Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Coronavirus lockdown effect on type 1 diabetes management on children wearing insulin pump equipped with continuous glucose monitoring system

Athanasios Christoforidis [a,*], *Evgenia Kavoura* [b], *Aggeliki Nemtsa* [a], *Konstantina Pappa* [a], *Meropi Dimitriadou* [a]

[a] *1st Paediatric Department, Aristotle University, Ippokration General Hospital, 49th Konstantinoupoleos str, P.C.: 54642, Thessaloniki, Greece*
[b] *Medtronic Hellas S.A., 9th klm Thessaloniki-Moudianion, P.C.: 55535, Pilea, Greece*

ARTICLE INFO

Article history:
Received 6 May 2020
Received in revised form
20 June 2020
Accepted 2 July 2020
Available online 8 July 2020

Keywords:
Type 1 diabetes
Children
Lockdown
Coronavirus
Quarantine

ABSTRACT

Aims: On the 10th of March, Greece imposed the closure of schools and universities and a full lockdown a few days later in order to counter the spread of the coronavirus outbreak. Our aim was to monitor the effect of the coronavirus lockdown in diabetes management in children with Type 1 Diabetes Mellitus (T1DM) wearing insulin pump equipped with continuous glucose monitoring system.
Methods: In 34 children with T1DM on Medtronic 640G insulin pump equipped with the Enlite Sensor uploaded CareLink data were categorized in 2 three-week periods before and after the 10th of March.
Results: Mean time in range (TIR) did not significantly differ between the two periods. However, a significantly higher Coefficient of Variation (CV) indicating an increased glucose variability in the pre-lockdown period was observed (39.52% versus 37.40%, p = 0.011). Blood glucose readings were significantly fewer during the lockdown period (7.91 versus 7.41, p = 0.001). No significant difference was recorded regarding the total daily dose of insulin and the reported carbohydrates consumed. However, the meal schedule has changed dramatically as the percentage of breakfast consumed before 10.00 a.m. has fallen from 80.67% to 41.46% (p < 0.001) during the lockdown. Correspondingly, the percentage of dinner consumption before 10.00 p.m. significantly fell during the lockdown period (60.22% versus 53.78%, p = 0.019).
Conclusions: Glycemic control during the coronavirus lockdown can be adequately achieved and be comparable to the pre-lockdown period in children with type 1 diabetes mellitus wearing insulin pump equipped with sensor.

1. Introduction

At the dawn of 2020, central China faced the outbreak of a highly transmittable, novel strain of the coronavirus, causing severe Illness that was subsequently named SARS-CoV-2 [1]. The coronavirus disease 19 (COVID-19) is characterized by severe acute respiratory syndrome and has a high mortality rate especially among the elderly and people with serious

* Corresponding author at: 49, Konstantinoupoleos str, 54642 Thessaloniki, Greece.
E-mail address: christoforidis@auth.gr (A. Christoforidis).
https://doi.org/10.1016/j.diabres.2020.108307
0168-8227/

underlying medical conditions irrespectively of age [2]. By the 11th of March and as more than 110 countries have reported numerous cases of COVID-19, WHO declared this outbreak as a pandemic [3]. As of the 13th of March, Europe was the active center of the pandemic and shortly after, all European countries began reporting confirmed cases and deaths. One after the other, most European countries have implemented various degrees of lockdowns to counter the spread of the coronavirus outbreak [4].

Greece imposed the closure of all educational institutions on the 10th of March after only 89 confirmed cases of COVID-19 and a full lockdown two weeks later, much earlier than many of its European neighbors. So far, these quick reflexes have been effective as the number of COVID-19 cases and deaths have been one of the lowest in Europe, nonetheless, there is a long way ahead.

