THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 5

RESEARCH ARTICLE

Further Problems in Tester Calibration and Control Solution in Home Monitoring of Pre-Diabetes

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OPEN ACCESS

PUBLISHED
31 May 2025

CITATION
Pavese, F., 2025. Further Problems in Tester Calibration and Control Solution in Home Monitoring of Pre-Diabetes. Medical Research Archives, [online] 13(5).
https://doi.org/10.18103/mra.v13i5.6516

DOI
https://doi.org/10.18103/mra.v13i5.6516

ISSN
2375-1924

ABSTRACT

In previous publications, the author has reported some specific problems in checking glycaemia level in marginal diabetes, mainly due to the accuracy of the checks in that very narrow range of values, an issue particular important because above the upper limit, 125 mg/dL, the diabetes disease is considered to have already begun, while below that max value a diet is considered sufficient.

Since the off-shelf calibration of the testers used for home glucose level checks has been found not stable over time, the systematic use of control solutions provided by tester manufacturers is mandatory. However, the procedure for identifying potential calibration problems, even after a home calibration of both the batch and tester, is largely inaccessible to most patients, as demonstrated in the paper. Thus, improvements in the precision of the strip testers is urgently needed for that range, and, if stability of the standard solution cannot be ensured over a sufficient long term, the deadline for recalibration must be specified and the certificate of the control solution should be provided according to ISO Standards—and also reported on the tester/strip instruction sheets. Finally, relevant Standards should be more specific about this critical range.

1. Introduction

In previous publications, [1–3] the author has highlighted specific problems in accurately checking glycaemia level in marginal diabetes, particularly due to the limited accuracy of measurements within the very narrow range of values: 100–125 mg/dL (±12 % only wide). The issue is particular important for its upper limit, above which the diabetes disease is considered to have formally begun, while below that maximum value, dietary management, potentially supplemented with Glucophage®, is often deemed sufficient.

The original calibration of the testers used for checking glucose level is not ensured to be provided and most calibrations were found not stable in time (generally drifting to higher indications), [1] thus requiring a *systematic* use of (calibrated) control solutions provided by the tester manufacturers—already often a too much specific requirement for most patients' capabilities.

Furthermore, patients often struggle to identify the correct control solution for the marginal range as manufacturers may not specifically cater to this range or may use varying terminology, such as "range 3" to describe it. In addition, as already pointed out in Ref. 1, a *control solution* is what in metrology/testing is called a "reference material", subjected to very specific requirements and controls for their production and use—e.g., ISO 15197-2015, [4] ISO 17034 and 33403.

This paper aims to report additional inconsistencies that have recently been found in using the instrumentation calibration procedure reported in Refs. 1–3, highlighting the possible need for double checks when switching test strip batch and/or control solution lots, particularly when their validity time is close to expiration date—when supplied.

2. Methodology of the test and Recall of the instruments calibration procedure

The methodology for conducting the home tests is the one already reported in Refs. 1—2.

A generic patient is supplied with the following means and information for the used instrumentation:

—*Batch of test strips* (in addition to lot name and deadline of use)

a) The range of valid measured strip values, say: 128—158 mg/dL (7.1—8.8 mmol/L);
b) Middle-range value, called "aimed value", in that case: 143 mg/dL (8.0 mmol/L).

—*Control solution sample*

c) Lot name (See Note 1 below) and use deadline;
d) "Range 3" or equivalent denomination—sometimes confusing—for the valid glucose concentration range.

—*Specific tester of the same manufacturer*

e) Instructions for use of the instruments.

Note 1: Considering the high cost of a control solution batch (4 mL), one cannot assume that it can only be used for the current test strip batch, but be valid for any strip batch used within the deadline time indicated for the solution.

Note 2: The currently used tester should measure the glycaemia value of each drop of the control solution by means of the current batch of test strips used for blood glycaemia level.

