Relationship of Glucose Variability and Daily Lifestyle by Continuous Glucose Monitoring (CGM)

Yamashita H[1], Kato Y[1], Bando H[2,3*], Kanazawa S[1], Tanaka M[1], Sueki E[1], Kanagawa H[1], Kawata T[1], Kawahito A[1], Aihara A[1], Miyashiro H[4]

[1]*Kanaiso Hospital, Tokushima, Japan*

[2]*Tokushima University / Medical Research, Tokushima, Japan*

[3]*Japan Low Carbohydrate Diet Promotion Association, Kyoto, Japan*

[4]*Miyashiro Co., Ltd., Tokushima, Japan*

Corresponding Author: **Hiroshi Bando, MD, Ph.D., FACP** [ORCID ID]

Address: Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943 Japan; Tel: +81-90-3187-2485; E-mail: pianomed@bronze.ocn.ne.jp

Received date: 08 August 2020; **Accepted date**: 13 September 2020; **Published date**: 20 September 2020

Citation: Yamashita H, Kato Y, Bando H, Kanazawa S, Tanaka M, Sueki E, Kanagawa H, Kawata T, Kawahito A, Aihara A, Miyashiro H. Relationship of Glucose Variability and Daily Lifestyle by Continuous Glucose Monitoring (CGM). Asp Biomed Clin Case Rep. 2020 Sept 20;3(3):206-12.

Abstract

Authors and collaborators have continued diabetic practice and research on low carbohydrate diet (LCD), continuous glucose monitoring (CGM), and so on. The case is a 64-year-old male with type 2 diabetes mellitus (T2DM) treated with multiple daily insulin injections (MDI). When his HbA1c was 8.2% before, he changed to take tofu instead of rice and bread. HbA1c decreased to 7.1% and 4kg of weight reduction in 2 months. Tofu is a traditional Japanese food made from soybeans, which is a suitable LCD with Protein:Fat:Carbohydrate (PFC) ratio=40:45:15 in this case. His HbA1c is recently unstable, then glucose variability was investigated by CGM using FreeStyle Libre. The glucose pattern was different due to his lifestyle, including working day, off day, playing golf, respectively. The average glucose was 143-167 mg/dL and the estimated HbA1c was 7.1%, whereas HbA1c in outclinic was 8.1%, respectively. This report will hopefully become reference data for future research.

Introduction

In the last decade, diabetes has been a more important disease to be managed adequately in the world [1]. It is necessary to evaluate the status of diabetic patients concerning the presence of micro- and macroangiopathy, such as neuropathy, retinopathy, nephropathy, and arterial sclerosis [2]. These include Type 1 and 2 diabetes mellitus (T1DM, T2DM). As regards to diet therapy, there has been a variety of nutritional treatments reported so far. These are low-carbohydrate diet (LCD), calorie restriction (CR) (low-fat), Mediterranean, vegetarian, moderate carbohydrate, high-protein, low glycemic index/ glycemic load (GI/GL), Palaeolithic, control, and others [3].

Case Report

Of these various diets, LCD has become more popular in recent years [4]. LCD was initially spread in Western countries by Dr. Bernstein and others [5]. Then, in Japan, authors and collaborators started LCD [6]. Successively, the clinical efficacy of LCD has been proven by various reports [7]. We have established the Japan LCD Promotion Association (JLCDPA) and developing several activities of LCD socially through papers, medical congress, seminars, and books [8]. From a research point of view, we performed LCD on thousands of patients and reported the effect of LCD, where the weight loss more than 10% or more was observed in 24%, and 5% or more was 59% [9]. There have been a variety of comparative discussions between LCD and CR [10].

On the other hand, a recent topic concerning diabetic practice includes the prevalence of continuous glucose monitoring (CGM) for patients with T1DM and T2DM [11]. Among them, there were several reports for detecting hypoglycemia episodes [12]. In addition, a variety of beneficial points were revealed such as easy management, reliability, higher self-efficacy, simultaneous response, and other useful technology [13,14]. In fact, CGM has been frequently used in diabetic practice. Through our diabetes practice, authors have also already reported some cases with CGM evaluation in detail [15]. We have recently experienced an impressive male patient with T2DM, then a general case report and some related discussion will be described in this article.

