

Fear of hypoglycemia in diabetes mellitus type 1 : a comparison between self-monitoring of blood glucose and flash glucose monitoring

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**FEAR OF HYPOGLYCEMIA IN TYPE 1 DIABETES MELLITUS
– A COMPARISON BETWEEN SELF-MONITORING OF BLOOD
GLUCOSE AND FLASH GLUCOSE MONITORING**

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LIST OF ABBREVIATIONS

CEG - Clark grid error

CGM - Continuous glucose monitoring

FGM - Flash glucose monitoring

FPG - Fasting plasma glucose

HAAF - Hypoglycemia- associated autonomic failure

HbA1c - Hemoglobin A1c

HFS - Hypoglycemia fear survey

HFS-B - Hypoglycemia fear survey- behavior

HFS-W - Hypoglycemia fear survey- worry

isCGM – Intermittent scanned continuous glucose monitoring

MARD - Mean absolute relative difference

OGTT- Oral glucose tolerance test

rtCGM - Real-time continuous glucose monitoring

SMBG - Self-monitoring of blood glucose

T1DM- Type 1 Diabetes Mellitus

1. INTRODUCTION

1.1 Definition of Diabetes Mellitus type 1

Type 1 diabetes mellitus is a chronic autoimmune disease characterized by insulin deficiency and resultant hyperglycemia (1). It is thought to be caused by an immune-associated destruction of insulin-producing β cells of the pancreas. Diabetes mellitus type 1 can occur at any age, but it is one of the most common chronic diseases of childhood (2, 3). Polydipsia, polyuria and polyphagia are known as the classical trio of symptoms at onset of the disease, while approximately one third of the population present with diabetic ketoacidosis (1-3).

An interaction between genetics and the environment is believed to cause diabetes mellitus type 1. The burden of type 1 diabetes-associated genes is highest in young children who develop clinical type 1 diabetes mellitus, more specifically related to the genes linked to the immune function (e.g., IL2RA, THEMIS, etc.). The genes related to immune function are associated with very early-onset type 1 diabetes mellitus and aggressive histopathology (4). Diabetes mellitus type 1 is a disease with twin concordance of 30-70%, sibling risk of 6-7%, and a risk of 1-9% for children who have a parent with the disease (1). There are two HLA class 2 haplotypes involved in the antigen presentation. However, how these haplotypes interact and determine the risk is poorly understood (1, 4).

Diagnosis of diabetes mellitus type 1 is based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75g oral glucose tolerance test (OGTT), or HbA1c criteria. These tests are equally appropriate for diagnostic screening, but do not necessarily detect diabetes in same individuals (3). HbA1c has several advantages in comparison to FPG and OGTT, including greater preanalytical stability, greater convenience and less day-to-day perturbations during situations like stress or illness, but is considered to be a test with lower sensitivity (1-3).

The criteria for the diagnosis of diabetes mellitus is FPG ≥ 126 mg/dL (7.0 mmol/L) or 2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT or HbA1c $\geq 6.5\%$ (48 mmol/mol) or in a patient with classic symptoms of hyperglycemia or hyperglycemic crises, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L), see Figure 1 (2, 3). If a patient presents with classic symptoms, measurement of plasma glucose is sufficient to make the diagnosis of the disease (3). Over 90% of people with newly diagnosed diabetes mellitus type 1 have measurable antibodies against specific β -cell proteins (1).

Criteria for the diagnosis of diabetes

| |
|--|
| FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.* |
| OR |
| 2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.* |
| OR |
| A1C $\geq 6.5\%$ (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.* |
| OR |
| In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L). |

Figure 1. Criteria for the diagnosis of diabetes (3).

Some patients with diabetes mellitus type 1 retain the ability to produce minimal endogenous insulin after diagnosis of the disease; the so-called "honeymoon period" associated with a partial recovery of insulin secretory function of the β -cells (1, 2). During this period, no to minimal exogenous supply is needed, but the duration of this period is different between patients. Many of these remaining β -cells are lost over time, however it has been shown that this decline does not progress to a complete loss of all β -cells. The mechanisms of the residual β -cells in patients with long-term diabetes mellitus type 1 remain unclear (1).

1.2 Detection of glucose levels

Patients with diabetes mellitus can choose between two different systems for measurement of their blood glucose levels. One choice is the use of conventional glucometers that determine the blood glucose (SMBG), whereas the second option is continuous glucose monitoring (CGM) system measuring glucose within interstitial fluid (5, 6). Monitoring of glucose levels allows the patient to detect their individual response to therapy and assess whether glycemic targets are being achieved. The results can be used as a tool for management of the disease, but also as a potential guide of medical nutrition therapy and physical activity (13).

SMBG is considered the standard approach, but the recent years have shown an increased use of sensors for CGM and flash glucose monitoring (FGM) (5, 6). FGM is also relying on measurement of the glucose concentration in the interstitial fluid (11). Examples of limitations associated with SMBG are unreliability of patient recorded data, hyperglycemic or hypoglycemic episodes due to intermittent monitoring and insufficient identification of glycemic variability (6). SMBG is related to fear of needles, pain, inconvenience and costs of needles and test strips (10). The accuracy of SMBG is dependent on the instrument and the user, showing the importance of evaluating the monitoring technique of each patient. There is a correlation between greater SMBG frequency and lower HbA1c levels. SMBG is important for insulin-treated patients, and they should be encouraged to assess glucose levels prior to meals, at bedtime, prior to exercise, when suspecting low blood glucose and when performing tasks like driving, in order to monitor and prevent hypoglycemia and hyperglycemia (13).

There are two types of CGM devices, those owned by the user, unblinded and intended for continuous use (real time (rt)CGM and intermittently scanned (is)CGM) and those owned by the clinic, which provide data that is blinded or unblinded for a discrete period of time (professional CGM) (5, 13). The real time-CGM together with insulin therapy serves as a tool to lower or maintain HbA1c, but also to reduce the incidents of hypoglycemia in patients with diabetes mellitus type 1 (13).

"Minimally invasive" needle CGM sensors introduced in 1999, contributed to development of new ways of measuring the blood glucose levels and daily management of diabetes mellitus. CGM sensors were first known to provide an almost continuous glucose trace delivering blood glucose readings every 1 to 5 minutes contributing to information about fluctuations and trends, but also revealing hypoglycemic and hyperglycemic events not visible by SMBG (7). In later years with advances in technology, CGM systems are now equipped with smart alarms for hypo-/hyperglycemic events, arrows showing changes in the blood

glucose trends, and require the user to scan the sensor by either app-enabled smartphone or a specific reader to obtain current glucose values (5-7).

There is a difference between FGM systems and CGM sensors when it comes to displaying the glucose values (8). In FGM, the glucose values are not constantly shown. In order to obtain the information about a person's glucose levels and trends, the sensor needs to be scanned, either by a reader or a smartphone (8, 11, 12). When the sensor is scanned, a reader or app on a smartphone will show the glucose information from the last eight hours, the current glucose value, but also arrows giving an indication of changes in the glucose levels (10). FGM has the ability to show a continuous real-time graph and are known for their good accuracy, small size, factory calibration and improved method for sensor insertion (12).

CGM systems require capillary blood calibrations, usually two times a day, in order to provide accurate glucose readings (6). There is an existence of a "lag time" between the plasma and the interstitial fluid that is responsible for the difference between interstitial glucose values and blood glucose concentration (6, 8, 13). These lag times can occur when the glucose levels are rising or falling rapidly (13).

Capillary blood calibrations enable an improved measurement accuracy, especially during rapid glycemic excursions (6, 8). Dexcom G6 CGM systems are the only sensors existing today that do not require a fingerstick for calibration, which means that they can be used without SMBG (5, 6, 9, 14). The benefits provided by the G6 system is a predictive low-glucose alert, warning the patients if a glucose level of <55mg/dL is predicted to occur within the next 20 minutes, enabling the patients to avoid hypoglycemia (14). FGM systems do not require calibration, mainly because of factory calibration, which eliminates the number of finger sticks needed and potential errors connected to the calibration process (6, 8, 10).

FreeStyle Libre, an FGM system, brought to the market in 2014, is a type of patch sensor about the size of a coin (6). It is worn on the arm for up to 14 days and the system uses a wired glucose oxidase enzyme co-immobilized on an electrochemical sensor (6, 11). The sensor displays the current glucose concentration in the interstitial fluid, as well as eight-hour historic and trend glucose data when scanned (11). Every 15 minutes, data are transferred from the sensor to the reader, and like with other FGM systems, real-time interstitial glucose values are not shown constantly and only when the sensor is scanned by the user (6).

1.3 Glycemic variability

Glycemic variability can be defined by the measurement of fluctuations of glucose or other parameters of glucose homeostasis over a period of time. More specifically referring to oscillations in blood glucose level within a day, between days or a longer period of time (15). HbA1c serves as a marker for average glycemic control, but it is also used as a diagnostic criterion for diabetes mellitus (2, 3, 15-17). There is an increased risk for development of hypoglycemia with a tightening in glycemic control. On the other hand, a reduction in hyperglycemia and targeting a HbA1c value of less than 7% is associated with a lower risk for micro- and macrovascular complications (16). Glycemic variability is characterized by frequency, amplitude and duration of the fluctuations; taking into account that both the timing of the blood glucose fluctuations and the amplitude contribute to the risks of hyperglycemia and hypoglycemia (20).

A difference between "short-term" and "long-term" glycemic variability exists. Short-term glycemic variability indicates the potential risks of episodes of hyperglycemia or hypoglycemia, mainly calculated from SMBG measurements in earlier years, whereas this is increasingly replaced by CGM in recent times. Long-term glycemic variability covers the ambient hyperglycemia, correlating with the mean blood glucose concentration or the mean HbA1c (18). The diurnal blood glucose profile is best demonstrated by use of SMBG, whereas CGM provides interstitial glucose measurements at 5-min intervals that therefore makes it a more comprehensive record covering both daytime and nighttime period, and thereby the golden standard for assessing short-term glycemic variability (16, 18).

Suboptimal glycemic control is challenged during puberty as a consequence of physiological factors related to hormonal changes and psychosocial factors. Faster linear growth during puberty is related to higher glucose variability, but also insulin resistance caused primarily by growth hormone and IGF-1 (19). HbA1c remains an important clinical measure of glycemic control also during puberty, but has its limitations related to no ability to provide information of short-term fluctuations in glycemia (3, 15-17, 19). CGM on the other hand, can give more comprehensive variables of glycemic control than HbA1c alone (16-19).

1.4 Definition of hypoglycemia

Hypoglycemia is an acute complication and a common side effect of diabetes therapy (21). It is defined as blood glucose levels less than 70mg/dL or 3,9mmol/L and is associated with a range of neuroglycopenic and neurogenic symptoms (21-24). Another definition of hypoglycemia is by Whipple triad; low blood glucose level measured, symptoms and signs associated with low blood glucose level and resolution of these signs and symptoms by intake of carbohydrates (23, 24). As symptoms of hypoglycemia are non-specific, establishment of Whipple triad needs to be made before concluding the diagnosis (24, 28).

Another way to define hypoglycemia is by three categories; 1. 61–70 mg/dL (3.4–3.9 mmol/L) is considered "low"; 2. 51–60 mg/dL (2.8–3.3 mmol/L) is "very low"; and 3. <50 mg/dL (2.8 mmol/L) is "dangerously low" (26). Major and minor episodes of hypoglycemia can also be defined, where minor hypoglycemia usually presents with symptoms of dizziness, sweating and tachycardia. Major hypoglycemic episodes usually require a third-party assistance and presents as a potential life-threatening event (23).

Hypoglycemia is common in patients with diabetes mellitus type 1, with 30-40% of the patients experiencing an average of one to three episodes of severe hypoglycemia each year. The definition of clinical hypoglycemia is a plasma glucose concentration low enough to cause symptoms and/or signs, including impaired brain function. For people with well controlled diabetes mellitus, the glycemic thresholds for symptoms of hypoglycemia shift to lower plasma glucose concentration, whereas it shifts to higher plasma glucose concentration in the patients with poorly controlled disease. This serves as a potential explanation for why the plasma glucose concentration at which responses occur is variable between and within individuals (28).

Glucose serves as the primary energy source used by the body, and its homeostasis is regulated by an interplay of different hormones, mainly talking about glucagon and insulin, produced by α (alpha) cells and β (beta) cells of the pancreas (21-23). In adults without diabetes mellitus, pancreas will decrease the secretion of insulin as a first response to hypoglycemia, whereas the liver will increase the secretion of glucagon and mediate glycogenolysis and gluconeogenesis (22, 23). The adrenals, along with the involvement of the peripheral nervous system, will produce epinephrine that will decrease the glucose clearance by primarily acting on the kidneys, fat and muscle. In a hypoglycemic episode, the neurotransmitters, namely acetylcholine and norepinephrine are also involved (23). Acetylcholine is responsible for symptoms like hunger and diaphoresis, whereas norepinephrine triggers palpitations and tremor (22, 23).

Symptoms of hypoglycemia can change with each episode and varies between individuals (22, 28). If the blood glucose levels drop below a value of 50mg/dL, neuroglycopenic symptoms like cognitive disorientation, seizures, fatigue, irritability and visual failure might occur (21, 22, 24, 29). Autonomic symptoms occur with a drop of plasma glucose concentration to a value of approximately 60mg/dL, but can further be divided into adrenergic and cholinergic symptoms (23, 24, 29). Adrenergic symptoms include tachycardia, anxiety and tremor, whereas cholinergic symptoms can present as sweating, hunger and nausea (24). