Assessing the impact of inaccurate insulin-to-carbohydrate ratio on the patient's glycemic targets and lifestyle management

Cite as: AIP Conference Proceedings **2293**, 260007 (2020); https://doi.org/10.1063/5.0026577
Published Online: 25 November 2020

Francisco Miranda, Carlos Abreu, and Paula Felgueiras

Assessing the Impact of Inaccurate Insulin-to-Carbohydrate Ratio on the Patient's Glycemic Targets and Lifestyle Management

Francisco Miranda[1,2], Carlos Abreu[1,a)] and Paula Felgueiras[1,3]

[1]*Instituto Politécnico de Viana do Castelo, Viana do Castelo, Portugal*
[2]*CIDMA, Universidade de Aveiro, Aveiro, Portugal*
[3]*Unidade Local de Saúde do Alto Minho, Hospital de Santa Luzia, Viana do Castelo, Portugal*

[a)]Corresponding author: cabreu@estg.ipvc.pt

Abstract. To mitigate the adverse consequences of chronic hyperglycemia, patients with type 1 diabetes mellitus must provide their bodies with insulin to control their blood glucose. In most cases, insulin therapy consists of a combination of basal insulin and bolus insulin, the so-called basal-bolus insulin therapy. To determine the bolus insulin, patients must know not only the carbohydrate content of each meal but also the values of the insulin-to-carbohydrate ratio and the insulin sensitivity factor. Although important, the blood glucose complex dynamics make determining these parameters a difficult and error-prone task, usually performed by experienced diabetologists using high-quality data. Moreover, the insulin-to-carbohydrate ratio and the insulin sensitivity factor vary over the day due to several factors. Thus, daily, patients use approximate values to determine their prandial bolus. In this paper, we propose an analytic method to find the safe maximum interval for the error in the estimates of the insulin-to-carbohydrate ratio and, therefore, avoid dysglycemia. Our study suggests that slimmer patients with smaller insulin-to-carbohydrate ratios need to be more careful when estimating it. Another significant finding of our work is that in such cases, having small meals reduces the adverse effect of inaccurate insulin-to-carbohydrate ratio estimates in the postprandial blood glucose.

INTRODUCTION

Patients with type 1 diabetes mellitus ($T1DM$) suffer from autoimmune destruction of insulin-secreting pancreatic β cells, experiencing a chronic hyperglycemic condition. To suppress their insulin needs, avoiding the deleterious effects of hyperglycemia, such patients must administer themselves with insulin. Often, insulin therapy consists of a combination of slow-acting insulin (i.e., basal insulin) and fast-acting insulin (i.e., bolus insulin). While the basal insulin dosage is periodically adjusted in collaboration with the healthcare team, the bolus insulin doses are estimated by each patient before each meal. To be effective, the bolus insulin dose must be accurate, and its accuracy depends on several factors, namely, the patient ability to estimate the carbohydrate content of each meal [1, 2], the Insulin-to-Carbohydrate Ratio (ICR), the Insulin Sensitivity Factor (ISF), the preprandial blood glucose [3], and the insulin remaining active from the last bolus [4]. Regarding the ICR and ISF factors, they are dynamic and correlated [5–7]. Moreover, they change along the day due to physical activity, stress, hormone cycle, among other factors [8]. Therefore, most of the time, the ICR and ISF values used to estimate the bolus insulin are not true values, but estimates obtained by experienced diabetologists using high-quality data. Even though the ICR and ISF estimates are reliable, there is often an error associated with it. Therefore, it is crucial to investigate how this error affects the postprandial blood glucose of each patient. We hypothesize that the impact of such error on the postprandial blood glucose levels is different on each patient, given its specificities. In this context, we propose an analytic method that uses the carbohydrate content of each meal, the preprandial blood glucose, the glycemic targets, and the bodyweight of each patient to compute the safe maximum interval for the error in the ICR estimates.

International Conference of Numerical Analysis and Applied Mathematics ICNAAM 2019
AIP Conf. Proc. 2293, 260007-1–260007-5; https://doi.org/10.1063/5.0026577
Published by AIP Publishing. 978-0-7354-4025-8/$30.00

MATHEMATICAL METHODS

Patients on insulin therapy use Equation 1 to determine the prandial and correction boluses to be administrated before each meal:

$$B = \frac{CHO}{ICR} + \frac{G - G_T}{ISF} - IOB, \tag{1}$$

where B [U] is the bolus insulin, CHO [g] are the carbohydrates planned to be consumed in that meal, G [mg/dL] is the preprandial blood glucose, G_T [mg/dL] is the blood glucose target, IOB [U] (Insulin-on-Board) is the insulin remaining active from the previously administrated bolus, and ICR [g/U] and ISF [mg/dL/U] are the insulin-to-carbohydrate ratio and the insulin sensitivity factor, respectively [4, 9].

