 diabetes [11]**.** The glucose meter readouts were plotted against reference standard values using R software and the error grid analysis (ega) package [12]. Measurements were performed in duplicate using seven different glucose meters. Strips were read on the glucose meter for which they were designed. Each experimental value was the mean of duplicate readouts. The duplicate reading of strips refers to the use of two separate glucose meters to read the same strip. In the event two glucose readouts differed by more than 15%, a third reading was performed using a third glucose meter, and only the two closest values were taken into account for calculating the mean value.

Antioxidant drug addition to the venous blood samples was performed as follows. Approximately 3 mL of each human blood sample from the residual blood sample bank mentioned above was used for inclusion in one of the three experimental groups shown in Table 1 (vitamin C, NAC, and glutathione groups). Within each experimental group, each blood sample was divided into four aliquots of 700 µL each for testing a given concentration of the antioxidant (no addition, and low, middle, and high drug concentrations). The antioxidants tested were available as vitamin C (ascorbic acid 1 g/5 mL, Bayer, Leverkusen, Germany), NAC (5 g/25 mL, Zambon, Bresso, Italy), and the reduced form of L-glutathione (Sigma-Aldrich, St. Louis, MO, USA). The vitamin C stock solution, which was a 10-fold dilution of the commercial preparation in distilled water, was added to the respective 700 µL aliquots (from the same blood sample) in the following volumes: zero (no drug addition, 0 mmol/L), 1.75 µL (low concentration, 0.28 mmol/L), 7 µL (middle concentration, 1.13 mmol/L), and 17.5 µL (high concentration, 2.84 mmol/L). For NAC, the commercial preparation was added undiluted to the respective 700 µL aliquots (from the same blood sample) as follows: zero (no drug addition, 0 mmol/L), 1.47 µL (low concentration, 2.57 mmol/L), 7.35 µL (middle concentration, 12.9 mmol/L), and 36.75 µL (high concentration, 64.3 mmol/L). In the case of the reduced form of L-glutathione, it was diluted in distilled water to prepare a 10 mg/mL (32.35 mmol/L) stock solution, which was then added to the respective 700 µL aliquots (from the same blood sample) as follows: zero (no drug addition, 0 mmol/L), 1.29 µL (low concentration, 0.06 mmol/L), 6.45 µL (middle concentration, 0.30 mmol/L), and 32.27 µL (high concentration, 1.5 mmol/L). For each 700 µL aliquot of spiked blood, 120 µL was used for measurement by the seven glucose meters and the remaining 580 µL was centrifuged for plasma preparation and analysis with the Cobas C502 automated glucose analyzer. A few blood samples were spiked with dehydroascorbate (Sigma-Aldrich, St. Louis, MO, USA), the oxidized form of vitamin C and were read with glucose meter A. In these human blood samples, dehydroascorbate was tested at the same mid-range (1.13 mmol/L) and high (2.84 mmol/L) concentrations used in tests using reduced vitamin C. All blood glucose values were corrected for the dilution factor caused by the additional volume of antioxidant drug solution.

2.2. Description of the glucose meter systems

The seven glucose meter systems (A to G) typically combined a cofactor-dependent enzyme (a glucose oxidoreductase) and an electron mediator. The enzyme cofactors were nicotinamide adenine dinucleotide, oxidized form (NAD^+); flavin adenine dinucleotide, oxidized form (FAD); and PQQ, oxidized form. In these systems, the electrons produced during the glucose-oxidizing enzyme reaction are transferred *via* the mediator from the enzyme cofactor to an electrode, which then

produces an electrical signal that is processed by the glucose meter to display the blood glucose value. The enzyme/mediator couples for the seven systems were as follows: an NAD^+-dependent glucose dehydrogenase and phenanthrenequinone (System A, Freestyle Optium Neo H, Abbott, Rungis, France), FAD-dependent glucose dehydrogenase and an osmium-based mediator (System B, Freestyle Papillon, Abbott), an FAD-dependent glucose dehydrogenase and nitrosoaniline (System C, Accu-Check Instant, Roche), an FAD-dependent glucose dehydrogenase and ferricyanide (System D, Nova Pro, Nova Biomedical, Les Ulis Courtaboeuf, France), a PQQ-dependent modified glucose dehydrogenase and nitrosoaniline (System E, Accu-Check Performa, Roche), a PQQ-dependent glucose dehydrogenase and 2,18-phosphomolybdic acid (System F, Accu-Check Mobile, Roche), and a modified glucose oxidase and ferricyanide (System G, Statstrip Xpress, Nova).
The glucose meters were calibrated for accuracy prior to their use by following the instructions given by the manufacturers.