In summary, the procedure suggested in Ref. 2 is the following, by using the current tester and strip batch:

1) First, the test *strip* batch is calibrated. Assuming, for example, that the nominal value for the range is 140 mg/dL and the mean value *indicated* by the tester is, e.g., 146 mg/dL, the correction value of the strip indications of that batch will be 146/140 = 1.043;
2) Then the *tester* calibration comes, using *another* strip of the same batch and a *second* drop from the control solution bottle—the first drop is discarded as can be contaminated by the leftover of the previous bottle use, to better ensure that the second has the same composition as the bulk in the bottle;
3) If the *tester reading* is, for example, 125 mg/dL, then the correction value for the tester indication will be 125/140 = 0.893;
4) Thus the total correction of any strip test value will be, in that case: 1.043×0.893 = 0.931 (–6.9%), valid only until the next calibration, mandatory for each subsequent strip batch. (*However, the tester calibration may be considered possibly obsolete if its last calibration is too old*).

3. Evidence of new tests becoming necessary in specific cases

The possibility of occurrence of the latter case above (in above (4)-parentheses) was recently observed as follows: (i) at the end of a strip batch, *no final* tester calibration was performed because all results of the glucose tests performed with it were considered reasonably consistent with each other; (ii) at the start of use of the next strip batch, a step up-change in the glucose level indication occurred. In order to check for its validity, not justified by the calibration of the strip batch, a new tester calibration was performed using the same control solution: a significant step-change of calibration was also obtained. That occurrence made necessary *exceptional* double checks to resolve the reliability of the observed occasional increase of the glucose level.

In Table 1, such check sequence is described in details together with the relevant previously recorded ones, and will be analysed in Section 4 and discussed in Section 5.

The difference in subsequent total (i.e. strip and tester) calibration correction between the strip batch A and the subsequent, B, in days 1 and 17 in Table 1 was found very large, 13%, more than acceptable: at the middle of the pre-diabetes range (only 25 mg/dL wide) this corresponds to 16 mg/dL, so that the corrected value (143 mg/dL)) comes above 125 mg/dL, the range limit, so bringing into the diabetes range—as confirmed by a second test.

The large variation between days 1 and 17 also in the tester calibration needed a double verification. On the subsequent day, day 18, a second test for patient blood resulted in a much lower indication and a third test on day 19 also a lower one.

Table 1. Series of strip batches and setup calibrations; glucose tests.

Day	Strip Batch & Control Solution*	Mean value mg/dL	Action	Tester: correction factor	Strip batch: correction factor	Total correction factor	Blood Glucose Level	
							Reading mg/dL	Corrected mg/dL
Note [1]	I51/2	146	Current strips Batch A (1 st) [2] calibration		1.043			
1	I28/4 (I51/2)		Tester current calibration (current solution I28/4 drop^)	0.894		0.932		
13			Patient (the author) glucose level on fasting morning:				111	**104** (107)[3]
16			End strip Batch A				118	**110**
17	J22/6a	148	New strips Batch B (2nd) calibration, 1st test		1.057 (+1.3%)		136	***143*** (+33%, min+23%)
17	I28/4 (J22/6a)		Tester calibration (current solution new drop)	0.997 +0.103 (10%)		1.054 +0.13 (+13%)		
18	J22/6a	148	New strips Batch B (2nd) calibration, 2nd test		1.057		120	**127**
18	I28/4 (J22/6a)		Tester, repeated	0.997		1.054		
19	J22/6a	143	New strips Batch C (3rd) calibration, 1st test		1.021		110	**112**
20	J22/6b	148	New strips Batch D [4] (4 th) calibration, 1st		1.057	0.944	125	**118**
20	I28/4 (J12/3)		Tester calibration (current solution new drop)	0.893		1.018	104	**106**
22	J12/3	143	New strips Batch C (3rd) calibration, 2nd test		1.021	0.912	121	**110**
24	I28/4 (J22/6a) B		Tester calibration (current solution new drop)	0.940 (+5% from day 20)				
24	I28/4 (J12/3) C		Tester calibration (current solution new drop)	0.817 [5]				
24	J17/2 (J22/6a) B		Tester calibration (*new* control solution batch)	0.940 (0%)				
24	J17/2 (J12/3) C		Tester calibration (*new* control solution batch)	0.856 (–5%) [6]				
26	J12/3	143	New strips Batch C (3rd) calibration, 3rd test	0.89	1.021	0.91 (–11%)	114	**104**

* In this case the subsequent Series indication in parenthesis indicates the used strip batch.