Case Report

History of Present Illness:

The case is a 64-year-old male patient with T2DM, who has a medical history of 12 years of duration. As to diabetic therapy, he has been given insulin treatment for a long. About 1 year ago, his HbA1c was 8.2% at a rather higher level. Then, he changed his diet content from rice, bread, noodles to tofu (a product from soybeans with protein: fat: carbohydrate (P:F:C) = 40:45:15) by our advice, and HbA1c has decreased to 7.1% and 4kg of weight reduction in 2 months. His control status has not been in a satisfactory status, where HbA1c persisted approximately 7.4-8.5 % so far. To evaluate his glucose variability, the relationship between the daily profile of blood glucose and his daily

activity was checked using FreeStyle Libre.

Physical Examination:

He had unremarkable status in physical examination or no remarkable abnormalities of consciousness disorders from hypo- or hyperglycemia. His vital signs were normal, and his body mass index (BMI) has been approximately 24.9 kg/m². He sometimes feels slight numbness in the extremities, which is supposed to be diabetic neuropathy. However, he was not pointed out to have retinopathy, nephropathy, or other significant macroangiopathic complications so far.

Laboratory Exam:

The results of laboratory exams were shown as follows. Obtained standard biochemical data were AST 14 U/mL, ALT 15 U/mL, r-GT 24 U/mL, BUN 19 mg/dL, Cre 1.0 mg/dL, Uric Acid 5.5 mg/dL, HDL 54 mg/dL, LDL 85 mg/dL, TG 119 mg/dL, WBC 4600 /μL, RBC 4.69 x 10^6/μL, Hb 14.8 g/dL, Plt 15.3 x 10^4/μL. Data related diabetes were HbA1c 8.1%, pre-prandial glucose 167 mg/dL.

Medication:

He has been provided some medicine for T2DM, hypertension, and hyperlipidemia. The prescription includes Ipragliflozin L-Proline 50mg 1Tab, Valsartan 80mg 1Tab, and Rosuvastatin 2.5mg 1 Tab. His blood pressure and lipids profile have been stable.

Insulin Therapy:

He has been given insulin therapy for years by the method of multiple daily insulin injections (MDI). He was given two kinds of insulin three times a day. The pattern of his MDI in recent years is as follows: Novo rapid (Novo Nordisk) is provided 2 times a day just before breakfast and lunch, which is 6 units and 8 units, respectively. Further, Humalog mix 50 is provided once a day just before the supper, which is 14-16 units.

Methods

In this case, his daily profile of blood glucose was investigated by the system of continuous glucose monitoring (CGM). His glucose variability was

Case Report

analyzed for 14 days. As regards to CGM, FreeStyle Libre (Abbott, USA) was applied [16]. It has been well-known for its stable reliability for the measurement of changes in blood glucose [17]. It has shown beneficial predominance including trend accuracy, point accuracy, sensor stability, calibration, alarms, traceability, and time lag [18]. Furthermore, it shows satisfactory results for the guideline of the Clinical and Laboratory Standards Institute (CLSI) [19].

The case has taken tofu in the clinical course. These products were produced by Morinaga Milk Industry Co., Ltd., Japan. Their beneficial points include two aspects as follows: i) Long-life technology: Food and containers are sterilized separately, and aseptically filled without using preservatives. As a result, it enables long-term storage and can be stored at room temperature for 6.5 months (195 days). It is from the technology that has applied aseptic filling and packaging of milk for many years. ii) Paper pack with 6 layers: Paper pack with high barrier property is used (**Fig-1**). By putting aluminum foil between the paper and polyethylene, it is difficult for air and oxygen to pass through them and the storage stability is remarkably maintained.

Results

This case was set on FreeStyle Libre for 14 days, and the daily profile of blood glucose was obtained. The results of the CGM were satisfactory and shown in **Fig-2**. Out of 14 days, glucose variability in 4 days were summarized on May 13, 16, 19, 24. He spent different daily activity in each day as follows. They are i) regular working day, and hyperglycemia is found after lunch period in the day, ii) no working day, and the patient kept still and had cakes in the afternoon, iii) regular working day, and it showed similar glucose profile to May 13, iv) patient played golf all day with normal glucose profile in the afternoon.