2.3. Description of the reference automated Cobas C502 system

In the reference automated Cobas C502 system, hexokinase converts glucose into glucose-6-phosphate, which is then oxidized by glucose-6-phosphate dehydrogenase in the presence of $NADP^+$ to form 6-phosphogluconate. The resulting NADPH produced is detected by spectrophotometry at 340 nm.

2.4. Studies on non-blood samples

Non-blood samples were also tested with the respective glucose meter strips. Either the low-glucose control solutions of the various glucose meter systems or a 5 mmol/L phosphate-buffered solution (pH 7.4) were used as the background media for studying the detection of glucose, antioxidants, or both by the glucose meters.

To study the effects of vitamin C on the glucose meter measurements of non-blood samples, 50 µL of a vitamin C stock solution with a 10-fold higher concentration than the final vitamin C concentration (50 µL of distilled water at zero concentration) was added to 450 µL of the low-glucose control solution (provided with glucose meter system G). To study the effects of antioxidant thiols (NAC, glutathione, L-cysteine, dithiothreitol, and dihydrolipoate) on the glucose meter measurements of non-blood samples, glucose meter A was used to read strips loaded with 5 mmol/L phosphate-buffered solutions (pH 7.4) containing glucose alone (at a fixed concentration), the thiol antioxidant alone (at concentrations up to 12.9 mmol/L), or a combination of the two.
Dehydroascorbate was studied at 1 and 3 mmol/L, using the protocol mentioned above for antioxidant thiols.

3. Results

3.1. Studies on human blood samples

Studies on human blood samples were performed to essentially assess the clinical risks that could be caused by three antioxidants (vitamin C, NAC, and glutathione) stemming from their generation of falsely elevated blood glucose measurements in seven different glucose meters *vs.* a central laboratory glucose (hexokinase) assay.

3.1.1. Background comparison of the central lab *vs*. glucose meter results

In this study, the reference automated glucose assay was insensitive to interference from the tested antioxidants. Importantly, in the absence of interfering compounds, the Parkes error grids for assessing clinical risks indicated no risks when the glucose meter values were plotted against the reference values, with all error grid points falling within area A (data not shown).

3.1.2. Comparison of the automated glucose sensor and glucose meters in the presence of antioxidants

The glucose meters were sensitive to the addition of vitamin C, NAC, or glutathione to the blood samples, whereas the central laboratory results were unaffected. The glucose meter use conditions that were the most critical risk factors for potentially harmful medical action are illustrated in **Fig. 1** for vitamin-C and **Fig. 2** for NAC and glutathione. A more complete account of the Parkes error grid analyses of the effects of each of these antioxidants on the set of tested glucose meters is given in **Supplementary Figs. 1 to 3**.

3.1.2.1. Clinical risks associated with biases caused by vitamin C

At the low (0.28 mmol/L) vitamin C concentration (not illustrated), all (glucose meter G) or most Parkes error grid points were in area A, with one point (glucose meters A, B, C, E) or a few points (glucose meters D and F) lying in area B. At the middle concentration, vitamin C caused interferences with glucose meters A, B, E, and F and led to a few potentially problematic points located in area C of the error grids (22.5%, 11.7%, 23.5%, and 3.9 % of the glucose meter values, respectively) (**Fig. 1**). At the high concentration (met in some medical protocols; see Discussion), the clinical risk was very significant, with most glucose meter values falling outside the safe zones; that is, most points were located in area C and occasional (i.e., for glucose meters D and F) and numerous (i.e., for glucose meters A and E) points in area D (**Fig. 1**, **Supplementary Fig. 1**).