[1] Control solution (4 mL): available from September 2024. (^ Solution validity is up to April 2025; left residual 75%).

[2] The 15 measurements done with Batch A in previous 53 days indicated a glycaemia mean value (105.7 ± 7) mg/dL, i.e. the range is fully and amply within the pre-diabetes one.

[3] According to tester calibration done 35 days earlier, and test on day 17.

[4] Batch D sold together with batch B, i.e. part of the same total strip lot.

[5] Max difference B/C using two different control solutions: –15% day 20, –10% day 24.

[6] Correction for mean day 24: 0.888.

On day 18, also the tester was recalibrated by using, as usual, a new drop from the same control solution. No difference was found, but except a significant change in patient's glucose level—though within the range limit.

Then, on day 19 a different strip batch, C, of strips from the same manufacturer but different supplier, was then used and measured twice on days 20 and 22. The correction resulted smaller and also the patient's glucose level was found quite lower, now near the centre of the pre-diabetes range.

As a further check, a second batch of strips C being available, here named batch D, on day 20 a strip from it was used for a blood test, basically obtaining a confirmation of the indication of batch C.

Finally, a second batch of the *control solution* having been received from the same manufacturer on day 22 (the first one being close to its 1-year deadline), it was possible to also re-check the tester calibration with the latter, and compare the results obtained from the two control-solution lots (and so also tester calibrations).

4. Analysis of the above tests

The anomaly observed in Table 1, "Glucose Level" columns, arises from the comparison of the blood test results of days 16 and 17.

On day 16, the end of batch A showed a glucose calibrated level of 110 mg/mL, while the first test of batch B on day 17 reported a calibrated level of 143 mg/dL, both taken on *fasting* morning as usual, and without any justification arising from peculiarities in the behaviour/competence/diet of the patient doing the tests. A **+23%** calibration difference is found, far above the normal repeatability of the procedure. The previous test with batch A was only a few mg/dL different, according to previous calibration done 35 days earlier and on day 17—being the difference of A and B batch calibrations only 1.3% different, while difference in "Total calibration factor" in Table 1 from day 1 and 17 was of +13%.

Thus, the tester calibration change does not justify the different values of blood tests. Then, an apparent inconsistency came up: a further test was made on day 18, with strip batch B, the total calibration provided a different/lower value, 127 mg/dL, 9% different from day 16 with tester calibration unchanged when still using the current control solution.

Consequently, other cross checks were necessary on days 19-22, also using strip batches C and D and the same control solution batch. The strip checks, using again batches B and C and with the tester check still changing calibration value, provided glucose levels basically within a range of corrected value 106-118 mg/dL.

The probability *can thus be considered high* for the *whole strip batch* B, J22/6, *being defective*—this is a quite different fact from finding a test providing a false indication, and new with respect to the facts discussed in Refs. 1–3.

Finally, to allow subsequent use of batch (J12/3), a re-calibration was performed on day 24 of the current *tester* calibration (I28/4) with the brand new batch (J17/2), by using both strip batches B and C: the calibration resulted to be identical for the two strip batches using the *old* control solution, while two values differing by 5% was obtained using the *new* control solution. The mean correction value of the 4 tests, 0.888, differs from the previous calibration of the first control solution, 0.997 by 9%, while the mean difference between the two control solutions was 11%, thus *larger than the dispersion* of the tests made in subsequent times with the same batch of strips that are of the order of 5%— note that the checks on control solution on the same tester depends also on the calibration of the strips batch used, which may be different over time.

