Detection of Postprandial Hyperglycemia in Type 1 Diabetes Mellitus Patients – Initial Assessment of Current Recommendations versus Alternatives

Mia Birkholm Lausten, Ole Hejlesen, Mette Dencker Johansen

Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark

Abstract

To minimize the risk of microvascular and macrovascular complications, it is important to focus on detecting postprandial hyperglycemia, but it is only recommended to measure blood glucose (BG) 60 – 120 minutes after a meal if the preprandial BG is normal and HbA1c is increased. Thus the aim of this study was to investigate whether an alternative measurement interval of 120 – 180 minutes after a meal would outperform the recommended interval. Continuous glucose monitoring data, spot capillary blood glucose and carbohydrate intake times were collected from 23 type 1 Diabetes Mellitus patients. BG levels within 180 minutes after a meal were investigated, and the time the patients spent in postprandial hyperglycemia (BG >10 mmol/L) was converted to percentage for each interval and compared to all meals together, and to breakfast, lunch and dinner, respectively. No significant differences were found between the recommended interval and the alternative interval.

Keywords:

Postprandial Hyperglycemia, Recommendations, Type 1 Diabetes Mellitus, Continuous Glucose Monitoring, Blood Glucose Self-monitoring.

Introduction

Diabetes Mellitus (DM) is a huge healthcare problem worldwide as 425 million individuals in the age of 20 -79 years were affected in 2017 [1]. 5 - 10% of the patients have type 1 Diabetes Mellitus (T1DM) [2,3], where an auto-immune attack on the insulin secreting pancreatic β-cells leads to absolute absence of insulin [1,2,4]. T1DM can be effectively controlled and glycemic control can be achieved by a proper management of the blood glucose (BG) levels with daily injections of insulin [2]. Achieving good glycemic control is of great importance to minimize the risk of both microvascular and macrovascular long term complications in T1DM patients [2,5-7].

A clear association exists between glycated hemoglobin (HbA1c), which is average glycemic control over 2-3 months [1,8,9], and the risk of long term complications [10-13]. In addition, limiting the time spent in postprandial hyperglycemia is found to be an important contributor to improvement of HbA1c and thereby also to reduce the risk of long term complications [6,7,9,13-15]. Postprandial hyperglycemia is defined as a BG level >10 mmol/L measured 60 – 120 minutes after a meal. The Danish Health Authority advise patients with T1DM to measure one value of BG in the time interval of 60 – 120 minutes after a meal as part of the daily self-monitoring of blood glucose (SMBG) routine, but only if the preprandial BG level is normal and HbA1c is increased. [16] Proper detection of postprandial hyperglycemia is essential, but as the recommended interval for measuring postprandial BG is wide, and only one measurement is to be performed within the interval [16], the risk of missing a case of postprandial hyperglycemia is significant [17].

Continuous glucose monitoring (CGM) may improve detection rates, but CGM has not gained as large a foothold on the market of diabetes therapy as the more frequently SMBG routine, which is cheaper and requires less care. Thus, the timing of the one SMBG measurement is the key to how well post-prandial hyperglycemia can be detected. To our knowledge, only few studies have investigated how well suited the recommended interval is for detecting postprandial hyperglycemia in T1DM patients [18-21]. Across meals, only 67 – 71% of patients have been found to have blood glucose peak times within the recommended interval [19,20].

Therefore the aim of this study was to investigate whether, in cases of actual postprandial hyperglycemia, an alternative measurement interval would contain a higher percentage of hyperglycemic glucose levels than would the recommended interval, as the higher percentage would increase the likelihood of detecting a hyperglycemic value when doing only one glucose sample.

Methods

Study Population and Design

In this retrospective study, CGM datasets from a clinical development phase of the SCGM 1 system (Roche Diagnostics, Mannheim, Germany) were included. The data were collected at four medical centers (Medical Department M, Aarhus University Hospital, Aarhus, Denmark; Profil Institute for Metabolic Research, Neuss, Germany; German Diabetes Research Institute at the Heinrich–Heine University of Dusseldorf, Germany; and Department of Pharmaceutical Technology and Biopharmacy, University Center of Pharmacy, University of Groningen, the Netherlands). The system recorded glucose concentrations every minute for up to 5 days. For each experiment, the first 18 hours of data were discarded.