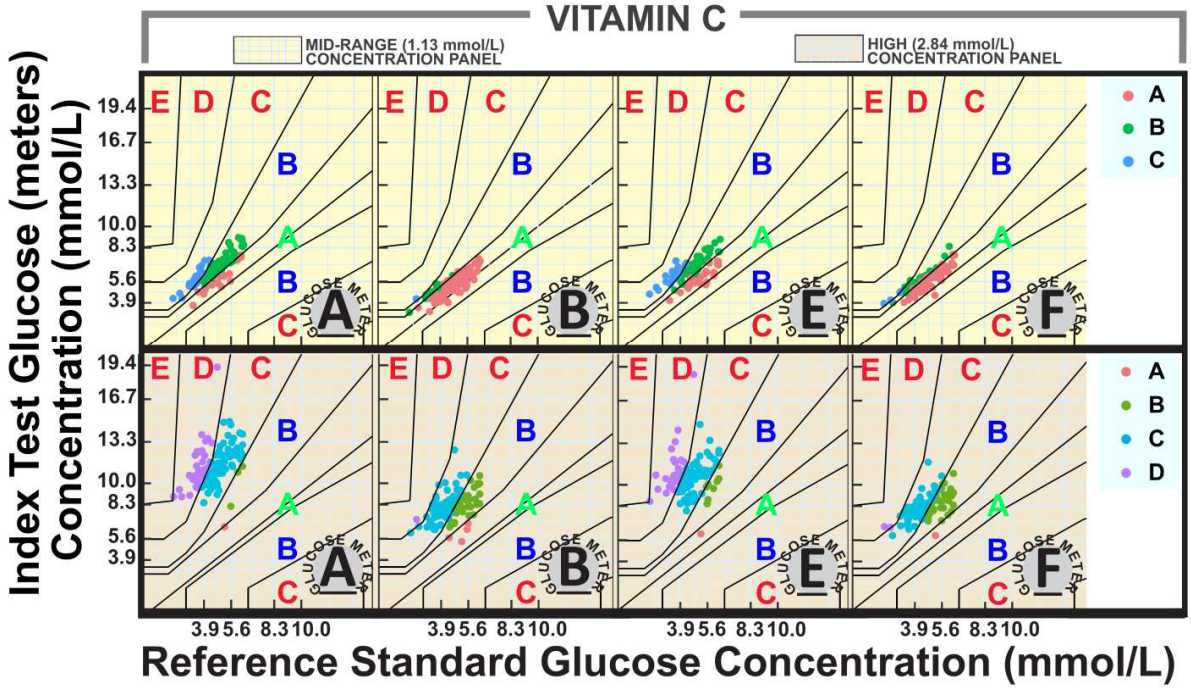

Fig. 1. Parkes error grid analyses of glucose meter results (index test) vs. reference standard (central laboratory) glucose values determined for human blood samples spiked with vitamin C *ex vivo*.
The most serious test conditions for patient risk in terms of potentially inappropriate medical treatment for mid-range and high vitamin C concentrations are illustrated. Individual error grids are divided into zones (or areas) A to E, which reflect progressive levels of increasing risk to patients. Results in the A and B zones of the grid will have little or no impact on clinical outcome while those in zones C, D, and E expose patients to increasing risk of overtreatment with glucose-lowering drugs. Underlined bold black letters refer to the different glucose meters as defined in the main text. Glucose meter data sets having all points in zones A and B are not illustrated, nor are data grids with insufficient data points. Point colors assigned by the software are defined in the upper right corner of the upper and lower panels of the error grids.

3.1.2.2. Clinical risks associated with biases caused by NAC

At the low NAC concentration, most points were located in area A of the Parkes error grids, with occasional points in area B for glucose meters B, C, D, and G, indicating little or no clinical risks (Supplementary Fig. 2). However, interferences associated with a clinical risk were detected at low concentrations with glucose meters A and E, with a substantial proportion of points being located in area B and, importantly, several points in area C (Fig. 2, Supplementary Fig. 2). At the mid-range concentration of NAC, the readouts produced by glucose meters B, C, and F were associated with little or no clinical risk (Supplementary Fig. 2). However, at this NAC concentration, all results obtained with glucose meter E fell within zones B and C of the error grid, indicating some clinical risk associated with these determinations (Fig 2). In addition, at this concentration of NAC, significant clinical risk was seen with meter A, with most of the values on the error grid falling into zones C and D, and one point in zone E (Fig 2). At the high concentration, NAC was associated with a potentially severe clinical risk with glucose meter A (all points distributed within the C, D, and E grid areas) (Fig. 2) and to a lesser extent with glucose meter E (all points lying in the B and C areas, with most values in the latter). The values measured with glucose meters B and F were not associated with a clinical risk for medical mismanagement (Supplementary Fig. 2).