Regarding the Accurate Insulin Management (AIM) System [5], the ICR and the ISF can be related as follows: $ISF = \alpha \cdot ICR/W$, where W [kg] is the patient's weight and α [dL^{-1}] is a nonzero positive constant [5–7]. Therefore, Equation 1 can be rewritten as $B = CHO/ICR + W \cdot (G - G_T)/(\alpha \cdot ICR) - IOB$. In the following analysis, we consider that ICR is properly estimated by a diabetologist and denoted by $\hat{ICR}$, and the CHO, W, G, and IOB are correct values.

Let δ_{ICR} be the ICR estimation error, i.e., $\delta_{ICR} = ICR - \hat{ICR}$. If $\delta_{ICR} \neq 0$ there is an error on B given by $\delta_B = B - \hat{B}$, where $\hat{B} = CHO/\hat{ICR} + W \cdot (G - G_T)/(\alpha \cdot \hat{ICR}) - IOB$. Therefore, we have:

$$\delta_B = \frac{\alpha \cdot CHO + W \cdot (G - G_T)}{\alpha \cdot ICR} - \frac{\alpha \cdot CHO + W \cdot (G - G_T)}{\alpha \cdot \hat{ICR}}. \tag{2}$$

The error in the bolus, δ_B, will act as an unplanned correction bolus, and therefore leading to an off-target postprandial blood glucose ($G_{postprandial}$) and an error given by $\delta_{G_{postprandial}} = G_{postprandial} - G_T = \delta_B \cdot \alpha \cdot ICR/W$. By replacing $\delta_B = \delta_{G_{postprandial}} \cdot W/(\alpha \cdot ICR)$ and $\hat{ICR} = ICR - \delta_{ICR}$ in Equation 2 we obtain:

$$\frac{\alpha \cdot CHO + W \cdot (G - G_T)}{ICR - \delta_{ICR}} = \frac{\alpha \cdot CHO + W \cdot (G - G_T) - W \cdot \delta_{G_{postprandial}}}{ICR}. \tag{3}$$

In the quest for the safe maximum interval for the error δ_{ICR} such that the error $\delta_{G_{postprandial}}$ does not imply that postprandial blood glucose goes beyond the pre-established limits of hypo and hyperglycemia it is necessary to consider the following propositions, whose proof is trivial.

Proposition 1. *The error δ_{ICR} is smaller than ICR.*

Proposition 2. *The value $\alpha \cdot CHO + W \cdot (G - G_T)$ is greater than zero.*

Regarding Equation 3 and considering Propositions 1 and 2, we obtain the following condition:

$$\delta_{G_{postprandial}} < \frac{\alpha \cdot CHO + W \cdot (G - G_T)}{W}. \tag{4}$$

Expressing the hyperglycemia and hypoglycemia limits as G_{Hyper} and G_{Hypo}, respectively, we can conclude from Equations 3 and 4 that δ_{ICR} has the safe maximum interval given by:

$$\delta_{ICR} = -\frac{W \cdot ICR \cdot \delta_{G_{postprandial}}}{\alpha \cdot CHO + W \cdot \left(G - G_T - \delta_{G_{postprandial}}\right)},$$

$$\text{with} \quad \delta_{G_{postprandial}} \in \left[G_{Hypo} - G_T, \min\left\{ G_{Hyper} - G_T, \frac{\alpha \cdot CHO + W \cdot (G - G_T)}{W} \right\} \right[. \tag{5}$$

In the following discussion, we will study Equation 5 in view to determine how the patient's characteristics (i.e., the patient's ICR, bodyweight, and the carbohydrates intake per meal) influence the magnitude of δ_{ICR} and, therefore, make them more or less sensitive to it.

DISCUSSION

Let's consider two patients, P_1 and P_2, characterized by $\{ICR_1, W_1, {CHO_1}^m\}$ and $\{ICR_2, W_2, {CHO_2}^m\}$, respectively, where ICR_i, W_i, ${CHO_i}^m$ are, respectively, the insulin-to-carbohydrate ratio, the bodyweight and the carbohydrates intake in the m-meal of the day of the patient P_i, $i = 1, 2$. Admit that both patients have the same G_{Hypo}, G_{Hyper}, G_T, and the preprandial blood glucose (G) is the same for the m-meal of each patient. Suppose that P_2 is less sensitive to δ_{ICR} than P_1, i.e., the patient P_2 has a greater interval of δ_{ICR} than P_1. In such circumstances, it is important to know the way that the characteristics of both patients relate.