The datasets contained information on time and amount of carbohydrate intake and insulin injections. During the experiment the patients were not given access to the CGM data [9].

The study was performed by accessing the datasets of 159 patients. Only patients with T1DM were included. Patients were excluded if they experienced sudden illness during the experiment, if no events (carbohydrate intake or insulin injections) were registered or if continuous subcutaneous insulin infusion was used. After application of these restrictions, 51 patients were included for further analysis. After calibration and meal selection, which is described below, a total of 23 patients were included in the study. Patients were excluded if they had no valid meals using the criteriae below.

Calibration

In order to calibrate the CGM values, SMBG glucose measurements from a finger-capillary were obtained by a nurse up to 20 times a day using a blood glucose meter. Due to CGM inaccuracies, a linear regression approach was used to calibrate the CGM with SMBG measurements [22,23]. For each patient, a maximum of four SMBG measurements per 24-hours were used for calibration. The four measurements were found by using the first SMBG measurement after the discarded 18 hours, and then the next measurement closest to 6 hours after, and so forth.

Due to a physiological delay from plasma to interstitial glucose levels, the CGM data was delayed 10 minutes before pairing them with the SMBG values [23]. In case of two reference SMBG measurements at the same minute, they were averaged before use. Before a CGM-SMBG pair was made, the CGM value was screened in order to reject measurements of poor quality. Firstly and due to the physiological limits of blood glucose, only CGM values in the range of 40 mg/dL – 400 mg/dL were considered valid [24]. CGM-SMBG pairs where the CGM value was outside this interval were discarded. Secondly and due to the limited physiological change rate of BG, a CGM value was considered valid only if it deviated less than 4 mg/dL/min compared with the previous and the following value [24,25]. In case of a CGM value difference above 4 mg/dL/min, the CGM-SMBG pair was excluded and replaced by the next available pair. Calibration was visualized in calibration graphs with a linear regression equation and goodness of fit (R^2). Patients were excluded if they did not have enough SMBG values for calibration, in case of signal drops >6 hours or if the patient had an R^2 <0.70.

Selection of Meals

In order to investigate BG levels for postprandial hyperglycemia, meals were selected based on the time of carbohydrate intake. Breakfast, lunch and dinner were defined as all meals in the time range from 5.00 am – 11.00 am, 11.01 am – 4.00 pm and 4.01 pm – 10.00 pm, respectively. The meal with the highest amount of carbohydrate ingestion within each interval was selected as the actual main meal of the type in question. Only clear, single meals were included, as meals were excluded if another meal was ingested in the time interval of 150 minutes before to 180 minutes after the meal. In addition, meals were excluded in case of signal drop ≥5 minutes within this time interval.

After selection of meals, the CGM values for the first 180 minutes after a meal were screened for outliers. A value was considered an outlier if the value increased or decreased more than 4 mg/dL/min. In such cases, the CGM value was replaced by the mean of the previous and the following valid CGM value. Then, moving averages of 5 minutes were calculated for each minute. Lastly, the CGM values were calculated to SMBG values with the calibration equation.

Statistics

Microsoft Excel (version 14.0.7190.5000, 2010, Microsoft, Seattle, Washington, USA) was used to process and analyze data. Each meal was controlled for postprandial hyperglycemic episodes, which was defined as a BG level ≥10 mmol/L for a consecutive period of minimum 15 minutes. If a postprandial hyperglycemic episode was found at any time within 180 minutes after ingestion of a meal, the meal was classified as a case of "true postprandial hyperglycemia" and thus used for further analysis. The recommended measure interval of 60 – 120 minutes and the alternative interval of 120 – 180 minutes were examined after each meal, and the time with BG levels were above 10 mmol/L was calculated. Afterwards, the time was converted to percentage for each meal at each interval and a total average value for all meals, and breakfast, lunch, and dinner, respectively, was calculated for each of the two intervals.

SPSS (version 24, IBM, SPSS®, USA) was used for statistical analyses. A Shapiro-Wilk test was used to test all data for normality. The data did not follow a normal distribution. Therefore, a Wilcoxon test was used to test whether the alternative interval had a higher percentage of time of postprandial hyperglycemia than the recommended interval. Data were considered statistically significant with a p-value <0.05.