Fig-1:

Japanese tofu with less carbohydrate suitable for LCD. Silky tofu in blue color (left) and protein-rich tofu in yellow color (right). Both type show 290g Vs 297g in weight, 33:51:15 Vs 40:45:15 in PFC ratio, 7.5g Vs 7.2g, in carbohydrate, respectively.
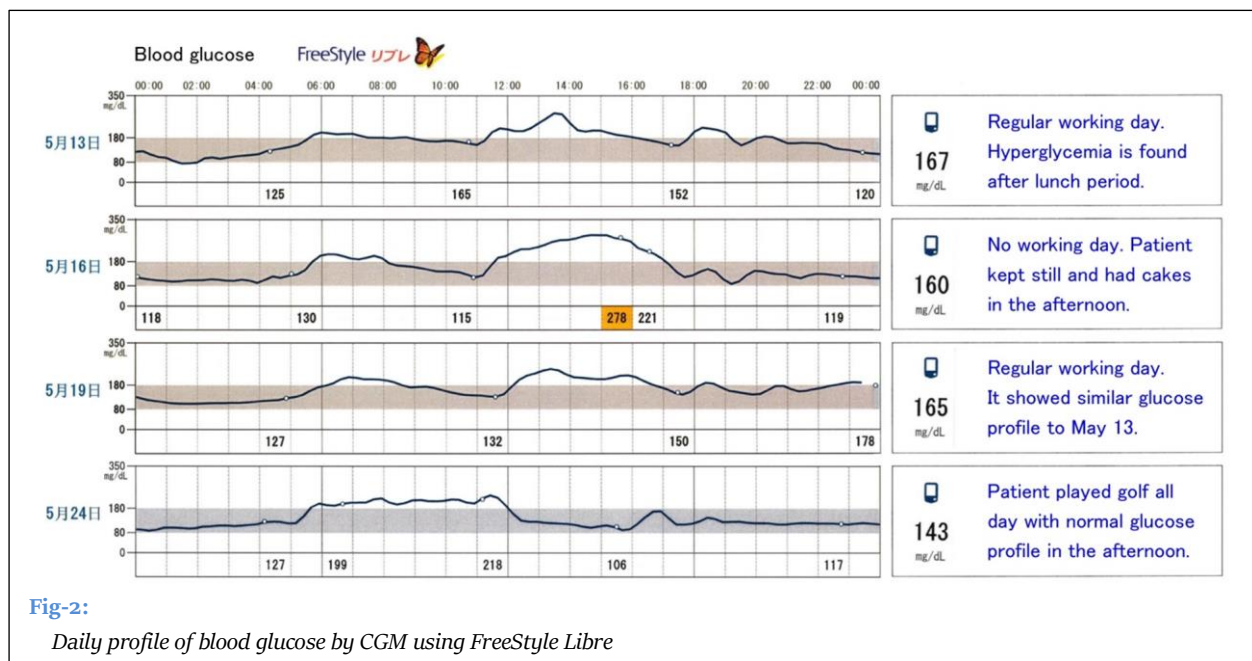
Case Report

Fig-2:

Daily profile of blood glucose by CGM using FreeStyle Libre

The average blood glucose in these days were 167 mg/dL, 160 mg/dL, 165 mg/dL and 143 mg/dL, respectively. They are almost the same, but the profile pattern and the activity content are completely different. The software of FreeStyle Libre analyzed HbA1c value from the obtained data of blood glucose. The estimated HbA1c value was 7.1% or 54 mmol/mol. On the other hand, the HbA1c value in our outclinic during the period was 8.1% or 62 mmol/mol. Both data have some discrepancies between them.

Discussion

As to the treatment of diabetes, there are currently standard guidelines. One is the 2019 "Consensus Statement by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) on the Comprehensive Type 2 Diabetes Management Algorithm" [20], and another is the American Diabetes Association (ADA) Standards of Medical Care in Diabetes—2020 [21]. Their important points include adequate diet therapy and the combination of injection treatment for necessary cases with postprandial hyperglycemia.

The authors have continued clinical and research on the comparison of LCD and CR for years. Regarding LCD, we have proposed three kinds of practical diet. They are petite-LCD, standard-LCD, and super-LCD including carbohydrate ratio as 40%, 26%, and 12%, respectively [22]. When a patient shows obesity and hyperglycemia and/or obesity to a higher degree, super-LCD would be recommended. When a patient shows these problems in a lower degree or on insulin treatment, petite-LCD or standard-LCD can be applied. In other words, three kinds of LCD can be useful due to the metabolic situation of the patient. In this case, he showed unsatisfactory diabetic control one year ago. He was on insulin treatment, then the recommended method would be not to drastically reduce carbohydrate, but to reduce carbohydrate moderately to some degree.

