The Effect of Physical Activity on Glycemic Variability in Patients With Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Purpose: The effect of physical activity on glycemic variability remains controversial. This meta-analysis aimed to assess the overall effect of physical activity treatment on glycemic variability in patients with diabetes.

Methods: PubMed/MEDLINE, Embase, and Cochrane databases were searched for clinical trials that conducted in patients with type 1 diabetes mellitus and type 2 diabetes mellitus with reports of the mean amplitude of glycemic excursion (MAGE), time in range (TIR), time above range (TAR), or time below range (TBR). Eligible trials were analyzed by fixed-effect model, random effect model, and meta-regression analysis accordingly.

Results: In total, thirteen trials were included. Compared with the control group, physical activity intervention was significantly associated with increased TIR (WMDs, 4.17%; 95% CI, 1.11 to 7.23%, P<0.01), decreased MAGE (WMDs, -0.68 mmol/L; 95% CI, -1.01 to -0.36 mmol/L, P<0.01) and decreased TAR (WMDs, -3.54%; 95% CI, -5.21 to -1.88%, P<0.01) in patients with diabetes, but showed insignificant effects on TBR. Patients with higher baseline BMI levels was associated with a greater decrease in MAGE (β=-0.392, 95% CI: -0.710, -0.074), and patients with lower baseline HbA1c levels was associated with a greater increase in TBR during physical activities (β=-0.903, 95% CI: -1.550, -0.255).

Conclusion: Physical activity was associated with significantly decreased glycemic variability in patients with diabetes. Patients with higher BMI might benefit more from physical activity therapy in terms of a lower MAGE. Hypoglycemia associated with physical activity treatment still warranted caution, especially in patients with intensive glycemic control.

Systematic Review Registration: PROSPERO [CRD42021259807].

Keywords: physical activity, glycemic variability, glycemic control, diabetes, continuous glucose monitoring
INTRODUCTION

Physical activity was considered as an easy and economical way to improve overall well-being (1, 2). In previous studies, physical activity was proved to improve glycemic control, manifested as reducing hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) (3–6). Recent studies indicated that even light physical activities breaking the prolonged sitting could bring metabolic benefits to patients with diabetes (7, 8). Hence, physical activity was recognized as a key non-pharmaceutical strategy for patients with diabetes in most international and national guidelines (9–11).

However, the efficacy of physical activity treatment on the improvement of HbA1c could only indicate the reduction in mean glucose level. Whether taking physical activities will expose diabetic patients to an increased risk of hyperglycemia or hypoglycemia is still under great debate (4, 5, 12–17). Since emerging evidence has built a positive relationship between glycemic variability and diabetes complications, the effect of physical activity on glycemic variability increasingly attracts public attention (18–21).

Accessing glycemic variability was not easy with traditional glucose monitor strategies, including self-monitoring of blood glucose, HbA1c measurement, and glycated albumin measurement. Nevertheless, with the availability of new glucose monitoring technics, especially continuous glucose monitoring (CGM), several computations turned out to be good indicators for glycemic variability. Among those computations, time in range (TIR), time above range (TAR), time below range (TBR), and mean amplitude of glycemic excursion (MAGE) were the most popular indicators for within-day glycemic variability and were wildly discussed in previous researches (22–24).

In this study, we used TIR, TAR, TBR, and MAGE to measure the glycemic variability. The main purpose of this meta-analysis was to evaluate the effect of physical activity treatment on glycemic variability in patients with diabetes.

MATERIALS AND METHODS

This meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (25). A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was created and showed in the Supplementary Materials. The study was previously registered on PROSPERO with ID CRD42021259807.

Data Sources and Searches

According to the Cochrane Handbook (25), one investigator (Xingyun Zhu) performed the systematic searches in EMBASE, MEDLINE (accessed by PubMed), and Cochrane Central Register of Controlled Trials for studies of physical activity intervention published between January 1980 and October 2021. The searching terms were as follows: “Exercise”, “Physical Activity”, “Circuit-Based Exercise”, “Cool-Down Exercise”, “Warm-Up Exercise”, “Exercise Movement Techniques”, “Exercise Therapy”, “Exercise Test”, “Resistance Training”, “Muscle Stretching Exercises”, “High-Intensity Interval Training”, “Diabetes Mellitus”, “Diabetes”, “Diabetes Mellitus”, “Randomized Controlled Trial”, “Randomized Controlled Trials”, “Controlled Clinical Trial”, “Continuous Glucose Monitoring”. The full electronic search strategy was shown in Supplementary Table S1.