Results

Demographic Characteristics

23 patients who participated in the clinical development phase of the SCGM 1 system were included in this retrospective study. After analyzing all meals, postprandial hyperglycemic episodes were found after 63 meals, and therefore they were included in the study. The 63 meals were distributed as follows; breakfast: 25, lunch: 19, and dinner: 19. Two of the patients did not have postprandial hyperglycemia and therefore, they were excluded from further analysis. The remaining 21 patients included 13 men and 8 women. The median age of the patients was 33 years (range 18-53). The patients had a duration of DM of 14.86 ± 12.19 years (mean ± SD), and an HbA1c value of 8.25 ± 1.71% (mean ± SD).

Postprandial Hyperglycemia after Breakfast, Lunch and Dinner

The time, a patient experienced postprandial hyperglycemia, was recorded in the two different intervals after a meal, and converted to percentage for each interval for breakfast, lunch and dinner, respectively. The intervals are referred to as interval 1 (the recommended interval; 60 – 120 minutes after the meal) and interval 2 (the alternative interval; 120 – 180

minutes after the meal). The median values of the percentage of time, the patients spent in postprandial hyperglycemia, suggested a difference between the intervals (*figure 1*). For all breakfast measurements, the percentage of time associated with postprandial hyperglycemia was higher at interval 1 compared to interval 2, with median values of 83.34% and 76.67%, respectively. Although, the values could indicate a difference between the intervals (p = 0.225), this was not statistically significant.

The opposite was observed for the lunch measurements with median values of 65.00% and 88.34% for interval 1 and 2, respectively. The difference between the intervals (p = 0.925) were, however, not statistically significant.

The median values for the dinner measurements were 85.00%, and 60.00% for interval 1 and 2, respectively. This indicated a difference between the intervals (p = 0.776), but the intervals were not statistical significantly different from each other.

Postprandial Hyperglycemia after All Meals

The median values of the percentage of the interval, the patients spent in postprandial hyperglycemia for all meals together, indicated a difference between the two intervals (figure 2). For all meals, the percentage of time in postprandial hyperglycemia was higher at interval 1 with a median value of 80.00% compared with a value of 76.67% for interval 2. However, the statistic test revealed no significant difference between the intervals (p = 0.376).

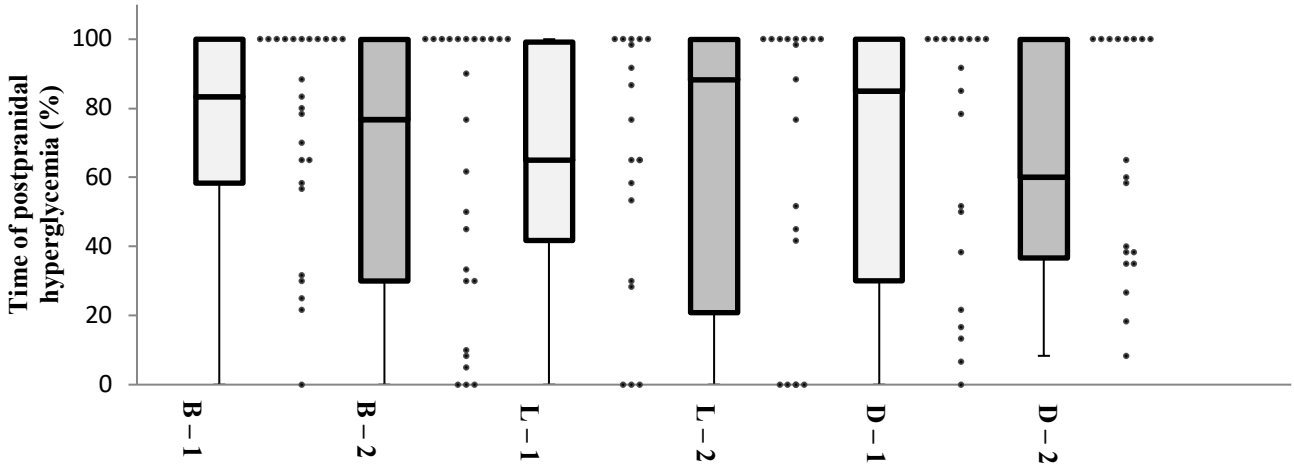

Figure 1- The amount of time spent in postprandial hyperglycemia in percentage (%) divided into breakfast (B), lunch (L), and dinner (D) for the two different intervals (median ± IQR). The data are named from the main meal (B: Breakfast, L: Lunch, D: Dinner) and the number of the interval (1 or 2). The colors represent the two different intervals, where BG levels were measured after a meal; light grey: interval 1 (60 – 120 mins.), and dark grey: interval 2 (120 – 180 mins.). The central rectangle spans the first quartile to the third quartile (IQR). The segment inside the rectangle shows the median and whiskers below the boxes show the minimum time associated with postprandial hyperglycemia. The dots represent the individual measurements for each patient stated for each meal and interval. %: percentage, IQR: interquartile range, BG: blood glucose.