By studying the monotonicity of δ_{ICR}, obtained from Equation 5, in relation to $\delta_{G_{postprandial}}$ defined in the same equation, we found that:

$$\frac{\partial \delta_{ICR}}{\partial \delta_{G_{postprandial}}} = -\frac{W \cdot ICR \cdot (\alpha \cdot CHO + W \cdot (G - G_T))}{\left(\alpha \cdot CHO + W \cdot \left(G - G_T - \delta_{G_{postprandial}}\right)\right)^2} < 0.$$

Thus, δ_{ICR} is continuous and strictly decreasing for $\delta_{G_{postprandial}}$ defined in Equation 5. Since $\delta_{ICR} > 0$ for $\delta_{G_{postprandial}} \in [G_{Hypo} - G_T, 0[$ and $\delta_{ICR} < 0$ for $\delta_{G_{postprandial}} \in]0, k[$, then the maximum relative error of the ICR estimation, $\max E_r^{ICR}$, that does not imply that postprandial blood glucose goes beyond the pre-established G_{Hypo} and G_{Hyper} is given by:

$$\max E_r^{ICR}\left(\delta_{G_{postprandial}}\right) = \begin{cases} -\dfrac{W \cdot (G_{Hypo} - G_T)}{\alpha \cdot CHO + W \cdot (G - G_{Hypo})} & \text{if} \quad \delta_{G_{postprandial}} \in \left[G_{Hypo} - G_T, 0\right[\\ \lim\limits_{\delta_{G_{postprandial}} \longrightarrow k} \dfrac{W \cdot \delta_{G_{postprandial}}}{\alpha \cdot CHO + W \cdot \left(G - G_T - \delta_{G_{postprandial}}\right)} & \text{if} \quad \delta_{G_{postprandial}} \in]0, k[\end{cases},$$

where $k = \min\{G_{Hyper} - G_T, (\alpha \cdot CHO + W \cdot (G - G_T))/W\}$.

The first conclusion is that the maximum admissible relative error, $\max E_r^{ICR}$, does not depend on the ICR value. However, the maximum admissible absolute error, $\max \Delta ICR = \max E_r^{ICR} \cdot ICR$, does. Indeed, the $\max \Delta ICR$ increases when ICR also increases. Therefore, regarding two patients, P_1 and P_2, if $ICR_1 < ICR_2$, $W_1 = W_2$ and ${CHO_1}^m = {CHO_2}^m$ then P_2 is less sensitive to δ_{ICR} than P_1 (e.g., see patients #1 and #2 in Table 1). Studying the variable CHO, it is easy to conclude that both maximum admissible errors increase when the CHO decreases, i.e., if ${CHO_1}^m > {CHO_2}^m$, $W_1 = W_2$ and $ICR_1 = ICR_2$ then P_2 is less sensitive to δ_{ICR} than P_1 (e.g., see patients #1 and #3 in Table 1). Now, regarding the patient's weight, we conclude that both maximum admissible errors increase when W also increases, because $\partial \max E_r^{ICR}([G_{Hypo} - G_T, 0[)/\partial W > 0$ and $\partial \max E_r^{ICR}(]0, k[)/\partial W > 0$, for $k = \min\{G_{Hyper} - G_T, (\alpha \cdot CHO + W \cdot (G - G_T))/W\}$, $W > 0$, and the same thing happening for the maximum admissible absolute error. Therefore, if $W_1 < W_2$, $ICR_1 = ICR_2$ and ${CHO_1}^m = {CHO_2}^m$ then P_2 is less sensitive to δ_{ICR} than P_1 (e.g., see patients #1 and #4 in Table 1). These conditions over ICR_i, W_i and ${CHO_i}^m$, $i = 1, 2$, are sufficient conditions to increase the maximum admissible errors of patient P_2. We can conjugate these conclusions to obtain the following another sufficient conditions for the same purpose:

1. $ICR_1 = ICR_2 \wedge W_1 < W_2 \wedge {CHO_1}^m > {CHO_2}^m$ (e.g., see patients #1 and #5 in Table 1);
2. $ICR_1 < ICR_2 \wedge W_1 < W_2 \wedge {CHO_1}^m = {CHO_2}^m$ (e.g., see patients #1 and #6 in Table 1);
3. $ICR_1 < ICR_2 \wedge W_1 = W_2 \wedge {CHO_1}^m > {CHO_2}^m$ (e.g., see patients #1 and #7 in Table 1);
4. $ICR_1 < ICR_2 \wedge W_1 < W_2 \wedge {CHO_1}^m > {CHO_2}^m$ (e.g., see patients #1 and #8 in Table 1).