Study Selection

The inclusion criteria for the meta-analysis were as follows: 1) Random controlled trials (RCTs) conducted in people with type 1 diabetes or type 2 diabetes. 2) RCTs that had at least one arm of physical activity intervention, compared with a no-exercise control group. 3) RCTs that monitored glucose variation with CGM. 4) RCTs with the reported result of any of the following as outcome variables: MAGE, TIR, TAR, TBR. The exclusion criteria for the meta-analysis were as follows: 1) RCTs conducted in patients with gestational diabetes, other special types of diabetes, or without diabetes. 2) Trials conducted in animal models. 3) Duplicate publications. 4) Reviews. In this study, physical activity was defined as any intervention that breaks prolong sitting.

Data Extraction and Quality Assessment

Two investigators (Xingyun Zhu and Lina Zhao) independently collected data of all studies, including publication details, population characteristics, physical activities, results of TIR, TAR, TBR, MAGE, etc. Definitions of hyperglycemia and hypoglycemia were also recorded. We invited a third investigator (Chu Lin) to join the discussion and resolved discrepancies by consensus. The risk of bias was evaluated according to the Cochrane risk of bias tool. The quality of the included evidence was evaluated by the GRADE Approach (26).

Data Synthesis and Analysis

The primary outcome was the changes in TIR and MAGE between the physical activity treatment group and the control group in patients with diabetes. The secondary outcomes included the changes in TAR and TBR between the physical activity treatment group and the control group in patients with diabetes.

Prespecified subgroup analyses were stratified by baseline age, sex, BMI, HbA1c, and disease duration. All the outcomes in analyses were continuous variables and evaluated by computing the weighted mean differences (WMDs) and 95% confidence intervals (CI). We used Higgins I² statistics to evaluate between-study heterogeneity, with an I² value >50 indicating a high level of heterogeneity. The prediction intervals of I2 were calculated according to a method described by previous studies (27, 28). The fixed-effects model was used for a low level of heterogeneity, and the random-effects model was used for a high level of

Abbreviations: CGM, continuous glucose monitoring; TIR, time in range; TAR, time above range; TBR, time below range; MAGE, mean amplitude of glycemic excursion; RCTs, Random controlled trials; WMDs, weighted mean differences; CI, confidence intervals; HbA1c, Hemoglobin A1c; BMI, body mass index; T1DM, type 1 diabetes; T2DM, type 2 diabetes.
heterogeneity. We used the Z test to compare the mean difference of effect sizes between subgroups. Meta-regression analyses were conducted to evaluate the associations between different potential influencing indicators (including age, sex, disease duration, baseline HbA1c level, body mass index) in outcomes. Publication bias was assessed via the Beggs test and funnel plot. Statistical significance was considered at $P < 0.05$.

RESULTS

Study Selection, Study Characteristics, and Quality Assessment

In total, 13 RCTs were included in this meta-analysis. Among all included trials, 11 were studies with crossover design, and 2 were studies with parallel design. Figure 1 summarized the selection process of included studies. Baseline characteristics of each included RCT were shown in Table 1. The descriptions of exercise in RCTs were summarized in the supplementary material (Supplementary Table S2). The overall risk of bias and selective reporting bias was low, and no significant publication bias was found (Supplementary Table S3 and Supplementary Figures S1, S2). According to the GRADE Approach, the quality of included trials in included outcomes was ranked low to moderate (Supplementary Table S4).

The Effect of Physical Activity on the TIR

Compared with the control group, patients that took physical activity had significantly higher TIR (WMDs, 4.17%; 95% CI, 0.95 to 7.46%, $P<0.01$, $I^2 = 0$). However, in patients with type 1 diabetes, TIR was not significantly different between groups (Table 2 and Supplementary Figure S3).