5. Discussion

Some of the above results exceeded with reasonable confidence the dispersion limit ~5% for the strips, and ~10% total. These findings confirmed that *strip batch B only* provided unreliable indications, with a higher probability of false readings exceeding the pre-diabetes range—i.e. higher than 125 mg/dL, so potentially miss-indicating that the patient health had drifted to diabetes disease.

A statistics of such an occurrence, the first observed by the author, is not at present available, but even this single occurrence is alarming, so worth to be reported, because its detection with high confidence is certainly out from the reach of the vast majority of the patients making their checks.

Even for an expert person it is not so easy to evaluate such situation, so it is reasonable to advise always performing a new tester calibration just *near the end* of the *current* strip batch (even if the tester correction could be found unchanged) and before starting a new *strip* batch.

The reported case, obtained with materials from a reputed manufacturer, confirms author's standing position: the need to insist increasing the *accuracy* of the test materials made available by the manufacturers, in two directions:

(a) *Decreasing* the case-to-case variability of the indications for each *single batch* (of minimum 25 strips), i.e. *increasing* the *precision* of the *strips*. This should not be confused with the indication already existing on the strip box, e.g., Level 3 128-158 mg/dL (143 mg/dL): the level in parentheses is the *mean value* taken as the "nominal" value for that batch (and the one to be used). The ±12.5% range only provides the range of *expected* valid strip batch readings of the patient's *blood*; it *is not* the valid *dispersion* of the indications for the same *blood drop* due to batch actual quality/reproducibility that one should expect. Should that be the intention of the manufacturer, it would not be correct.

(b) The above test does not indicate yet the *accuracy* of the measurement, i.e. the true interest of the patient/doctor, because the *tester* itself may introduce false readings, even exceeding the

5% reproducibility *necessary* for that very narrow range. The subject matter of this paper demonstrates just the fact that the manufacturers do not provide a warranty about the testers being sold calibrated off-shelf, or remaining calibrated over time. Direct experience has too often shown that not ensuring calibration is a common case, confirmed and demonstrated above and in Refs. 1–3. The only remedy provided by the manufacturer is the "control solution", in metrological term a "reference material", whose characteristics and use (the "specs") are regulated by ISO standards, also valid for them. As already discussed in Refs. 1–3 this is not the real situation: nothing is certified about the provided solutions, often not even about the nominal value and expected precision, only validity (i.e. stability?) in time, typically for 1 year.

6. Conclusions

As demonstrated in this paper, a reliable procedure for identifying potential issues with strip batch, even after a home calibration of both batch and tester, is largely inaccessible to most patients in case of evidence of dubious test results.

The issue is aggravated by the fact that patients, in such preliminary phase of their possible evolution to the full disease, tend to scarcely feel committed in making frequent checks (e.g. 3/week and for half yearly weeks should be a minimum), also due to the cost and to the need for frequent *fasting morning tests*; on the other hand, the author got information about a current medical procedure where *two tests* under passing the 125 mg/dL limit for a *few days* are sufficient to consider the patient having got the full disease, and possibly already needing insulin—and consequent daily mandatory checks.

In conclusion, improvements in the precision of the test strips is still urgently needed, and, if stability of the standard solution cannot be ensured over a sufficient long term, the term of recalibration must be specified and a *certified* control solution should be mandatory and provided according to the specific ISO standards—and alerting instructions also be reported on the tester/strip guidance sheets.

Furthermore, also ISO standards, in their present elaboration, are missing due attention to the specific pre-diabetes range 100–125 mg/dL: at present the guidelines (e.g. [4]) concern only two continuous field, <100 mg/dL and 100–150 mg/dL, so missing the *pre-diabetes boundary* 125 mg/dL, a regulation formally inconsistent and critical for diabetes classification related to the patients tests.

In the mean time, the pre-diabetes patients *must correct* the tester indications at least according to the calibration of each new-used strip batch, by using the correct (middle) range value *reported on the strip box*, a very simple operation (or the tester manufacturer should include it—unknown to him—as *mandatory* among the (patient's manual) tester functions).

References

(The references are basically limited to those concerning previous author publications including other references concerning the more general issue, because this paper is reporting a new case)

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