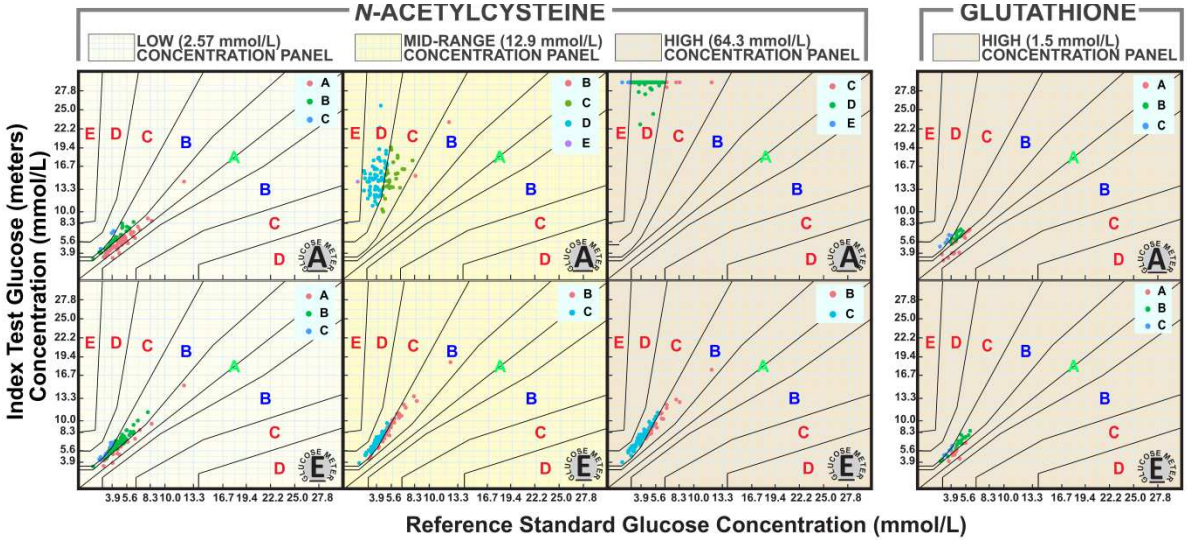

Fig. 2. Parkes error grid analyses of glucose meter results (index test) vs. reference standard (central laboratory) glucose values determined for human blood samples spiked with NAC or glutathione *ex vivo*.
The most serious tested conditions for patient risk in terms of inappropriate treatment for low, mid-range, or high NAC or high glutathione blood levels are illustrated. See the legend to Figure 1 for interpretation of the error grid zones, the underlined black letters, the point colours, and the sets of glucose meter values.

3.1.2.3. Clinical risks associated with biases caused by glutathione

At the low (0.06 mmol/L) and middle (0.3 mmol/L) concentrations of glutathione, all (for glucose meters C, E, F) and most points were located in area A, with one (for glucose meter G) or more points (for glucose meters A, B, D) lying in area B of the error grids (**Supplementary Fig. 3**). At the high concentration (1.5 mmol/L), glutathione exposed glucose meters A and E to the potential for generating clinical risk, as several points were located in grid area C (**Fig. 2**).

3.2. Studies on non-blood samples

These studies were aimed at better characterizing the interference of antioxidants with glucose meter results. In these experiments, vitamin C, NAC, glutathione, and other antioxidants were tested. The most representative results are illustrated in **Fig. 3A**, **B**, and **C** (for the respective compositions of the non-blood samples, see Methods).

As shown in **Fig. 3A**, the interference caused by vitamin C was dependent on the glucose meter tested and, when present, caused linear changes in the glucose values for increasing vitamin C concentrations of up to 2.84 mmol/L for all the non-blood solutions (or triggered an error message, as was the case for glucose meter G [shown] and glucose meters C and D [not shown]). Glucose meter C generated an error message for all non-blood solutions. Overall, vitamin C triggered an increase in glucose meter readouts in proportion to its concentration, as highlighted in the inset of **Fig. 3A**.

Fig. 3B depicts the glucose-mimicking properties of the interfering antioxidant (first histogram bar for each NAC concentration). The signals generated by the antioxidant and glucose (*i.e.*, values

generated by solutions containing both glucose and the antioxidant [third histogram bar for each NAC concentration]) were additive and approximated the theoretical sum of the glucose meter readouts on solutions with each of these compounds alone (last histogram bar of each histogram series).

As illustrated in Fig. 3C, at a similar 12.8 mmol/L concentration of antioxidants (tested alone or in the presence of 8 mmol/L glucose), dithiothreitol was the most potent interfering compound, followed by cysteine, glutathione, and NAC. This figure also shows the effect of increasing concentrations of the most potent interfering thiol compound of this series (dithiothreitol) on the glucose meter A readouts of non-blood samples. On the basis of these experiments and of one other using 1 mmol/L dihydrolipoate (not shown), it was estimated that 1 mmol/L NAC, glutathione, cysteine, vitamin C, dihydrolipoate, and dithiothreitol mimicked 0.7, 1.0, 1.2, 2.6, 3.7, and 5.5 mmol/L glucose concentrations, respectively. Under similar conditions, oxidized lipoate and oxidized vitamin C (dehydroascorbate) were found to induce little or no shift in the glucose values.

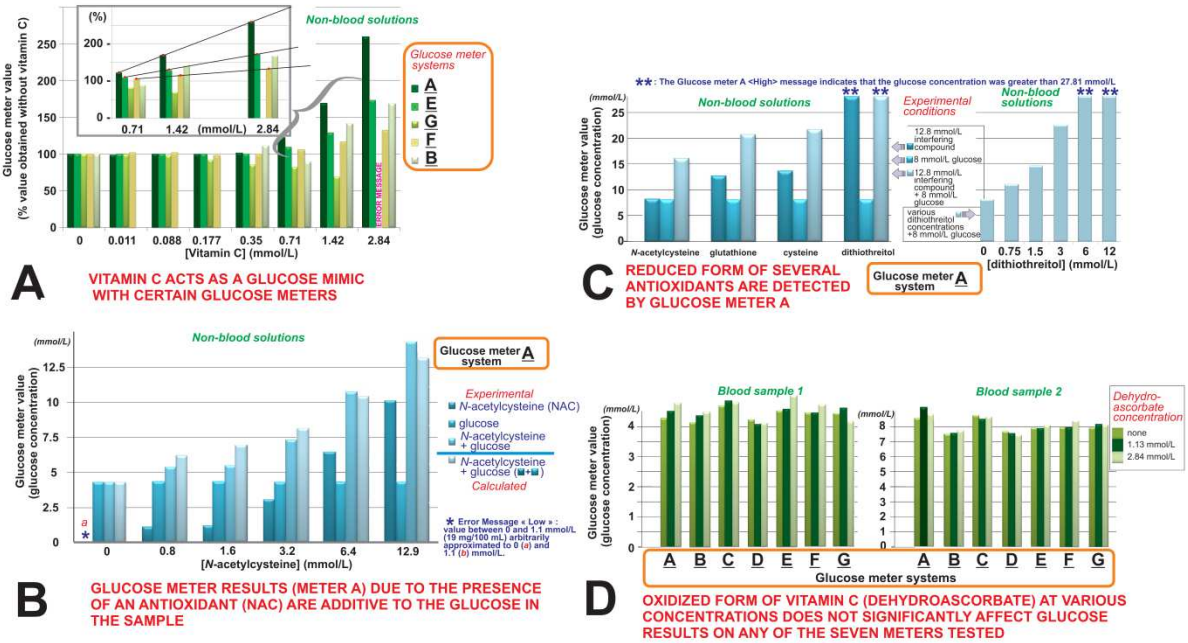

Fig. 3. Major characteristics of the interference of antioxidants with glucose meter measurements. Representative experiments showing that (**A**) the antioxidant behaves as a glucose mimic, (**B**) the glucose and antioxidant signals detected by a glucose meter are additive, (**C**) reduced forms of various thiol antioxidants may be detected, and (**D**) in contrast to the reduced form (ascorbate), the oxidized form (dehydroascorbate) of vitamin C induces little or no bias in the glucose readouts generated by the glucose meters. The non-blood solutions (Panels **A**, **B**, and **C**) are detailed in the Methods and Methods.