The lockdown and the subsequent social distancing practices, which, in some cases, meant complete isolation, has caused a major change in people's daily living routines. Emerging evidence supports that people have become less physically active and frequently consume a nutritionally unbalanced diet [5]. People with chronic health conditions might have limited access to the healthcare system and even to health supplies and equipment. For children and adolescents with type 1 diabetes mellitus (T1DM) all these factors may lead to impaired glycemic control as physical activity, healthy eating and even a steady daily routine contribute substantially in a more effective diabetes management [6,7].

The aim of this study was to monitor the effect of the coronavirus lockdown in glycemic variability, insulin requirements and eating portions and habits in children with T1DM wearing insulin pump equipped with continuous glucose monitoring system. Thus, a direct comparison of all these parameters was conducted between a three-weeks period during the lockdown and an equal time period prior to the lockdown.

2. Materials and methods

We invited children with type 1 diabetes, followed in our pediatric diabetes outpatient clinic and wearing a Medtronic MiniMed 640G Insulin pump accompanied with Enlite™ Sensor and Guardian™ 2 Link transmitter to upload their data on the CareLink System one month since the initiation of the coronavirus lockdown. The study was performed in accordance with the Helsinski Declaration of 1975 and was approved by the Scientific and Administrative Council of Hippokration General Hospital of Thessaloniki. Children and their caregivers were informed for the nature and the purpose of the study and a verbal consent was obtained for every participant. Exclusion criteria included: i) Recent diagnosis of T1DM (less than 6 months), ii) chronic or acute medical condition or medication that would be likely to interfere with glucose metabolism for 2 weeks prior and 2 weeks after the study period, iii) less than 3 months experience with the pump and the sensor iv) sensor duration for the study period of less than 75%, v) incomplete or missing data, or inability to upload data using the CareLink system and v) unwillingness to participate in the study. Fig. 1 shows a flow chart of the study population selection.

CareLink data that were uploaded by the patients and their caregivers were analyzed as categorized into 2 periods: i) lockdown period (3 weeks period starting from the 11th of March 2020) and ii) period prior to the lockdown (3 weeks period ending on the 10th of March 2020). Demographic data regarding date of birth, date of T1DM diagnosis and date of Medtronic 640G pump first use were extracted from patients' medical files. Additionally, anthropometric parameters including weight and height and pubertal status were extracted from the records of patient's last visit to the Clinic, and their BMI was calculated as the ratio weight/height^2 (kg/m^2, Quetelet index). For every anthropometric parameter, Z-scores were calculated according to CDC standards[8]. Recent HbA1c values were also recorded for every patient.

For statistical analysis and graphical demonstration Microsoft Excel® for Mac version 16.16.8 and IBM corp. SPSS Statistics® version 24.0.0.0 were used. Results are presented as means ± Standard Deviation (SD) or means ± Standard Error (SE). The Shapiro-Wilk test was used for assessing the normality of the studied parameters. Comparison of the means was performed with Student's *T*-test for paired samples and Wilcoxon Signed Ranks Test for parameters with normal and skewed distribution respectively. In parameters with normal distribution linear correlations were calculated with the Pearson's correlation coefficient, whereas Spearman's correlation coefficient was employed for non-parametric variables. A P value of 0.05 or less was considered statistically significant.

3. Results

Thirty-four children (16 boys, 47,06%) with T1DM were finally enrolled in the statistical analysis. Their decimal mean age at the time of the study was 11.37 ± 4.45 years, ranging from 2.52 to 18.59 years. Mean age at the time of the diagnosis of T1DM was 6.23 ± 3.43 years. Mean time using insulin pump was 2.66 ± 2.06 years. Descriptive demographic and anthropometric characteristics of the studied population are presented in Table 1.

Following data stratification in the two studied periods, a few significant differences arose. Mean glucose values obtained with sensor did not differ between the two studied periods (168.76 ± 21.87 mg/dl before lockdown versus 170.26 ± 22.79 during lockdown, p = 0.466). Blood glucose readings were significantly fewer during the lockdown period (7.91 ± 3.45 mg/dl versus 7.41 ± 3.27 mg/dl, p = 0.001) and glucose levels obtained by blood measurements had a significantly higher Coefficient of Variation (CV) in the pre-lockdown period (39.52 ± 5.67% versus 37.40 ± 5.97%, p = 0.011). However, lockdown period did not significantly affect glycemic control as mean time in range (TIR) did not differ significantly between the two periods (60.71 ± 13.23% versus 60.50 ± 14.75%, p = 0.872).

With regards to insulin requirements, no significant difference was recorded regarding the total daily dose of insulin in the two periods (36.24 ± 25.17 U versus 35.80 ± 23.32 U, p = 0.739). There was a trend of a higher percentage of basal rates during the lockdown period (35.82 ± 8.20% versus 37.21

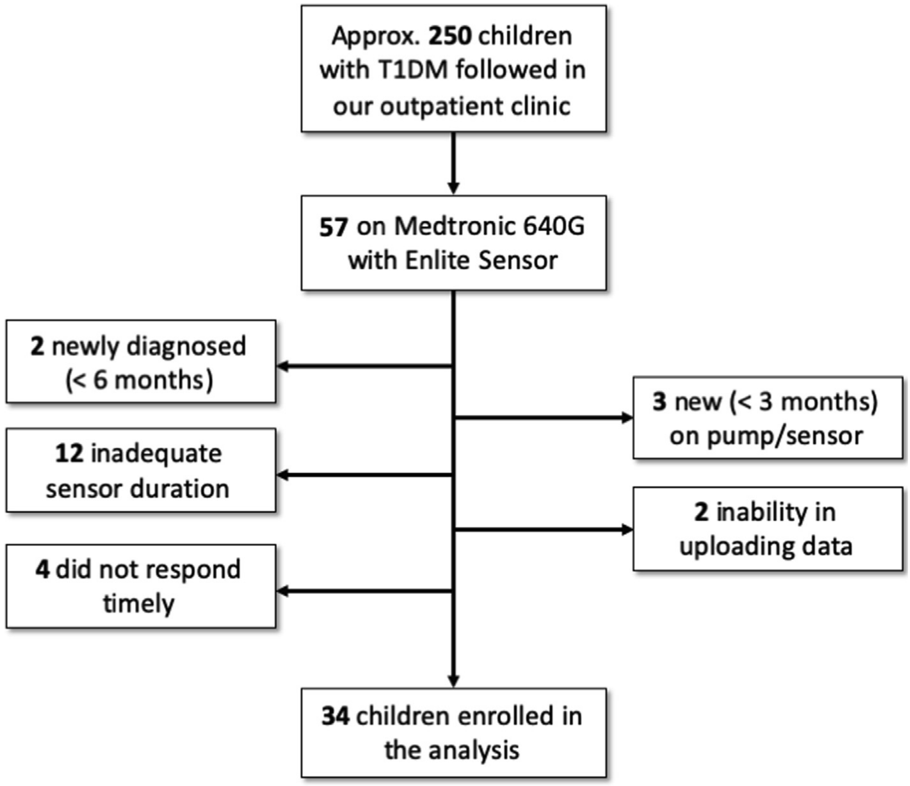

Fig. 1 – Flow chart of the study population selection including patient recruitment, exclusion criteria and non-responders.

± 8.63%, p = 0.074) but again without reaching statistically significance. Similarly, no difference was recorded regarding the reported carbohydrates during the lockdown period and the preceding 3-weeks period (195.29 ± 106.90 versus 198.06 ± 109.13, p = 0.966). However, the meal schedule has changed dramatically during the lockdown period. Thus, the percentage of breakfast consumption before 10.00 a.m. has drastically fallen from 80.67 ± 16.11% before the lockdown to 41.46 ± 34.61% (p < 0.001). Correspondingly, the percentage of dinner consumption before 10.00 p.m. has significantly fallen during the lockdown period (60.22 ± 26.39% versus 53.78 ± 28.97%, p = 0.019). Comparisons of the means between the studied periods are presented in Table 2, whereas Fig. 2 illustrates the significant changes in meal timing.

Table 1 – Descriptive demographic and anthropometric data of the studied population (results are expressed as mean ± Standard Deviation).

Parameter	Value
n	34
Boys (n, %)	16 (47.06)
Age (years)	11.37 ± 4.45
Age at Diagnosis (years)	6.23 ± 3.71
Disease duration (years)	5.14 ± 3.43
TIME IN PUMP (years)	2.66 ± 2.06
Age at Pump Start (years)	8.71 ± 4.35
Disease duration at Pump Start (years)	2.48 ± 2.91
Height (cm)	141.59 ± 24.43
Height Z-score	−0.13 ± 0.80
Weight (Kg)	41.934 ± 18.87
Weight Z-score	0.34 ± 0.86
BMI (Kg/m^2)	19.64 ± 3.52
BMI Z-score	0.54 ± 0.86
Hba1c (%)	7.43 ± 0.83

4. Discussion

Our data showed that glycemic control during the coronavirus lockdown period can be adequately achieved and be comparable to the pre-lockdown period in children with type 1 diabetes mellitus wearing insulin pump equipped with sensor. Our results are in accordance with those reported in 2 emerging studies showing no difference in glycemic control during coronavirus lockdown period in both adults [9] and adolescents [10] with T1DM on hybrid closed loop system. Interestingly, Bonora et al have just shown improved metabolic control in adult patients with T1DM that have stopped working, in contrast, no difference in glycemic control was reported in those that continue to work during the lockdown period [11].

Although the reported amount of carbohydrates consumed did not differ significantly between the two periods in our data, meal timing has drastically moved to a looser routine with frequent late-night eating and a significantly increased percentage of consuming the first meal of the day later that 10.00 a.m. In a large, recent study on adult population with T1DM, skipping breakfast was associated with lower odds of reaching good glycemic control and higher mean blood glucose values [12]. However, in our study, we could

Table 2 – Parameters of glycemic control, insulin requirements and carbohydrates consumption during the three studied (results are expressed as mean ± Standard Error).

	Parameter	Before	Lockdown	p
Blood Glucose	Mean glucose (mg/dl)	181.41 ± 5.02	184.47 ± 5.15	0.397
	Standard Deviation (mg/dl)	71.26 ± 2.22	68.79 ± 2.51	0.199
	Coefficient of Variation (%)	39.52 ± 0.97	37.40 ± 1.02	**0.011**
	Readings (n)	7.91 ± 0.59	7.41 ± 0.56	**0.001**
	% Readings in TIR (70–180) (%)	52.48 ± 2.63	50.71 ± 2.81	0.430
	% Readings > 180 mg/dl (%)	44.93 ± 2.81	47.09 ± 2.96	0.340
	% Readings < 70 mg/dl (%)	2.59 ± 0.42	2.21 ± 0.56	0.079
Sensor	Mean glucose (mg/dl)	168.76 ± 3.75	170.26 ± 3.91	0.466
	Standard Deviation (mg/dl)	60.12 ± 1.69	60.24 ± 1.99	0.948
	Coefficient of Variation (%)	35.57 ± 0.54	35.46 ± 1.07	0.083
	Duration (hours/week)	149.38 ± 3.09	147.03 ± 3.89	0.510
	Time in Range (70–180 mg/dl) (%)	60.71 ± 2.27	60.50 ± 2.53	0.812
	Time > 180 mg/dl (%)	37.56 ± 2.40	38.06 ± 2.63	0.709
	Time < 70 mg/dl (%)	1.74 ± 0.26	1.644 ± 0.26	0.206
Insulin	Total Daily Dose-TDD (Units)	36.24 ± 4.32	35.80 ± 4.00	0.739
	Standard Deviation (Units)	5.43 ± 0.90	5.31 ± 0.71	0.775
	Basal TTD (%)	35.82 ± 1.41	37.21 ± 1.48	0.074
	TTD/Weight (Units/Kg)	0.82 ± 0.04	0.82 ± 0.04	0.745
	Bolus TTD/Weight (Units/Kg)	0.53 ± 0.04	0.52 ± 0.03	0.275
Carbs	Mean Daily Carbs (gr)	195.29 ± 18.33	198.06 ± 18.72	0.966
	Standard Deviation (gr)	55.29 ± 6.89	55.09 ± 5.87	0.726
	Breakfast before 10 a.m. (%)	80.67 ± 2.76	41.46 ± 5.93	**<0.001**
	Dinner before 10 p.m. (%)	60.22 ± 4.53	53.78 ± 4.97	**0.019**
	Carbs/TDD (gr/Units)	6.72 ± 0.60	6.67 ± 0.58	0.270
	Carbs/Bolus TDD (gr/Units)	10.74 ± 1.01	10.78 ± 0.97	0.858
	Carbs/Kg (gr/Kg)	5.14 ± 0.39	5.20 ± 0.39	0.780
	Carbs/BMI (gr/Kg/m_2)	9.91 ± 0.75	10.04 ± 0.279	0.740

TIR: Time In Range, TTD: Total Daily Dose, BMI: Body Mass Index.

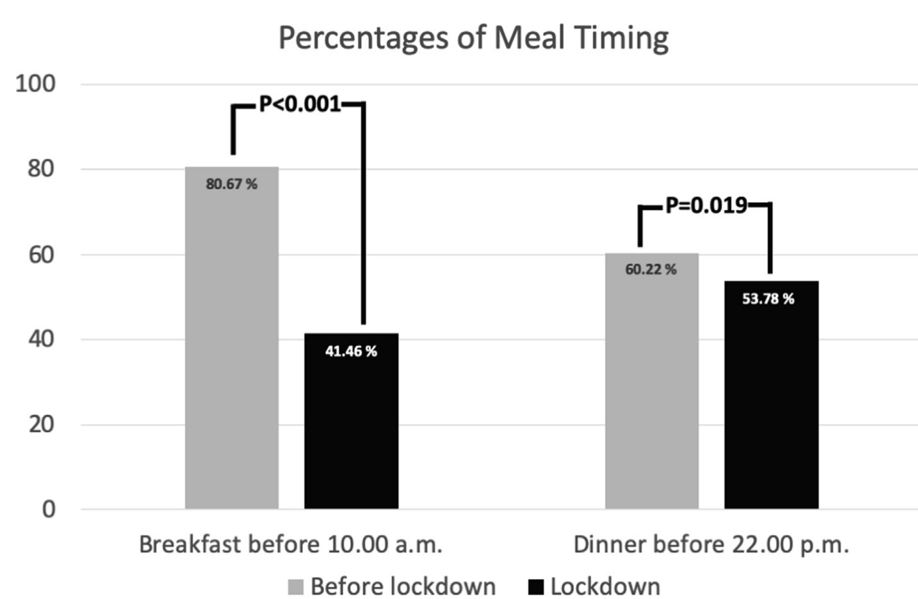

Fig. 2 – The percentage of breakfast consumed before 10.00 a.m. has drastically fallen from 80.67% before the lockdown to 41.46%, p < 0.001 and the percentage of dinner consumed before 22.00 p.m. has significantly fallen during the lockdown period (60.22% versus 53.78%, p = 0.019).

not declare our population as "breakfast skippers" or "late-awakers", as the information regarding the actual wake up time is not available through the report obtained from the CareLink system. In the previous study, higher number of reported meals during the day was also associated with a higher variability in blood glucose measurements; nevertheless, with a better overall glycemic control [12]. Better glycemic control was also associated with higher number of eating occasions in two studies performed in adolescents with T1DM [7,13], whereas skipping meals was associated with higher odds of suboptimal HbA1c in a study of 655 children with T1DM [14]. Of particular interest, skipping breakfast has been associated with increased postprandial glycemic response after lunch in a recent, experimental study of healthy young individuals [15].

Regarding physical activity, in a recent study assessing the health and wellbeing of normal Chinese adults living and working after one month of restrictions to contain the COVID-19 outbreak results showed that for those who exercise regularly and over 2.5 h per day, life satisfaction was negatively associated with the level of restrictive measures [5]. On the other hand, individuals who exercise less than half an hour a day, life satisfaction was significantly positively associated with the level of restrictive measures in more severely affected locations, reflecting a better justification or rationalization of their inactive lifestyles [5]. In patients with T1DM, regular physical activity associates with several positive physical health effects including improvement of cardiovascular function and blood lipid profile as well as enhancement in psychological well-being [16]. However, these beneficial effects on health-related outcomes do not perfectly coordinate with improvements in glycemic control something which is mainly attributed to increased glucose variability during exercise [17]. In accordance to that, our results showed a statistically decreased Coefficient of Variation (CV) of mean blood glucose values, an indirect and inverse indicator of glucose variability, during the lockdown period. On the other hand, in the recent study by Tornese et al, 8 adolescents with T1DM that continued their physical activity during the lockdown period showed improved glycemic control compared to 5 adolescents who discontinued their regular physical activity [10]. Additionally, in our study, the percentage of basal insulin requirements was increased during the lockdown period indicating increased sedentary behavior, however, with no increase in the total daily insulin dose indicating a compensatory bolus reduction as a result of reduced carbohydrates consumption.

Finally, our data showed that there was a significant reduction in blood glucose readings during the lockdown period. As expected, the number of blood glucose readings was inversely correlated to age ($r = -0.400$, $p = 0.019$, data are not shown), and also the difference in blood glucose readings performed during the lockdown and the period before the lockdown was inversely correlated to the frequency of testing prior to lockdown period with a correlation that was approaching significance ($r = -0.326$, $p = 0.060$, data are not shown). Could this reduction in using glucose strips reflect an endogenous stressor associated with fear of running out of medical supplies? Shortages in basic and medical supplies have been considered a major stressor during quarantine and continues to be associated with anxiety and anger even 4–6 months after release [18]. In order to be prepared and provide effective pharmaceutical care for the general population and patients with chronic diseases during the coronavirus outbreak, Chinese pharmacists have recently published recommendations and guidelines [19].

One of the study's main limitation derives from the subjective nature of information provided in the CareLink system, especially in the reported carbohydrates consumed and the absence of reporting physical activity and sleep patterns. Additionally, our study population includes only patients wearing insulin pump and sensor, representing a group of patients and caregivers familiar with technology and usually aiming at achieving the best possible glycemic control; thus, generalization of our results to all patients with T1DM should be avoided. Furthermore, as this is a single-center study, readers should be cautious not to expand our conclusions in different populations and clinical scenarios. Also, the nature of traditional control study does not allow the adjustment of some potential confounders such as accompanying policies related to the outcomes. On the other hand, our study's statistical strength stems from the paired comparison of each patient serving as a control to themselves. Thus, we manage to show that during the coronavirus lockdown period, children with type 1 diabetes on insulin pump with continuous glucose monitoring and an automated insulin suspension system can achieve adequate glycemic control regardless of decreased physical activity, and possibly a nutritionally imbalanced diet and unpredictable meal schedules. Despite all these limitations, our patients and caregivers proved that they are well-trained and experienced in dealing with any possible unpredictabilities that might come in their way and maintain a good glycemic control.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank Mrs Vivian Pavlopoulou for the linguistic revision of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

[1] Chen Y, Li L. SARS-CoV-2: virus dynamics and host response. Lancet Infect Dis 2020. https://doi.org/10.1016/s1473-3099(20)30235-8.

[2] Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ 2020;368. https://doi.org/10.1136/bmj.m1198 m1198.

[3] WHO. World Health Organization holds news conference on the coronavirus outbreak. 16 March 2020 11a.m EDT 2020:1.

[4] Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, et al. COVID-19: towards controlling of a pandemic. Lancet 2020;395:1015–8. https://doi.org/10.1016/S0140-6736(20)30673-5.

[5] Zhang SX, Wang Y, Rauch A, Wei F. Unprecedented disruption of lives and work: Health, distress and life satisfaction of working adults in China one month into the COVID-19 outbreak. Psychiatry Res 2020. https://doi.org/10.1016/j.psychres.2020.112958 112958.
[6] 13. Children and adolescents: Standards of medical care in diabetesd2019. Diabetes Care 2019;42:S148–64. doi: 10.2337/dc19-S013.
[7] Wisting L, Reas DL, Bang L, Skrivarhaug T, Dahl-Jørgensen K, Rø Ø. Eating patterns in adolescents with type 1 diabetes: Associations with metabolic control, insulin omission, and eating disorder pathology. Appetite 2017;114:226–31. https://doi.org/10.1016/j.appet.2017.03.035.
[8] Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, et al. Centers for disease control and prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002;109:45–60. https://doi.org/10.1542/peds.109.1.45.
[9] Maddaloni E, Coraggio L, Pieralice S, Carlone A, Pozzilli P, Buzzetti R. Effects of COVID-19 lockdown on glucose control: continuous glucose monitoring data from people with diabetes on intensive insulin therapy. Diabetes Care 2020:1–2. https://doi.org/10.2337/dc20-0954.
[10] Tornese G, Ceconi V, Monasta L, Carletti C, Faleschini E, Barbi E. Glycemic control in type 1 diabetes mellitus during COVID-19 quarantine and the role of in-home physical activity. Diabetes Technol Ther 2020. https://doi.org/10.1089/dia.2020.0169.
[11] Bonora BM, Boscari F, Avogaro A, Bruttomesso D, Fadini GP. Glycaemic control among people with type 1 diabetes during lockdown for the SARS-CoV-2 outbreak in Italy. Diabetes Ther 2020;11:1369–79. https://doi.org/10.1007/s13300-020-00829-7.
[12] Ahola AJ, Mutter S, Forsblom C, Harjutsalo V, Groop PH. Meal timing, meal frequency, and breakfast skipping in adult individuals with type 1 diabetes – associations with glycaemic control. Sci Rep 2019:9. https://doi.org/10.1038/s41598-019-56541-5.
[13] Virtanen S. Metabolic control and diet in Finnish diabetic adolescents. Acta Pædiatrica 1992;81:239–43. https://doi.org/10.1111/j.1651-2227.1992.tb12212.x.
[14] Øverby NC, Margeirsdottir HD, Brunborg C, Dahl-Jørgensen K, Andersen LF, Bjerknes R, et al. Sweets, snacking habits, and skipping meals in children and adolescents on intensive insulin treatment. Pediatr Diabetes 2008;9:393–400. https://doi.org/10.1111/j.1399-5448.2008.00381.x.
[15] Ogata H, Hatamoto Y, Goto Y, Tajiri E, Yoshimura E, Kiyono K, et al. Association between breakfast skipping and postprandial hyperglycaemia after lunch in healthy young individuals. Br J Nutr 2019;122:431–40. https://doi.org/10.1017/S0007114519001235.
[16] Jendle JH, Riddell MC. Editorial: physical activity and type 1 diabetes. Front Endocrinol (Lausanne) 2019:10. https://doi.org/10.3389/fendo.2019.00860.
[17] Houlder SK, Yardley JE. Continuous glucose monitoring and exercise in type 1 diabetes: Past, present and future. Biosensors 2018:8. https://doi.org/10.3390/bios8030073.
[18] Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020;395:912–20. https://doi.org/10.1016/S0140-6736(20)30460-8.
[19] Zheng S Qian, Yang L, Zhou P xiang, Li H bo, Liu F, Zhao R sheng. Recommendations and guidance for providing pharmaceutical care services during COVID-19 pandemic: A China perspective. Res Soc Adm Pharm 2020. doi: 10.1016/j.sapharm.2020.03.012.