Facts and artefacts regarding correlation between skin electrical impedance spectroscopy (EIS) and blood glucose

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Abstract. Earlier observations on possible co-variation between skin EIS and blood glucose prompted us to map and include other factors at play in the predictive model. Skin pH would be one such factor. A cohort of 20 diabetics was investigated, taking around 30 measurements spread over each of two different days 2-21 days apart. Each measurement comprises skin EIT in the frequency range 1kHz to 2.5MHz, skin pH, and immediately evaluated blood samples. There is a co-variation for some, but not all, test persons. The relationship gets stronger on the group level by adding pH-information, but is still poor or non-existent for some test persons. Non-invasive EIS measurements on skin is influenced by skin hydration, blood glucose, skin pH, body location, season, environmental factors, and variables not yet understood. Since impedance related parameters are used to estimate skin hydration, users of such devices should be aware that skin pH may influence as much as the water content of the stratum corneum.

1. Background

An easy-to-use and reliable device to non-invasively monitor blood glucose (BG) would be the holy grail of diabetes management. In 1999, Elden was awarded a patent [1] involving dielectric properties of skin based on simultaneous measurements with a device intended to estimate skin water content and a common BG meter. The idea has been further investigated in clinical studies in the US, and in a Master thesis by Birgersson and Neiderud 2004 [2]. It was found that there is correlation between information in electrical impedance spectra and BG, but not for every person. Defining more rigorous procedures in the preparation of the skin before measurements improved correlation somewhat, but still correlation was weak or non-existing for many persons. Pondering possible confounding factors revealed that skin pH could be a strong factor modulating the impedance – while pH inside the human body varies very little, skin pH naturally varies between 3.5 and 7, and may rise to about 10 after washing with a hard soap, then slowly returning to baseline during several hours. Skin pH also has diurnal fluctuations [3].

The rational for including skin pH in the model is that many organic acids, in particular fatty acids, but also DNA-residues, would migrate from the living epidermis into the stratum corneum during its continuous rejuvenation, and possibly this acid pool could be represented as pH-value. Other charge carriers such as sodium, potassium, and chlorine ions would also be part of the impedance space, but reasonably under control by a standardized inundation procedure before EIS measurement. In the frequency range used, the impedance spectrum would be dominated by the stratum corneum layer, as has been shown by Birgersson et al. [4]. Since the glucose molecule is uncharged, the measured alterations of electric or dielectric properties elicited in tissue by variation in BG must be attributed to
secondary effects, and a coupling mechanism might be sought in composition of interstitial liquid in the skin or in cell membranes, although the stratum corneum consists of dead keratinized cells. Clinically interesting BG-levels (up to about 25 mmol/L) are not sufficient to impede the mobility of sodium ions in solution enough to explain the observed alterations in the impedance spectra. Subtle structural changes in the stratum corneum may be at play [5]. In short: The coupling mechanism between skin EIS and BG is not understood, but the phenomenon exists. A co-variation between pH and impedance is necessary according to the laws of electrochemistry.

2. Materials and methods
The study was approved by the Regional Ethics Committee, and 20 diabetics type 1, 10 men, 10 women, ages 25-70 were recruited. The test persons spent two full days in our lab. High glycemic food was used to increase BG at coffee breaks and lunch, and apart from the somewhat unnatural food intake, the test persons managed their insulin as usual. Skin EIS was measured with a SciBase II instrument (SciBase AB, Stockholm, Sweden). Skin pH was measured with a Skin-pHMeter PH 905 (Courage & Khazaka GmbH, Cologne, Germany). Venous and capillary blood was sampled every 15 minutes (longer intervals at coffee breaks and lunch) by qualified nurses, simultaneously with EIS and pH measurements. All measurements were done by the same operator (IN). Both Venous and capillary BG was measured with HemoCue Glucose 201 (HemoCue AB, Ängelholm, Sweden). One PLS model [6] using all data with or without pH was calculated for the first day, and also individual models. As an index of goodness, the number of predicted points falling into Clark zones A or B was used [7-10].

3. Results

![Figure 1: Clarke grid for predicted BG using both skin EIS and skin pH. Note scales: 18mg/dl = 1mmol/L BG. The graphics template places BG in the range 400-500 mg/dl at 400 mg/dl.](image)
In this context, zone A is considered good and an error in zone B is not good but neither dangerous nor does it require any intervention such as administration of insulin or sugar. Clarke grid was chosen because it is commonly used, although the so called BD grid is somewhat more realistic in defining the error zones. For the outcome of this study it does not matter.

| Test person | n tot | n in A+B | % in A+B | n in A+B | % in A+B |
|-------------|-------|----------|----------|----------|----------|
| All pooled  | 543   | 326      | 60.0     | 348      | 64.1     |

An ocular inspection of the above plot (Figure 1) is not encouraging, there is no obvious correlation in the pooled data, and for a couple of test persons the correlation appears to be negative. The number of data points falling in Clarke zones A or B increases 4 percent units after including pH in the model based on all 20 test persons. However, as we have seen good correlation in some test persons in earlier studies, a closer look on an individual level using the number of data points falling in zones A or B is presented/was performed, with or without pH data in the model.