3.3. Miscellaneous

In contrast to the effects seen with reduced vitamin C (Figs 1 and 3A), dehydroascorbate in the human blood samples had little or no effect on the glucose readouts generated by each of the tested glucose meters (Fig. 3D).

Discussion

Several, although not all, of the glucose meters tested in this study detected antioxidants in addition to glucose. This poses a serious potential clinical risk to patients taking these antioxidants and monitoring their blood glucose levels with one of the affected glucose meters. Precise glucose monitoring instructions should therefore be provided to such patients. The *a priori* assessment of clinical risk by the Parkes error grid analysis of the various blood sample groups (Table 1), all with similar baseline parameters (glucose level, pO2, pH, and hematocrit), effectively rules out biases between the sample groups attributable to variations in these parameters.

Based on data presented in this study, it seems likely that patients taking large amounts of vitamin C or other antioxidants could be at significant medical risk if their continuing glucose monitoring system is subject to the same antioxidant interferences as seen with other point-of-care glucose monitoring systems. For instance, Freestyle Libre and Dexcom G5 are two popular continuous tissue glucose monitoring systems which, like glucose meter A, rely on glucose oxidase. Their sensitivity to vitamin C interference is now recognized, and in clinical studies using these systems, participants may be advised to not take this vitamin [13].

Intravenous infusions of 50-200 mg/day of vitamin C are well tolerated [14-19], and may lead to vitamin C blood levels as high as 22-28 mmol/L [16]. This creates a 7-10-fold higher blood vitamin C level than the levels used in this study. Patients receiving such intravenous infusions may therefore be exposed to very significant biases in glucose meter values, which may lead to overtreatment with glucose-lowering drugs. Vasudevan and Hirsh [20] in fact reported the case of a patient infused with vitamin C that had their glucose level measured with a glucose meter that used glucose oxidase-based strips (One-touch, Lifescan, Inc., Milpitas, CA, USA). The glucose level reported by the meter was double the actual glucose level, resulting in inappropriate insulin treatment and the death of the patient [20].

Similar to vitamin C, millimolar blood concentrations of other antioxidants can lead to false readouts on some glucose meters. Plasma levels of NAC may range from 2.6 to 18.4 mmol/L at 40 min after oral intake of 4–5 mg/kg [9]. At an oral dose of 600 mg twice a day (which, depending on the glucose meter type, might potentially expose patients to falsely elevated glucose values), NAC is effective in improving inherent components of the metabolic syndrome (high blood pressure, dyslipidemia, and blood oxidative stress markers) [21] as well as in reducing diabetic neuropathy and improving antioxidative defenses [22]. At high intravenous doses of this antioxidant, some cardiovascular protection is seen. For instance, in the NAC in Acute Myocardial Infarction (NACIAM) trial, which combined 29 g of NAC over 2 days with low-dose nitroglycerin, the infarct size was successfully reduced in patients who had undergone percutaneous coronary intervention for ST-segment elevation myocardial infarction [23]. NAC is also routinely and effectively used to protect the liver and other organs in cases of acetaminophen/paracetamol overdose. A plasma concentration threshold of 150-200 mg/dl (which falls in the mmol/L range) is required for NAC to act efficiently as an antidote, some protocols being based on initial boluses of up to 1 g/l (6-7 mmol/L) [24-26].