The patient has been the president of a trading company, and he has been mainly engaged in the management of milk and tofu. Formerly, his diet was close to CR. At that time, he was advised to change food intake from rice and bread to tofu instead. There is a principle concerning carbohydrates and increasing glucose in T2DM [23]. For example, 300 g of rice contains 108 g of carbohydrate, while 300 g of tofu contains 5 g of carbohydrate. According to the textbook of Harper's biochemistry, patients with T2DM raise blood glucose by 3 mg/dL by intake of 1g of carbohydrate. Therefore, rice 300 g increases 324 mg/dL of blood glucose, while tofu 300 g increases only 15 mg/dL of blood glucose, showing a large difference in the actual daily life [23].

Case Report

Tofu has been one of the traditional Japanese food, which is a fermented product and made from soybeans [24]. Generally, tofu has been known as healthy food including much protein of soybeans and fewer carbohydrates. In this study, the case had two kinds of tofu, which are silky tofu and protein-rich tofu (**Fig-1**). Each product showed 290 g vs 297 g in weight per pack, 68 kcal vs 62 kcal / 100 g weight, 33:51:15 vs 40:45:15 in PFC ratio, respectively. Calculating the carbohydrate amount in one pack of tofu, it has only 7.5 g vs 7.2 g, respectively. Consequently, by continuing to make the most of tofu for some period, it is expected that the LCD will be easy and successful.

Regarding the research on tofu, the quality of soybeans with high vs low protein content (44.8% vs 39.1%) and with vs without 11X globulin polypeptide were investigated [25]. The results showed that soybeans with higher protein have smaller seeds which produced significantly firmer tofu gels associated with creamier color. There was a report concerning tofu consumption and arteriosclerosis [26]. Japanese men (n=652) were studied for the intake of soy food, fermented soy products, and brachial-ankle pulse wave velocity (baPWV) as an index of arterial stiffness. As a result, more consumption showed reduced arterial stiffness, suggesting the efficacy of isoflavone.

In this study, CGM was conducted successfully and blood glucose fluctuation pattern was perfectly observed. Regarding the four patterns shown in **Fig-1**, some discussion can be described in each day as follows: i) blood glucose value of 1200h-1500h was higher on a working day, suggesting the influence of the lunch, ii) glucose on 1200h-1700h was higher on non-working days, suggesting that the situation involves eating sweets and keeping stable with not moving, iii) similar diurnal fluctuation was observed as usual working days, iv) when playing golf, blood glucose remained normal level from 1200h to 2400h, suggesting the effect of exercise therapy for rather long. It is noteworthy that blood glucose had kept lower with the ideal level during the afternoon in iv) compared with that of i), ii), iii).

In one of our previous studies on CGM, precise, and detailed blood variability was observed. The example was that blood glucose was acutely dropped 3 hours after the first administration of sodium-glucose cotransporter 2 (SGLT2) inhibitor [27]. These data suggested remarkably useful evidence from a pathophysiological point of view.

Blood glucose levels measured by FreeStyle Libre are said to be lower than the actual levels. One of the reasons would be from the analysis mechanism that blood glucose level in the interstitial fluid has been calculated by the device. It is not the glucose value in the blood vessels. In previous reports, FreeStyle Libre measurements showed sufficient safety, accuracy, and tolerability [17]. However, data values measured with FreeStyle Libre generally tended to be low. As regards the degree of a discrepancy, the average ± standard deviation shows a large value of approximately -43.4±20 mg/dL [28]. Furthermore, postprandial hyperglycemia may be underestimated [29]. For previous report, the mean absolute relative difference (MARD) glucose levels were 20.3%, 14.7%, and 9.6% in three glucose ranges (<72 mg/dL, 72-180 mg/dL, <181 mg/dL), respectively [30].

In summary, glucose variability measured by CGM and discussion was described in this article. CGM has been more prevalent and useful [31]. Furthermore, it is expected to evolve into a compact and convenient device [32]. Furthermore, the clinical efficacy of LCD with practical usefulness of tofu were also introduced. This report will be hopefully some reference in diabetic practice and research in the future.