The Effect of Physical Activity on the MAGE

Overall, compared with the control group, physical activity led to significant reductions in MAGE in patients with type 2 diabetes (WMDs, -0.68 mmol/L; 95% CI, -1.01 to -0.36 mmol/L, $P<0.01$, $I^2 = 78$%) (Table 2 and Supplementary Figure S4).

Compared with the control group, MAGE was significantly decreased in patients with baseline HbA1c $\geq$7% in the physical activity group (WMDs, -1.13 mmol/L; 95% CI, -1.44 to -0.82, $P<0.01$, $I^2 = 52$%), but not in patients with baseline HbA1c<7% in the physical activity group. When stratified by baseline BMI level, compared with the control group, MAGE was significantly decreased in patients with BMI$\geq$30 kg/m² in the physical activity group (WMDs, -1.08 mmol/L; 95% CI, -1.45 to -0.71, $P<0.01$, $I^2 = 68$%), as well as in patients with BMI<30 kg/m² in physical activity group (WMDs, -0.44 mmol/L; 95% CI, -0.82 to -0.06, $P<0.01$, $I^2 = 0$%). When compared with the control group, a significant decrease in MAGE was revealed in patients with shorter disease duration in the physical activity group (WMDs, -1.13 mmol/L; 95% CI, -1.44 to -0.82, $P<0.01$, $I^2 = 58$%), but was not observed in patients with longer disease duration in the physical activity group (Table 2).

The Effect of Physical Activity on the TAR and TBR

Overall, physical activity was associated with significant decrease in TAR (WMDs, -3.54%; 95% CI, -5.21 to -1.88%, $P<0.01$, $I^2 = 0$%) with no effect on TBR (WMDs, 0.36%; 95% CI,
-1.79 to 2.51%, \( P=0.74, I^2 = 92\% \) when compared to the control group.

When compared to the control group, physical activity was associated with a significant decrease in TAR (WMDs, -3.61%; 95% CI, -5.30 to -1.92%, \( P<0.01, I^2 = 0\% \)) in patients with type 2 diabetes, while with no effect on TAR in patients with type 1 diabetes (Table 2 and Supplementary Figure S5). Physical activity was not associated with a significant change in TBR in patients with type 1 diabetes, or type 2 diabetes (Table 2 and Supplementary Figure S6).

### TABLE 1 | Baseline characteristics of each included random controlled trials.

| Author, year | Exercise duration | Treatment group | Standard diet | No. of patients | Age (years) Men (%) | BMI (kg/m²) | Duration of diabetes (years) | Baseline HbA1c (%) | Definition of hypoglycemia and hyperglycemia (mmol/L) |
|--------------|-------------------|-----------------|---------------|-----------------|---------------------|-------------|-------------------------------|-------------------|------------------------------------------|
| Paddy 2017 (29) | 24 hours | Light-intensity walking Simple resistance activities | yes | 24 | 62 ± 6 | 58.3 | 33.0 ± 3.4 | 6.8 ± 5.1 | 7.2 ± 0.7 | 3.9; NA; 10; |
| Jonida 2015 (30) | 72 hours | Continuous walking | yes | 9 | 58.2 ± 6.6 | 100 | 30.2 ± 3.1 | 5.2 ± 4.3 | 7.0 ± 0.6 | NA; |
| Jordan 2019 (31) | 6 days | Exercise | yes | 63 | 64.4 ± 8.0 | 46 | 30.5 ± 6.5 | 9.7 ± 6.1 | 6.8 ± 0.7 | 4; |
| Zheng Li 2018 (32) | 2 days | Exercise | yes | 29 | 51 ± 11.2 | 75.9 | 24.8 ± 3.4 | 5.7 ± 6.0 | 7.3 ± 1.3 | NA; |
| Richard 2018 (33) | 3 days | Reduced-exertion high-intensity interval training (REHIT) Moderate–vigorous-intensity continuous exercise 30 min (MICT) High-intensity interval training (HIIT) | yes | 11 | 52 ± 6 | 100 | 29.7 ± 3.1 | 4 ± 3 | 7.0 ± 0.8 | NA; |
| Kristian 2016 (34) | 2 weeks | Continuous walking training Interval walking training | NA | 14 | 65 ± 2 | 78.6 | NA | NA | 6.5 ± 0.3 | 10; |
| Myette-Côté 2015 (35) | 24 hours | Exercise | yes | 10 | 59.0 ± 9.6 | 50 | 29.5 ± 4.7 | 7.7 ± 5.2 | NA | 4; |
| Tasuku 2016 (36) | 24 hours | Moderate-intensity continuous exercise High-intensity interval exercise | yes | 10 | 60 ± 6 | 80.0 | 30.8 ± 5.4 | 6.8 ± 4.6 | 7.1 ± 1.0 | 4; |
| Jennifer 2018 (37) | 24 hours | Morning walk after breakfast Post-meal breaks from sitting | yes | 30 | 64 ± 8.2 | 46.7 | 31.7 ± 5.4 | 10 ± 7.8 | 7.4 ± 1.1 | NA; |
| Matthew 2020 (38) | 12 days | Morning Exercise Afternoon Exercise Evening Exercise | yes | 14 | 65 ± 9.0 | 57.1 | 27.2 ± 3.5 | 10.5 ± 6.7 | 6.7 ± 0.6 | 4; |
| RavI 2018 (39) | 3 weeks | Aerobic exercise Resistance exercise | yes | 10 | 33 ± 6 | 40.0 | 24.4 ± 2.1 | 18 ± 10 | 7.4 ± 1 | 3.9; |
| Kamilla 2018 (40) | 11 weeks | Endurance training High-intensity interval training | yes | 12 | 58 ± 8 | 58.3 | 27.4 ± 3.1 | 6 ± 4 | 6.9 ± 0.9 | 3.9; |
| Angela 2020 (41) | 12 weeks | High-intensity interval training | NA | 15 | 46.1 ± 10.5 | 67 | 31.6 ± 3.4 | 22.5 ± 10.0 | 8.37 ± 0.71 | 10; |

HbA1c, Hemoglobin A1c; BMI, body mass index; NA, not available.
**Meta-Regression of the Associated Factors and TIR, MAGR, TAR, and TBR**

According to meta-regression analysis, patients with higher baseline BMI was associated with greater decrease in MAGE during physical activity ($\beta=-0.392$, 95% CI: -0.710, -0.074). And patients with lower baseline HbA1c levels was associated with greater increase in TBR during physical activity ($\beta=-0.903$, 95% CI: -1.550, -0.255) (Table 3 and Supplementary Figures S7–S10).

**DISCUSSION**

By analyzing data from RCTs of physical activity treatment in patients with diabetes, we found that when compared with the control group, physical activity intervention was associated with significantly increased TIR and significantly decreased MAGE and TAR in patients with diabetes, but was not associated with an increase in TBR. Furthermore, patients with higher baseline BMI levels tended to have a greater decrease in MAGE during physical activities. Moreover, patients with lower baseline HbA1c levels showed a more significant increase in TBR during physical activities.

It was well known that physical activity treatment could improve glycemic control (4, 5), and our results further unveiled that physical activity might improve glycemic control by reducing the time that patients stay in hyperglycemic statues and increasing the time within the normal range. In addition to overall glycemic control, it also suggested that physical activity was associated with significantly decreased within-day glycemic variability. There were systemic reviews that also suggested that physical activity might be associated with a reduction in glycemic variability, but those reviews did not perform meta-analysis to synthesize the pooled effect of physical activity on glycemic variability and failed to conclude (42, 43). In this study, we took a step forward to quantitatively analyze the pooled effect of physical activity on glycemic variability and provided new evidence to the assumption that physical activity might reduce glycemic variability.

Concerns of hypoglycemia events have cast a shadow over the application of physical activity treatment in the clinical management of diabetes. And according to our analysis, generally speaking, physical activity would not significantly increase the time patients spent in hypoglycemia. However, we found a significant increase in TBR in patients with type 2 diabetes, and the sample size of type 1 diabetes was too small to conclude. Furthermore, patients with lower HbA1c levels tended to have more increments in TBR during physical activity. Hence, close glucose monitoring before, during, and after physical activity is crucial to preventing hypoglycemia, especially in patients with good glycemic control.

We also tried to explore which kind of patient was more suitable for physical activity treatment. Results from this study indicated that in type 2 diabetes, patients with higher baseline BMI level and short disease duration might get more reduction in glycemic variability through physical activity treatment. It might be assumed that physical activity may improve glycemic control by alleviating insulin resistance. At the early stage of type 2 diabetes, patients may have sufficient islet function, and insulin resistance tends to be the leading cause of hyperglycemia, especially in obese patients (44–46). Thus, these patients could benefit more from physical activity. However, no significant improvement in glycemic variability was found in patients with long disease duration or patients with type 1 diabetes, which might suggest that patients with poor islet function might have limited benefit in glycemic control from physical activity. Nevertheless, this hypothesis still needs further evidence to validate.

Several factors could potentially affect the effect of physical activity on glycemic variability. First of all, compensatory eating after physical activity would diminish the beneficial effect of physical activity. To evaluate the influence of compensatory eating on our results, we summarized the diet status of included studies (Table 1). According to the result, 11 over 13 included studies provided their participants with a standard diet during the experiment. Hence, in this study, compensatory eating after physical activity was unlikely to post a substantial influence on the beneficial effect of physical activity. Another important influencing factor was the adherence to the exercise plan. The mean adherence of patients in the included studies was summarized in Supplementary Table S2. Among 13 studies, 6 studies reported 99%-100% adherence of patients to the exercise plan; 1 study reported 65%-70% adherence to the exercise plan, and 6 studies did not report the adherence of patients. Thus, poor adherence of patients would probably affect the outcomes by lessening the beneficial effect of physical activity. The frequency and the intensity of physical activity would also alter the effect of physical activity on glycemic control (47). The detailed exercise plan of included studies was displayed in Supplementary Table S2. However, it was difficult to identify how the exercise frequency and intensity affected the effect of physical activity based on existing data. There were other characteristics, such as medication usage and comorbidities that might interfere with the glycemic control outcomes. Despite we attempted to extract and adjust these variables, they were not commonly reported in the studies. Further investigations were required to identify the influence of these variables on the effect of physical activity on glycemic variability.

Our study has its own contributions to the field. According to our knowledge, this was the first systematic review and meta-analysis to assess the relationship between physical activity and glycemic variability in patients with diabetes. Moreover, our results indicated that physical activity was associated with a significant reduction in glycemic variability, which might promote physical activity therapy in clinical practice. Several limitations should also be noted. Firstly, the sample size in type 1 diabetes was too small to draw a definite conclusion. Secondly, the definition of hypoglycemia and hyperglycemia was slightly different from trials. We summarized the definition of hypoglycemia and hyperglycemia of each trial in Table 1. Differences in the definition of targeted range might affect the
### Table 2 | Effect of physical activity on TIR, MAGE, TAR, and TBR.

| Group or Subgroup | No. of participants (physical activity/control) | WMDs 95% CI of WMDs | P value | I² | 95% CI of I² |
|-------------------|-----------------------------------------------|---------------------|---------|----|------------|
| Effect of physical activity on TIR  | | | | | |
| Overall           | 120/112                                      | 4.17%               | 1.11%, 7.23% | <0.01 | 0% 0%, 75% |
| T1DM              | 32/35                                        | 3.87%               | -5.04%, 12.78% | 0.39 | 1% 0%, 90% |
| T2DM              | 88/77                                        | 4.21%               | 0.95%, 7.46% | <0.01 | 0% 0%, 90% |
| Effect of physical activity on MAGE | | | | | |
| Overall           | 303/311                                      | -0.68mmol/L         | -1.01 mmol/L, -0.36 mmol/L | <0.01 | 78% 66%, 86% |
| T1DM              | 143/143                                      | -0.38mmol/L         | -0.81 mmol/L, -0.04 mmol/L | 0.08 | 60% 9%, 83% |
| T2DM              | 160/168                                      | -1.13mmol/L         | -1.44 mmol/L, -0.82 mmol/L | <0.01 | 52% 7%, 75% |
| Male percentage ≥75% | 111/119                                      | -0.58mmol/L         | -1.02 mmol/L, -0.14 mmol/L | <0.01 | 40% 0%, 71% |
| Disease duration<7.1 years | 143/143                                      | -0.38mmol/L         | -0.81 mmol/L, 0.04 mmol/L | 0.08 | 60% 9%, 83% |
| Disease duration≥7.1 years | 160/168                                      | -1.13mmol/L         | -1.44 mmol/L, -0.82 mmol/L | <0.01 | 52% 52%, 90% |
| Effect of physical activity on TAR | | | | | |
| Overall           | 265/265                                      | -3.54%              | -5.12%, -1.88% | <0.01 | 0% 0%, 49% |
| T1DM              | 32/35                                        | -1.43%              | -11.07%, 8.30% | 0.77 | 40% 0%, 81% |
| T2DM              | 233/230                                      | -3.61%              | -5.30%, -1.92% | <0.01 | 0% 0%, 52% |
| Effect of physical activity on TBR | | | | | |
| Overall           | 95/87                                        | 0.36%               | -1.79%, 2.51% | 0.74 | 92% 87%, 95% |
| T1DM              | 32/35                                        | -0.89%              | -5.22%, 3.44% | 0.69 | 34% 0%, 78% |
| T2DM              | 63/52                                        | 0.69%               | -1.78%, 3.15% | 0.58 | 95% 92%, 97% |