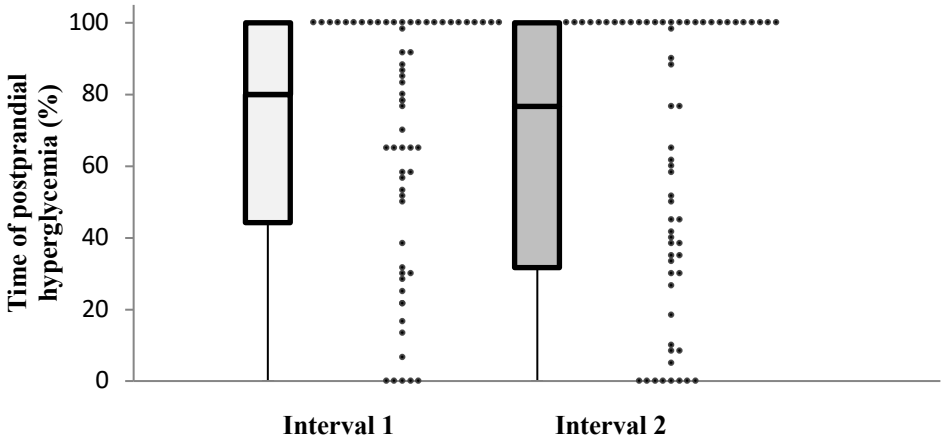

Figure 2-The amount of time spent in postprandial hyperglycemia in percentage (%) after all meals divided into the two intervals (median ± IQR). The colors represent the two different intervals, where BG levels were measured after a meal; light grey: interval 1 (60 – 120 mins.), and dark grey: interval 2 (120 – 180 mins.). The central rectangle spans the first quartile to the third quartile (IQR). The segment inside the rectangle shows the median and whiskers below the boxes show the minimum time associated with

postprandial hyperglycemia. The dots represent the data points for all meals at each interval. %: percentage, IQR: interquartile range, BG: blood glucose.

Discussion

This retrospective study investigated whether an alternative measurement time interval of 120 – 180 minutes after a meal would increase the likelihood of detecting postprandial hyperglycemia (>10 mmol/L) with postprandial SMBG, compared with the recommended interval of 60 – 120 minutes after a meal. This was evaluated based on the percentage of time the patients spent in hyperglycemia after a meal in the two intervals.

Findings from this study did not demonstrate any statistical significant differences between the recommended interval (interval 1) and the alternative interval (interval 2), which suggested that the alternative interval was not better for detecting postprandial hyperglycemia than the recommended interval and vice versa. Based on the median values, an indication of a higher percentage of time spent in postprandial hyperglycemia was however observed at interval 1 after breakfast (p = 0.225), dinner (p = 0.776), and when all meals were compared (p = 0.376). The opposite was observed after lunch, where an indication of a higher percentage of time spent in postprandial hyperglycemia was observed at interval 2 compared to interval 1 (p = 0.925).

Postprandial Hyperglycemia after All Main Meals

As postprandial hyperglycemia affects HbA1c and thereby also the risk of complications [6,9,13-15,26], it is important to focus on detection of postprandial hyperglycemia to ultimately minimize the occurrence.

Previously studies investigated mainly the timing of SMBG to detect postprandial hyperglycemia [18-21]. These findings are not easily compared with the findings of this study, as only peak times and peak values were reported. However, one of the studies also reported mean increase and decrease rate, which makes it possible to calculate the duration of postprandial hyperglycemia [20].