| Test person | n tot | n in A+B | % in A+B | n in A+B | % in A+B |
|-------------|-------|----------|----------|----------|----------|
| FP-1        | 30    | 21       | 70.0     | 21       | 70.0     |
| FP-2        | 30    | 25       | 83.3     | 25       | 83.3     |
| FP-3        | 32    | 20       | 62.5     | 20       | 62.5     |
| FP-4        | 30    | 24       | 80.0     | 24       | 80.0     |
| FP-5        | 30    | 27       | 90.0     | 27       | 90.0     |
| FP-6        | 30    | 27       | 90.0     | 27       | 90.0     |
| FP-7        | 30    | 28       | 93.3     | 28       | 93.3     |
| FP-8        | 30    | 26       | 86.7     | 26       | 86.7     |
| FP-9        | 30    | 29       | 96.7     | 29       | 96.7     |
| FP-10       | 30    | 30       | 100.0    | 30       | 100.0    |
| FP-11       | 30    | 28       | 93.3     | 28       | 93.3     |
| FP-12       | 30    | 29       | 96.7     | 29       | 96.7     |
| FP-13       | 30    | 29       | 96.7     | 29       | 96.7     |
| FP-14       | 20    | 13       | 65.0     | 13       | 65.0     |
| FP-15       | 30    | 20       | 66.7     | 20       | 66.7     |
| FP-16       | 30    | 7        | 23.3     | 6        | 20.0     |
| FP-17       | 20    | 3        | 15.0     | 3        | 15.0     |
| FP-18       | 19    | 8        | 42.1     | 8        | 42.1     |
| FP-19       | 20    | 10       | 50.0     | 10       | 50.0     |
| FP-20       | 12    | 9        | 75.0     | 9        | 75.0     |

Using individual models for calibration, the average number of points in zones A or B increased to 76% while the influence of skin pH now became negligible.

4. Discussion

Predicted values of BG falling into Clarke error zones C-E do have clinical consequences and can be fatal, e.g. a predicted value of, say, 25 mmol/L (450 mg/dl) while the true value is 1.5 mmol/L (27 mg/dl) would suggest administration of an insulin dose that may be highly dangerous for the patient. Any reliable device should give values only within error zone A, although a few points falling into error zone B may be acceptable. There are a number of skin research instruments intended to estimate skin hydration (water content of the stratum corneum) based on EIS or subsets of such data (detecting...
conductivity or capacity only, at one or more frequencies), and using a variety of probes/electrode systems [11,12]. Some observed variation in skin hydration studies might be explained by the pH contribution, in particular on intact healthy skin which can be quite acid.

5. Conclusions

There is a co-variation between skin EIS and blood glucose. The co-variation is not strong enough to merit a device based on this phenomenon only. Skin surface pH is one confounding factor, but adding this parameter to the model is not enough to merit a device based on measurement of both EIS and pH. However, impedance related parameters are used to estimate skin hydration, and investigators using such devices should be aware that alterations in skin pH may influence impedance parameters as much as the water content of the stratum corneum, depending on actual baseline of pH changes.

References

[1] Elden HR. United States Patent 1999, No. 5,890,489
[2] Birgersson U and Neiderud F 2004 Bioelectrical parameters related to glucose level. M.Sc. thesis. (Royal Institute of Technology (KTH), Stockholm)
[3] Yosipovitch G, Xiong GL, Haus E, Sackett-Lundeen L, Ashkenazi I and Maibach HI 1998 Time-dependent variations of the skin barrier function in humans: Transepidermal water loss, stratum corneum hydration, skin surface pH, and skin temperature. J. Investig. Dermatol. 110 20–4
[4] Birgersson U, Birgersson E and Ollmar S 2012 Estimating electrical properties and the thickness of skin with electrical impedance spectroscopy: Mathematical analysis and measurements. J. Electrical Bioimpedance 3 51–60
[5] Iwai I, Han HM, den Hollander L, Svensson S, Öfverstedt LG, Anwar J, Brewer J, Bloksgaard M, Laloeuf A, Nosek D, Masich S, Bagatolli LA, Skoglund U and Norlén L 2012 The human skin barrier is organized as stacked bilayers of fully extended ceramides with cholesterol molecules associated with the ceramide sphingoid moiety. J. Investig. Dermatol. 132 2215–25
[6] Eriksson L, Johansson E, Kettaneh-Wold N and Wold S 1999 Introduction to Multi- and Megavariate Data Analysis using Projection Methods (PCA & PLS). (Umetrics, Umeå)
[7] Clarke WL, Cox D, Gonder-Frederick LA, Carter W and Pohl SL 1987 Evaluating clinical accuracy of systems for self-monitoring of blood glucose. Diabetes Care 10 622–8
[8] Cox DJ, Richards FE, Gonder-Frederick LA, Julian DM, Carter WR and Clarke WL 1989 Clarification of error-grid analysis Diabetes Care 12 235–6
[9] Gough DA and Botvinick EL 1997 Reservations on the use of error grid analysis for the validation of blood glucose assays Diabetes Care 20 1034–6
[10] Parkes JL, Slatin SL, Pardo S and Ginsberg BH 2000 A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose Diabetes Care 23 1143–8
[11] Fluhr JW, Gloor M, Lazzerini S, Kleesiz P, Grieshaber R and Berardesca E 1999 Comparative study of five instruments measuring stratum corneum hydration (Corneometer CM820 and CM 825, Skicon 200, Nova DPM 9003, Dermalab) Part I. In vitro Skin Res. Technol. 5 161–70
[12] Fluhr JW, Gloor M, Lazzerini S, Kleesiz P, Grieshaber R and Berardesca E 1999 Comparative study of five instruments measuring stratum corneum hydration (Corneometer CM820 and CM 825, Skicon 200, Nova DPM 9003, Dermalab) Part II. In vivo Skin Res. Technol. 5 171–8