Conflicts of Interest

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

Case Report

References

[1] IDF Diabetes Atlas. 9th Ed. International Diabetes Federation; 2019. Available from:

https://diabetesatlas.org/en/

[2] Mauricio D, Alonso N, Gratacòs M. Chronic Diabetes Complications: The Need to Move beyond Classical Concepts. Trends Endocrinol Metab. 2020 Apr;31(4):287-95. [**PMID**: 32033865]

[3] Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C, Boeing H. Impact of different dietary approaches on glycemic control and cardiovascular risk factors in patients with type 2 diabetes: a protocol for a systematic review and network meta-analysis. Syst Rev. 2017 Mar 20;6(1):57. [**PMID**: 28320464]

[4] Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, Tangi-Rozental O, Zuk-Ramot R, Sarusi B, Brickner D, Schwartz Z, Sheiner E, Marko R, Katorza E, Thiery J, Fiedler GM, Blüher M, Stumvoll M, Stampfer MJ; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med. 2008 Jul 17;359(3):229-41. [**PMID**: 18635428]

[5] Bernstein RK. Dr. Bernstein's diabetes solution: the complete guide to achieving normal blood sugars. New York: Little, Brown and company; 1997.

[6] Ebe K, Ebe Y, Yokota S, Matsumoto T, Hashimoto M, Sakai Y. Low Carbohydrate diet (LCD) treated for three cases as diabetic diet therapy. Kyoto Medical Association Journal. 2004;51:125-29.

[7] Muneta T, Kawaguchi E, Nagai Y, Matsumoto M, Ebe K, Watanabe H, Bando H. Ketone body elevation in placenta, umbilical cord, newborn and mother in normal delivery. Glycat Stress Res. 2016 Sep 30;3(3):133-40.

[8] Bando H, Muneta T, Bando M, Yonei Y. Effect of low carbohydrate diet on type 2 diabetic patients and usefulness of M-value. Diabetes Res Open J. 2017 Feb 13;3(1):9-16.

[9] Nakamura T, Kawashima T, Dobashi M, Narita A, Bando H. Effective Nutritional Guidance for Obesity by Low Carbohydrate Diet (LCD). Asp Biomed Clin Case Rep. 2019 Jan 27;2(s1):16-21.

[10] Tay J, Thompson CH, Luscombe-Marsh ND, Wycherley TP, Noakes M, Buckley JD, Wittert GA, Yancy WS Jr, Brinkworth GD. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. Diabetes Obes Metab. 2018 Apr;20(4):858-71. [**PMID**: 29178536]

[11] Slattery D, Choudhary P. Clinical Use of Continuous Glucose Monitoring in Adults with Type 1 Diabetes. Diabetes Technol Ther. 2017 May;19(S2):S55-61. [**PMID**: 28541131]

[12] Carlson A, Kanapka L, Miller K, Ahmann A, Chaytor N, Fox S, Kiblinger L, Kruger D, Levy C, Peters A, Rickels M. OR22-2 Exposure to Hypoglycemia in Older Adults with Type 1 Diabetes: Baseline Characteristics Using Continuous Glucose Monitoring Data. J Endocr Soc. 2019 Apr;3(Supplement_1):OR22-2.

[13] Messer LH, Cook PF, Tanenbaum ML, Hanes S, Driscoll KA, Hood KK. CGM Benefits and Burdens: Two Brief Measures of Continuous Glucose Monitoring. J Diabetes Sci Technol. 2019 Nov;13(6):1135-41. [**PMID**: 30854886]

[14] Taylor PJ, Thompson CH, Luscombe-Marsh ND, Wycherley TP, Wittert G, Brinkworth GD. Efficacy of Real-Time Continuous Glucose Monitoring to Improve Effects of a Prescriptive Lifestyle Intervention in Type 2 Diabetes: A Pilot Study. Diabetes Ther. 2019 Apr;10(2):509-22. [**PMID**: 30706365]

[15] Bando H, Kato Y, Kanazawa S, Tanaka M, Sueki E, Kanagawa H, Kawata T, Kawahito A, Aihara A. Daily improvement of glucose variability by Continuous Glucose Monitoring (CGM). Recent Research in Endocrinology and Metabolic Disorder. 2020 Mar 18;2(1):18-22.