For the relative error of the ICR estimation we can verify the obtained results to W and CHO in Figure 1. The relative error increases when bodyweight also increases and insulin-to-carbohydrate ratio decreases.

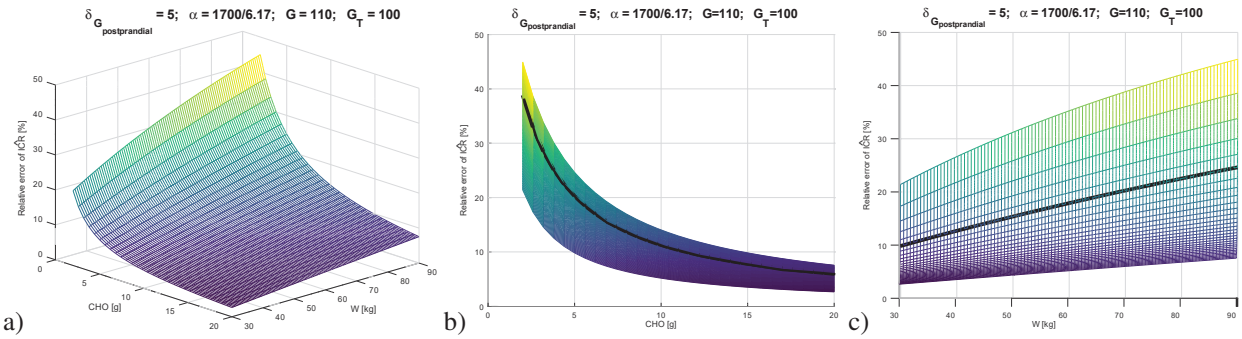
Considerations Regarding Lifestyle Management

As already mentioned, patients with diabetes may experience relevant changes in their ICR. Such changes often result in inaccurate bolus insulin, and consequently off-target postprandial blood glucose values. For those more sensitive to ICR changes, the proposed method gives some insights about how to behave to minimize the effects of inaccurate ICR estimations. In this context, the next commentaries will focus on the patient's bodyweight and carbohydrates intake management. Therefore, patients more sensitive to δ_{ICR} will be categorized into three groups:

TABLE 1. The maximum admissible relative and absolute errors of the $\hat{ICR}$ for different values of ICR, W, and CHO.

Patient	ICR [g/U]	W [Kg]	CHO [g]	G [mg/dL]	max $E_r^{ICR}\left(\left[G_{Hypo}-G_T, 0\right[\right)$ [%]	max $E_r^{ICR}\left(]0, k[\right)$ [%]	max $\Delta ICR\left(\left[G_{Hypo}-G_T, 0\right[\right)$ [g/U]	max $\Delta ICR\left(]0, k[\right)$ [g/U]
#1	11.80	70	50	110	12.67	63.09	1.49	7.44
#2	13.37	70	50	110	12.67	63.09	1.69	8.44
#3	11.80	70	40	110	15.19	91.49	1.79	10.80
#4	11.80	80	50	110	14.14	78.27	1.67	9.24
#5	11.80	80	40	110	16.88	118.06	1.99	13.93
#6	13.37	80	50	110	14.14	78.27	1.89	10.47
#7	13.37	70	40	110	15.19	91.49	2.03	12.23
#8	13.37	80	40	110	16.88	118.06	2.26	15.78

Note:
$k = \min\left\{G_{Hyper} - G_T, \left(\alpha \cdot CHO + W \cdot (G - G_T)\right)/W\right\}$.
To calculate the maximum admissible relative and absolute errors were used the following values:
$G_{Hypo} = 70$ mg/dL, $G_{Hyper} = 180$ mg/dL, $G_T = 100$ mg/dL, and $\alpha = 1700/6.17$ dL^{-1} [5].



a) b) c)

FIGURE 1. a) The relative error E_r^{ICR} for $30 \leq W \leq 90$ and $2 \leq CHO \leq 20$; b) The relative error E_r^{ICR} for $30 \leq W \leq 90$ and $2 \leq CHO \leq 20$, including the particular case when $W = 70$ (bold plot); c) The relative error E_r^{ICR} for $30 \leq W \leq 90$ and $2 \leq CHO \leq 20$, including the particular case when $CHO = 5$ (bold plot).

1) Patients with normal bodyweight for height:
In such cases, patients should reduce the carbohydrates intake at each meal and do more meals throughout the day to maintain normal bodyweight. From Proposition 2 one must take into account that $CHO > W \cdot (G_T - G)/\alpha$.

