Mini Review

Findings from a Metrological Analysis of Test-Strip Use in Diabetes Home-Care Control: A Confirmation

*Franco Pavese**

Metrologist, Formerly at Italian National Research Council; then Istituto Nazionale di Ricerca in Metrologia, Italy

Abstract

Recently a study by this author has been published about critical inconsistencies affecting this extremely extended type of control in home care. It was shown that basically the tests could be false or inconclusive due to insufficient rules of normalization governing this kind of test. In particular, the meaning of the advised (marginal) use of "control solutions" is mistaken, by being considered only a qualitative check of the tester readings, with no correlation with the capillary-blood glucose-level measured values. Instead, according to basic standard rules governing the field of testing, that solution has to be considered a "reference material" and consequently the way to check the calibration of the testers-whose recalibration should then be allowed when necessary (a feature presently not allowed).

The previous study was conducted on 4 popular testers (among the dozens existing) and their strips. Now an additional semi-professional one has been used for the same purpose, on the same patient-note that this study directly concerns the quality of the instruments, the testers, not the measurement on the glucose level in capillary blood in the pre-diabetes stage of a population of patients.

A one-year use of the new tester showed a quite different situation of consistent readings, based on an off-shelf correct calibration of the tester-persisting during the tests' full period. The previous ones, sparingly checked again with their respective strips, confirmed (a) their off-calibration condition, (b) the validity of the suggested method to recover the calibration, and (c) the urgent need for an ISO specific normalization of the control-solution features and use.

After a short recall of the previous findings, the paper compares them to new ones and discusses the resulting metrological/testing (and some clinical) consequences.

Previous Findings

Since middle 2016 the Author started a personal collation of home-made systematic checks of glucose in capillary blood, due to a diagnosis of pre-diabetes and the need to keep it under control. In so doing, his metrological competence solicited his scientific curiosity to make an analysis of the collected results and also to extend it to 4 different testers, among the many available on the market, not of the professional type but sold for home checks.

The results of this analysis exclusively based on the pre-diabetic range (nominal 100 mg/dL-125 mg/dL for plasma, i.e. 90 mg/dL-113 mg/dL for capillary blood) for the period up to August 2018 and about 1000 data have recently been published [1]. The main finding consisted in the apparent evidence of out-of-calibration condition of the testers provided by the measurements on their respective "control solution", on the inadequacy of the control solutions as a "reference material", on the incorrect function attributed to the control solution by the instructions to the user (and in most literature), and on the lack on the testers of means for re-adjust the calibration. The correction of the readings based on the out-of-calibration factor obtained from a correct use of the readings on the control solution showed the

possibility to obtain a much better consistency between the readings of all testers.

Subsequently, a tester #5 of a newer brand semi-professional type was used. Its different behavior, indicating a higher reliability, prompted a continuation of the study, whose results are reported here in the Figure 1 below (together with the summary of the previous ones-up to test 1395) to show that the hypotheses advanced in the previous part of the study were confirmed, including the method of performing corrections used with the previous testers.

Control Solution: definition, meaning and use

A small amount of control solution is provided by each specific supplier of a tester in order to check "if the tester reading are within the range indicated by the tester" for the specific portion in use of the lot. The user is encouraged to perform the check if she has a doubt about the regularity of the tester readings, but that is not a mandatory requirement.

Each individual box of strips is supplied with a numerical indication, consisting of a range of "valid indications" of the corresponding control solution. According to the current ISO17197 standard regulating the specifications of the testers, an uncertainty on the blood glucose level of ±15% is allowed, which is also valid for the readings on the control solution (basically a simple glucose in water solution). For the marginal (pre-diabetic) range (nominal 100 mg/dL-125 mg/dL for plasma, i.e. 90 mg/dL-113 mg/dL for capillary blood), most of the relevant solutions have a concentration of glucose of 100 mg/dL.

This is not mandatory, so other values can be provided by different manufacturers; however the indicated range for the used strip box is centered on the nominal value of the solution, whose uncertainty is never reported: in the study a 1% precision was assumed. Lacking information is that the "valid" solution range is simply the ISO one:

this implies that a calibrated tester measuring a sample of the control solution should read 100 mg/dL.

On the contrary, the only information provided in the tester instruction sheet is stressing that: (a) a reading on blood is valid if the reading on the control solution is within the provided range, (b) there is no correlation between the readings on the control solution and the readings on blood. The indication (b) is correct meaning that the glucose concentration in the patient blood has no correlation with the glucose concentration in the control solution. The indication (a) is formally correct (those readings are all within the ISO uncertainty of a measured value equal to the mean value of the range), but this was not always the case.