The 0.3 mmol/L concentration of glutathione used in the present study is exceeded in several therapeutic protocols, with a pharmacokinetics study indicating a blood concentration close to the millimolar range after intravenous high-dose infusion of the drug [27].
In patients with COVID-19, the administration of antioxidants (*e.g.*, glutathione [28] and NAC [29]), alone or with other drugs, has been reported. More than 30 trials addressing this disease and involving antioxidants have been registered [30], with several of them testing high doses of NAC (intravenous 6 g/day, NCT04374461; oral 2.4 g/day, NCT04419025) [30]. Additionally, there are at least three registered trials using unique or repeated intravenous administrations of 600 mg lipoic acid to improve endothelial function and limit stroke in patients with diabetes (NCT00490867, NCT04041167, and NCT01895699) [30]. Our study suggests that oxidized lipoate and not reduced dihydrolipoate be used, thereby limiting the bias in reported glucose levels for patients tested using glucose meters. The actual in vivo rate of lipoate reduction to dihydrolipoate remains to be clarified.

5. Conclusion

Falsely elevated glucose values potentially expose patients to overdoses of glucose-lowering drugs. This represents a potential concern for patients whose glycemic control relies on glucose meters, especially those being administered reduced forms of antioxidant drugs concomitantly with vitamin C. A limitation of this study might lie in the fact that the glucose range tested on the blood samples (as stressed in Figs. 1 and 2) was quite narrow and the sample numbers in each selected blood sample group were limited (~30 samples only). Nevertheless, our finding that some of the glucose meters tested were indeed sensitive to the antioxidants tested reveals that a warning to patients about false readouts is warranted and should be implemented immediately, especially given the recent increased uses of vitamin C and antioxidant therapies.

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TABLE

Table 1
Range of glucose and other baseline values in the various blood sample groups tested.

Biological parameters	Human blood sample groups		
	Vitamin C (n=35)	NAC (n=28)	Glutathione (n=31)
Baseline glucose (mmol/L)	4.72 ± 0.9 [2.97-6.7]	4.97 ± 2 [2.64-13.2]	4.81 ± 0.85 [3.08-6.49]
pH	7.39 ± 0.06 [7.24-7.56]	7.38 ± 0.05 [7.23-7.47]	7.39 ± 0.06 [7.23-7.54]
pO_2 (mmHg)	110.4 ± 51 [38-200]	120 ± 45 [38.3-209]	119 ± 43 [36.7-195]
Hematocrit (%)	36.74±6.86 [25.6-51.1]	34.25 ± 4.8 [27.3-47.5]	35.5 ± 4.8 [27.2-48.4]

Biological data are expressed as the mean ± SD, with range values indicated within square brackets.

Figure Legends

Fig. 1. Parkes error grid analyses of glucose meter results (index test) vs. reference standard (central laboratory) glucose values determined for human blood samples spiked with vitamin C *ex vivo*.
The most serious test conditions for patient risk in terms of potentially inappropriate medical treatment for mid-range and high vitamin C concentrations are illustrated. Individual error grids are divided into zones (or areas) A to E, which reflect progressive levels of increasing risk to patients. Results in the A and B zones of the grid will have little or no impact on clinical outcome while those in zones C, D, and E expose patients to increasing risk of overtreatment with glucose-lowering drugs. Underlined bold black letters refer to the different glucose meters as defined in the main text. Glucose meter data sets having all points in zones A and B are not illustrated, nor are data grids with insufficient data points. Point colors assigned by the software are defined in the upper right corner of the upper and lower panels of the error grids.

Fig. 2. Parkes error grid analyses of glucose meter results (index test) vs. reference standard (central laboratory) glucose values determined for human blood samples spiked with NAC or glutathione *ex vivo*.
The most serious tested conditions for patient risk in terms of inappropriate treatment for low, mid-range, or high NAC or high glutathione blood levels are illustrated. See the legend to Figure 1 for interpretation of the error grid zones, the underlined black letters, the point colours, and the sets of glucose meter values.

Fig. 3. Major characteristics of the interference of antioxidants with glucose meter measurements.
Representative experiments showing that (**A**) the antioxidant behaves as a glucose mimic, (**B**) the glucose and antioxidant signals detected by a glucose meter are additive, (**C**) reduced forms of various thiol antioxidants may be detected, and (**D**) in contrast to the reduced form (ascorbate), the oxidized form (dehydroascorbate) of vitamin C induces little or no bias in the glucose readouts generated by the glucose meters. The non-blood solutions (Panels **A**, **B**, and **C**) are detailed in the Methods and Methods.