2) Patients with low bodyweight for height:
Under these circumstances, the proposed method suggests that patients may experience some benefits if they have a bodyweight gain [1]. Nevertheless, it's important to bear in mind that diet to increase bodyweight must not increment the carbohydrates intake per meal.

3) Patients with high bodyweight for height:
Although patients with high bodyweight are less sensitive to the error in the ICR estimates, evidence shows that maintaining a normal bodyweight brings several benefits for health, in particular for those with diabetes [10]. In such cases, it is recommended a slimming diet poor in carbohydrates.

CONCLUSION

Patients on basal-bolus insulin therapy rely on several factors to accurately determine their prandial bolus, being the insulin-to-carbohydrate ratio one of the most important and difficult to determine. The challenge to accurately determine the value of the insulin-to-carbohydrate ratio relates to its dynamic since it changes throughout the day due to several causes, being the physical activity, the stress or the hormone cycle, just a few examples. So, daily, patients use approximate values to calculate the bolus insulin for each meal. Even though such approximations are, indeed, reliable, there is an error associated with them. Therefore, it is crucial to investigate how this error affects the prandial bolus and, consequently, the postprandial blood glucose levels. In this context, we proposed an analytic method that uses patient-specific data to compute the safe maximum interval for the error of the insulin-to-carbohydrate ratio estimations. Moreover, our method could be used to quantify the impact of lifestyle changes on patient health,

[1] By AIM system, we can consider that the insulin-to-carbohydrate ratio does not change when the bodyweight changes, because the Total Daily Dose (TDD) insulin is linearly dependent of bodyweight. In AIM system is considered that $TDD = k_1 \cdot W$, where k_1 is a nonzero positive constant. As $ICR = k_2 \cdot W/TDD$, where k_2 is also a nonzero positive constant, we obtain $ICR = k_2/k_1$ which is a constant that does not depend of bodyweight [5].

e.g., we found that patients having a normal bodyweight for height may mitigate the adverse effects of inaccurate insulin-to-carbohydrate ratio estimations by reducing the carbohydrates intake on each meal and increasing the number of meals per day.

ACKNOWLEDGMENTS

This work was supported by the Portuguese Foundation for Science and Technology (FCT - Fundação para a Ciência e a Tecnologia), through CIDMA - Center for Research and Development in Mathematics and Applications, within project UID/MAT/04106/2019.

REFERENCES

[1] Abreu C., Miranda F., and Felgueiras P. Carbohydrate counting: How accurate should it be to achieve glycemic control in patients on intensive insulin regimens? *AIP Conference Proceedings*, 2116(1):250009, 2019.

[2] Abreu C., Miranda F., and Felgueiras P. The impact of accurate carbohydrate counting on patient's glycemic targets. In *Diabetes Technology & Therapeutics*, volume 21, pages A66–A66. Mary Ann Liebert, Inc., 140 Huguenot Street, 3rd Floor, New Rochelle, NY 10801 USA, 2019.

[3] Abreu C., Miranda F., Dabrowska A., and Felgueiras P. Home glucose meters: How accurate should they be to avoid dysglycemia in patients using carbohydrate counting? *AIP Conference Proceedings*, 2116(1):250010, 2019.

[4] Walsh J., Roberts R., Bailey T. S., and Heinemann L. Bolus advisors: Sources of error, targets for improvement. *Journal of Diabetes Science and Technology*, 12(1):190–198, 2018.

[5] Davidson P., Hebblewhite H., Steed R., and Bode B. Analysis of guidelines for basal-bolus insulin dosing: Basal insulin, correction factor, and carbohydrate-to-insulin ratio. *Endocrine Practice*, 14(9):1095–1101, 2008.

[6] Walsh J., Roberts R., and Bailey T. Guidelines for insulin dosing in continuous subcutaneous insulin infusion using new formulas from a retrospective study of individuals with optimal glucose levels. *Journal of Diabetes Science and Technology*, 4(5):1174–1181, 2010.

[7] Walsh J., Roberts R., and Bailey T. Guidelines for optimal bolus calculator settings in adults. *Journal of Diabetes Science and Technology*, 5(1):129–135, 2011.

[8] Torrent-Fontbona F., Massana J., and López B. Case-base maintenance of a personalised and adaptive CBR bolus insulin recommender system for type 1 diabetes. *Expert Systems with Applications*, 121:338–346, 2019.

[9] Schmidt S. and Nørgaard K. Bolus calculators. *Journal of Diabetes Science and Technology*, 8(5):1035–1041, 2014.

[10] Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: A comprehensive review. *Circulation*, 133(2):187–225, 2016.