In conclusion, the presently prescribed use of the control solution is at least deceptive, but the author have also demonstrated that the control solution should be considered a Standard Reference Material (SRM), thought presently it does not comply with the rules of production and use of a SRM. A better use of control solutions was already suggested in [2].

Tester Calibration: definition, meaning and correction

As any measuring instrument, also each off-shell tester must be supplied calibrated, in order for it to show the numerical values effectively in mg/dl (or in mmol/mol).

Definition: In the present case, the fact that the indicated numerical value is expressed in the measurement unit mg/dL (or mmol/mol) must been ensured within the precision of the control solution concentration value-i.e. in this study (100 ± 1) mg/dL.

The previous part of this study has shown that, instead, the mean value of the "valid" range provided by the manufacturer on most strip boxes was not complying this mandatory rule: values up to 109 mg/dL-141 mg/dL were found.

Meaning: The mean value reported on the box is assumed to be assigned by the manufacturer on the basis of some (unknown) criteria, but it contradicts the value reported on the bottle of the control-solution, often as simple as having glucose in a concentration of 0.1%. The range, instead, is merely a ± 15% extension according to the present ISO 17197 ! Thus, it contradicts the assumed unit indication in mg/dL (or mmol/mol).

Correction: This is a normal operation that is done on instruments, like the tester is, for re-calibration. In the case of these instruments, on the contrary it is an unknown requirement, at least in the case of thus intended for private use. However, any user could make it by using the information from the manufacturer if supplied: the mean value of the indicated range can be used for this purpose. On the contrary, one could not use the value of any control solution as measured by the tester, because of the uncertainty of the latter. Consequently, the correction is only valid for the full batch of strips (e.g., 25 units) in the box. This fact may mask a change of the calibration of the tester during the period of time needed to exhaust a strip box: this limitation can be avoided only if the next box is from the same strip batch and with the same nominal mean value.

As a consequence, the advised check of the tester with the control solution might not seem to have any practical sense, not even the one assumed by the manufacturer-and also from a scientific view-point. In fact, it depends on the "typical" reproducibility of each specific tester, which can be, actually, up to 10 times better than its accuracy.

That means that, if one is performing several checks with the control solution during the time of use of a strip box, one may observe: Case (a), a good reproducibility of a specific value: one could use the mean of that dataset instead of the manufacturer offset with respect to the nominal concentration value of the control solution; Case (b), a significant trend: one could consider that as a short-term drift of the tester calibration has occurred; Case (c), random sparse values: bad reproducibility, one can only use the manufacturer range mean-value for the re-calibration.

In all instances, all such checks are out the reaches of a normal user, for lack of competence-and anyway the correction could not be registered on the current testers.

Results of the Study after June 2021

A semi-professional new tester, #5, was acquired and used since July 2021, with only some more measurements done with the previous #1-#4 testers. Its control solution is made with a glucose concentration of 140 mg/dL. The "valid range" indicated on the strip box supplied with the tester had a mean value of 140 mg/dL exactly, so one should expect that the off-shell supplied tester is calibrated, at least initially, differently from the previously-used testers.

Figure 1 chronologically reports, from March 2018 to June 2022, the overall results of the new and previous study obtained for the measurements on capillary blood with all 5 testers, the previous #1-#4 and the #5.

Some discontinuity or change in data dispersion can be observed at the change of a tester (in the order from tester #1 to #5). In autumn 2020 there is also evidence of two anomalous boxes of strips.

Figure 1 does not report the occasional double checks on capillary blood made with previous testers, sparingly done along the full study and found consistent after calibration correction (most then reported in Table 1). The Figure neither reports the checks with the respective control solution, which were more frequently performed with tester #5, in order to check, in addition: (a) any detectable instability of the tester with time; (b) the level of discrepancy of the tester readings on the control solution concentration value with the value supplied by the manufacturer (due to both tester and solution).

Most notable new findings and final remark

(1) The need for a tester indication correction is confirmed, to ensure that the numerical values are correctly expressed in mg/dL (within an estimated ± 5%).

(2) In Figure 1 the correction makes use of the departure of the manufacturer's strip-box strip-range mean value from the nominal control solution concentration value. This correction has no associated uncertainty since it does not arise from user's measurements: the reason is that it is due to remedy for a manufacturer inconsistency.

(3) However, the above correction does not take into account yet the possible tester out-of-calibration, so concerning measured values having an ISO uncertainty of ± 15%.