[16] Freestyle.FreeStyle Libre pro System. Professional Continuous Glucose Monitoring System. Abbott Diabetes Care. [Cited 2020 August]. Available from: https://www.myfreestyle.com/freestyle-libre-pro-cgm-system

[17] Edge J, Acerini C, Campbell F, Hamilton-Shield J, Moudiotis C, Rahman S, Randell T, Smith A, Trevelyan N. An alternative sensor-based method for glucose monitoring in children and young people with diabetes. Arch Dis Child. 2017 Jun;102(6):543-49. [**PMID**: 28137708]

[18] Klonoff D, Bernhardt P, Ginsberg BH, Joseph J, Mastrototaro J, Parker DR, Vesper H, Vigersky R. Performance metrics for continuous interstitial glucose monitoring; approved guideline. CSLI. 2008;28(33).

Case Report

[19] Slattery D, Choudhary P. Clinical Use of Continuous Glucose Monitoring in Adults with Type 1 Diabetes. Diabetes Technol Ther. 2017 May;19(S2):S55-61. [**PMID**: 28541131]

[20] Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, Dagogo-Jack S, DeFronzo RA, Einhorn D, Fonseca VA, Garber JR, Garvey WT, Grunberger G, Handelsman Y, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Rosenblit PD, Umpierrez GE. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2019 Executive Summary. Endocr Pract. 2019 Jan;25(1):69-100. [**PMID**: 30742570]

[21] American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2020*. Diabetes Care. 2020 Jan;43(Suppl 1):S98-10. [**PMID**: 31862752]

[22] Bando H, Ebe K, Muneta T, Bando M, Yonei Y. Clinical effect of low carbohydrate diet (LCD): Case report. Diabetes Case Rep. 2017 Jun 10;2(2):124.

[23] Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA. Harper's Illustrated Biochemistry. 31st edition. New York: McGraw-Hill; 2018.

[24] Zhu Y, Wang Z, Zhang L. Optimization of lactic acid fermentation conditions for fermented tofu whey beverage with high-isoflavone aglycones. LWT. 2019 Aug 1;111:211-17.

[25] James AT, Yang A. Interactions of protein content and globulin subunit composition of soybean proteins in relation to tofu gel properties. Food Chem. 2016 Mar 1;194:284-89. [**PMID**: 26471556]

[26] Uemura H, Katsuura-Kamano S, Nakamoto M, Yamaguchi M, Fujioka M, Iwasaki Y, Arisawa K. Inverse association between soy food consumption, especially fermented soy products intake and soy isoflavone, and arterial stiffness in Japanese men. Scientific reports. 2018 Jun 25;8(1):1-9.

[27] Ebe K, Bando H, Muneta T, Bando M, Yonei Y. Remarkable Improvement of Glucose Variability by Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors using Continuous Glucose Monitoring (CGM). Diabetes Case Rep. 2019 Jan 28;4(1):1-5.

[28] Schierenbeck F, Franco-Cereceda A, Liska J. Accuracy of 2 Different Continuous Glucose Monitoring Systems in Patients Undergoing Cardiac Surgery. J Diabetes Sci Technol. 2017 Jan;11(1):108-16. [**PMID**: 27257168]

[29] Fokkert MJ, van Dijk PR, Edens MA, Abbes S, de Jong D, Slingerland RJ, Bilo HJ. Performance of the FreeStyle Libre Flash glucose monitoring system in patients with type 1 and 2 diabetes mellitus. BMJ Open Diabetes Res Care. 2017 Feb 17;5(1):e000320. [**PMID**: 28243449]

[30] Ólafsdóttir AF, Attvall S, Sandgren U, Dahlqvist S, Pivodic A, Skrtic S, Theodorsson E, Lind M. A Clinical Trial of the Accuracy and Treatment Experience of the Flash Glucose Monitor FreeStyle Libre in Adults with Type 1 Diabetes. Diabetes Technol Ther. 2017 Mar;19(3):164-72. [**PMID**: 28263665]

[31] American Diabetes Association. 7. Diabetes Technology: *Standards of Medical Care in Diabetes-2019*. Diabetes Care. 2019 Jan;42(Suppl 1):S71-80. [**PMID**: 30559233]

[32] Kebede MM, Schuett C, Pischke CR. The Role of Continuous Glucose Monitoring, Diabetes Smartphone Applications, and Self-Care Behavior in Glycemic Control: Results of a Multi-National Online Survey. J Clin Med. 2019 Jan 17;8(1):109. [**PMID**: 30658463]