HbA1c, Hemoglobin A1c; BMI, body mass index; T1DM, type 1 diabetes; T2DM, type 2 diabetes; TIR, time in range; TAR, time above range; TBR, time below range; MAGE, mean amplitude of glycemic excursion; WMDs, weighted mean differences; CI, confidential interval.

### Table 3 | Meta-regression analysis for the associated factors and change in TIR, MAGE, TAR, and TBR.

| Variables | Meta regression analysis |
|-----------|--------------------------|
| Time in range | β | 95%CI |
| Baseline HbA1c | -0.015 | -0.112, 0.082 |
| Baseline BMI | -0.006 | -0.170, 0.158 |
| Baseline age | 0.005 | -0.025, 0.034 |
| Baseline male percentage | -0.009 | -0.086, 0.068 |
| Disease duration | -0.240 | -0.864, 0.305 |
| Time above range | β | 95%CI |
| Baseline HbA1c | 0.358 | -0.066, 0.783 |
| Baseline BMI | 0.003 | -0.101, 0.106 |
| Baseline male percentage | -0.007 | -0.016, 0.003 |
| Disease duration | 0.028 | -0.024, 0.079 |
| Time below range | β | 95%CI |
| Baseline HbA1c | -0.903* | -1.550, -0.255 |
| Baseline BMI | -0.015 | -0.689, 0.660 |
| Baseline age | 0.040 | -0.002, 0.082 |
| Baseline male percentage | 0.030 | -0.011, 0.071 |
| Disease duration | -0.124 | -0.267, 0.019 |
| MAGE | β | 95%CI |
| Baseline HbA1c | -2.347 | -5.482, 0.789 |
| Baseline BMI | -0.392* | -0.710, -0.074 |
| Baseline age | -0.068 | -0.205, 0.088 |
| Baseline male percentage | 0.021 | -0.017, 0.059 |
| Disease duration | 0.008 | -0.325, 0.342 |

*p value < 0.05; HbA1c, Hemoglobin A1c; BMI, body mass index; T1DM, type 1 diabetes; T2DM, type 2 diabetes; TIR, time in range; TAR, time above range; TBR, time below range; MAGE, mean amplitude of glycemic excursion; CI, confidential interval.

### Conclusions

According to our study, physical activity intervention was significantly associated with decreased glycemic variability in patients with diabetes. Patients with higher BMI level and shorter disease duration might benefit more from physical activity therapy. Overall, physical activity intervention was not associated with increased time in hypoglycemia. However, hypoglycemic events related to physical activity treatment still warranted caution, especially in patients with intensive glycemic control.
DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS
XZ, XC, JC, LZhan, and LJ conceptualized this study and designed the systematic review protocol. XZ and L.Zhao performed the study selection and data extraction. XZ, SH, FL, and XC performed the statistical analyses. XZ, CL, and XC prepared the outlines and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.767152/full#supplementary-material

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