Actually, as also evident from the Figure, the short-term dispersion of the measurements, which can partially arise from the tester, was found more limited: for the overall reported data on blood they are close to ± 10% for the tester as is, and ± 8% after the correction (2). In details, 21 checks with tester #5 on control solution samples during one year now showed indications on samples of the control solution having a s.d. of 15 mg/mL, randomly distributed and consistent

with the tester ISO uncertainty, and a mean off-calibration of (-5% ± 5%) after elimination of 3 outliers, i.e. a mean value of (114 mg/mL ± 8 mg/mL). Table 1 shows cases of possible improvement of the consistency between contiguous readings of different testers obtained after correction (i.e., after their "re-calibration").

The check made at tester arrival with the same control solution in July 2021 had indicated 125 mg/mL, i.e. -10%, consistent with the subsequent checks. The offset fitted over the full year was a drift in time from 91% to 99% of the nominal value of the control solution, with a mean value of (94% ± 4%), corresponding to (132 mg/dL ± 6 mg/dL). It is not statistically significant, but it could be taken into consideration for a further correction of the strip-tests on blood, as it will be relevant to the concentration of glucose in blood in the pre-diabetic stage that has a range of only 25 mg/dL.

In conclusion, also that additional correction could also be applied to the tester indications, with an estimated uncertainty of about ± 5%. However, this issue still requires further confirmation, and has not been used/shown here (Figure 1).

It demonstrates that checks with a control solution must be considered mandatory, as they can have an important use, though different from the one presently declared by the manufacturer under the existing rules.

(4) The control solution must became an effective SRM, and consequently a specific ISO standard should be issued and be mandatory for the manufacturers too.

(5) Item (4) also requires the users be able to re-calibrate the tester and store in the instrument the relevant data (or any equivalent action is possible).

Conclusion

In the critically restricted range of the pre-diabetes, the imprecision due to possible lack of tester calibration, would prevent the medical doctor to obtain the correct information necessary for prescribing effective clinical measures.

References

1. Pavese F. A testing/metrological look at the accuracy of glucose strip measurements in home care for marginal diabetes, for mitigating diabetic kidney disease. J Nephrol.

Table 1: Patient capillary-blood, example of tester indication before and after correction to effective mg/dL units.

2020	Blood reading Tester #1ᵃ	Central value of control solution	Δ (mean blood) - (central value)	Correction: 100/(central value)	Corrected blood/mg/dL	Blood reading Tester #3ᵃ	Central value of control solution	Δ	Correction: 100/(central value)	Corrected blood/mg/dL
Annual Mean	153 ± 18	143	-10	0.7	102	122	115	9	0.87	108
Tester #2ᵃ						**Tester #4ᵃ,ᵇ**				
2021										
January	**154**	143	+11	0.7	**109**	**108**	92	+26	1.09	**118**
February						**107**	92	+25	1.09	**117**
Tester	**#1**	**#2**	**#3**	**#4**	**#5ᵇ**					
August	101		136							
corr	**103**		**106.3**							
September	111		118							
corr	**113**		**126.9**							
December	107		111							
corr	**109.3**		**119.1**							
2022										
January			159	102	**114**					
corr			**124.2**	109.5	**114.2**					
April	157	111		110	**117**					
corr	**111.3**	**103.8**		118.2	**117.9**					
June				104	101					
corr				111.4	**102.3**					
July		135		108	112					
corr		**95.7**		116.2	**114.7**					

ᵃTesters #1-#4 are sold calibrated at 100 mg/dL, tester #5 is sold calibrated at 140 mg/dL. Testers #4 and #5 indication shows mmol/mol and their original calibration is almost correct. ᵇAfter conversion to capillary blood.
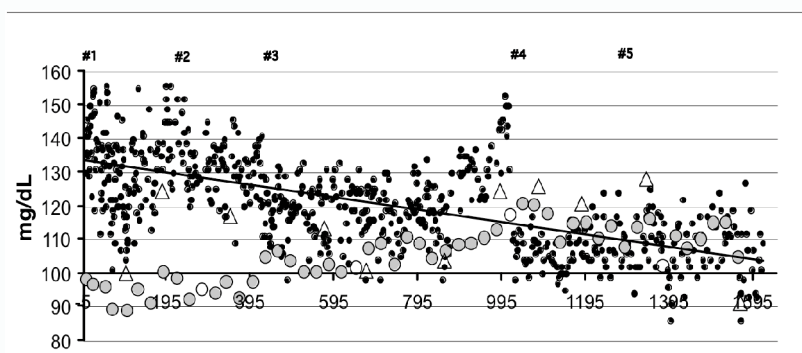

Figure 1: The black dots are all the collected indications of the testers. The large circles indicate the monthly indication mean, after correction for re-calibration (departure of the strip-range mean value from the nominal control solution concentration value). The white circles indicate the month of January since 2019. The triangles indicate the hospital checks (changed to capillary blood). The headings indicate the period of normal use of tester **#**.