The peak times were reported to be within 57 - 100 minutes after breakfast, lunch and dinner [18,20,21], but the duration of postprandial hyperglycemia might be lengthy since a mean duration of a postprandial hyperglycemic episode was found to be 2.3 ± 1.1 hours (mean ± SD) for T1DM patients [27]. Daenen et al. found durations of postprandial hyperglycemia to last from 37 – 126 minutes, from 81 to 100 minutes and from 70 to 106 minutes after breakfast, lunch and dinner, respectively [20]. These were converted to percentages of time spent in postprandial hyperglycemia for the two intervals, which resulted in the highest percentage at interval 1 after breakfast, lunch and dinner. The percentage of time spend in postprandial hyperglycemia was 0% for interval 2 for all meals except from breakfast where it was 9.48%. The finding of interval 1 as the better interval for detection of postprandial hyperglycemia than interval 2 is consistent with the results of the present study for breakfast, dinner and when all meals were compared. Although for lunch this study found an indication of interval 2 as a better time to measure BG to detect postprandial hyperglycemia.

Similar findings were observed when all meals were investigated together. Studies reported that 67 - 71% of the patients' peak times were within the recommended interval 1 [19,20], whereas 0% were within interval 2 [20]. These findings are consistent with the indications found in this study, as the longer duration is expected to be found around the peak time.

Generally, the findings of this study indicate that the detection rate is probably better in the recommended interval (interval 1). Still, the risk of missing postprandial hyperglycemia remains a challenge as the patients, when all meals are investigated together, did not have postprandial hyperglycemia in 20.00% (12 minutes) of this interval. In addition, it may be difficult to recommend one interval for all T1DM patients, as studies have reported large inter-individual differences [18-20] and as factors such as gender, HbA1c and DM duration might affect postprandial hyperglycemia.

Limitations

This study has limitations that need to be considered before drawing any firm conclusions. The study was a retrospective study and this may introduce some bias in the outcome. Generally, prospective cohorts that allow inclusion of subjects for the actual purpose, yield more reliable results. The relatively small sample size and the low number of meals might influence the power of this study. Preprandial BG levels, HbA1c, gender and duration of DM was not considered and could have affected the outcomes. Furthermore, data were obtained in Germany, Denmark and the Netherlands, and there may be large variations in dietary habits across the countries. Lastly, this study was performed in a hospitalization setting, and therefore the results may not truly reflect the everyday lives of T1DM patients.

Conclusion

This study found no statistical significant difference between the recommended interval and the alternative interval among postprandial hyperglycemia after all main meals in T1DM patients. An indication of a larger percentage of time spent in postprandial hyperglycemia was however observed when BG levels were measured at the recommended interval of 60 – 120 minutes after breakfast, and dinner, and when all meals were compared. This indicates that the recommended interval is a better time to measure BG levels for detecting postprandial hyperglycemia than the alternative interval. Further research in a larger group is however needed to validate the indications found in this study.

References

[1] IDF Diabetes Atlas 2017, 8th edition. Brussels, Belgium.: International Diabetes Federation 2017.

[2] Daneman D. Type 1 diabetes. Lancet 2006; 367: 847-858.

[3] Global report on diabetes 2016. Switzerland.: World Health Organization 2016.

[4] Vieira A, Druelle N, Avolio F, Napolitano T, Navarro-Sanz S, Silvano S, et al. Beta-Cell Replacement Strategies: The Increasing Need for a "beta-Cell Dogma". Front Genet 2017; 8: 75.

[5] Brod M, Nikolajsen A, Weatherall J, Pfeiffer KM. Understanding Post-Prandial Hyperglycemia in Patients with Type 1 and Type 2 Diabetes: A Web-based Survey in Germany, the UK, and USA. Diabetes Ther 2016; 7(2): 335-348.

[6] International Diabetes Federation Guideline Development Group. Guideline for management of postmeal glucose in diabetes. Diabetes Res Clin Prac. 2014; 103(2): 256-268.

[7] Ketema EB, Kibret KT. Correlation of fasting and postprandial plasma glucose with HbA1c in assessing glycemic control; systematic review and meta-analysis. Arch Public Health 2015; 73: 43

[8] Pfeiffer KM, Sandberg A, Nikolajsen A, Brod M. Postprandial glucose and healthcare resource use: a cross-sectional survey of adults with diabetes treated with basal-bolus insulin. J Med Econ 2018; 21(1): 66-73.

[9] Nielsen JK, Gravholt CH, Djurhuus CB, Brandt D, Becker J, Heinemann L, et al. Continuous subcutaneous glucose monitoring shows a close correlation between mean glucose and time spent in hyperglycemia and hemoglobin A1c. J Diabetes Sci Technol 2007; 1(6): 857-863.

[10] Writing Group for the DCCT/EDIC Research Group, Orchard TJ, Nathan DM, Zinman B, Cleary P, Brillon D, et al. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2015; 313(1): 45-53.

[11] McCarthy M. American Diabetes Association issues new guidelines for type 1 diabetes. BMJ 2014; 348: g4119.

[12] Martin CL, Albers JW, Pop-Busui R, DCCT/EDIC Research Group. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 2014; 37(1): 31-38.

[13] Madsbad S. Impact of postprandial glucose control on diabetes-related complications: How is the evidence evolving? J Diabetes Complications 2016; 30(2): 374-385.

[14] Gingras V, Taleb N, Roy-Fleming A, Legault L, Rabasa-Lhoret R. The challenges of achieving postprandial glucose control using closed-loop systems in patients with type 1 diabetes. Diabetes Obes Metab 2018; 20(2): 245-256.

[15] Ceriello A. The glucose triad and its role in comprehensive glycaemic control: current status, future management. Int J Clin Pract 2010; 64(12): 1705-1711.

[16] Kliniske retningslinier for behandling af voksne med type 1 diabetes 2010. Denmark.: Dansk Endokrinologisk Selskab 2010.

[17] Bergenstal RM, Ahmann AJ, Bailey T, Beck RW, Bissen J, Buckingham B, et al. Recommendations for standardizing glucose reporting and analysis to optimize clinical decision making in diabetes: the Ambulatory Glucose Profile (AGP). Diabetes Technol Ther 2013; 15(3): 198-211.

[18] Taki K, Nishimura R, Morimoto A, Tsujino D, Miyashita Y, Tajima N. Analysis of 24-hour glycemic excursions in patients with type 1 diabetes by using continuous glucose monitoring. Diabetes Technol Ther 2010; 12(7): 523-528.

[19] Johansen MD, Gjerlov I, Christiansen JS, Hejlesen OK. Interindividual and intraindividual variations in postprandial glycemia peak time complicate precise recommendations for self-monitoring of glucose in persons with type 1 diabetes mellitus. J Diabetes Sci Technol 2012; 6(2): 356-361.

[20] Daenen S, Sola-Gazagnes A, M'Bemba J, Dorange-Breillard C, Defer F, Elgrably F, et al. Peak-time determination of post-meal glucose excursions in insulin-treated diabetic patients. Diabetes Metab 2010; 36(2): 165-169.

[21] Manuel-y-Keenoy B, Vertommen J, Abrams P, Van Gaal L, De Leeuw I, Messeri D, et al. Postprandial glucose monitoring in type 1 diabetes mellitus: use of a continuous subcutaneous monitoring device. Diabetes Metab Res Rev 2004; 20(Suppl 2): 24-31.

[22] Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care 2017; 40(12): 1631-1640.

[23] Cengiz E, Tamborlane WV. A tale of two compartments: interstitial versus blood glucose monitoring. Diabetes Technol Ther 2009; 11(Suppl 1): 11-16.

[24] Mahmoudi Z, Dencker Johansen M, Christiansen JS, Hejlesen OK. A multistep algorithm for processing and calibration of microdialysis continuous glucose monitoring data. Diabetes Technol Ther 2013; 15(10): 825-835.

[25] Facchinetti A, Sparacino G, Cobelli C. An online self-tunable method to denoise CGM sensor data. IEEE Trans Biomed Eng 2010; 57(3): 634-641.

[26] Jiang J, Zhao L, Lin L, Gui M, Aleteng Q, Wu B, et al. Postprandial Blood Glucose Outweighs Fasting Blood Glucose and HbA1c in screening Coronary Heart Disease. Sci Rep 2017; 7(1): 14212-017-14152-y.

[27] Bode BW, Schwartz S, Stubbs HA, Block JE. Glycemic characteristics in continuously monitored patients with type 1 and type 2 diabetes: normative values. Diabetes Care 2005; 28(10): 2361-2366.

Address for correspondence

Mia Birkholm Lausten
MSc in Medicine with Industrial Specialization
Email: Mia.lausten@hotmail.com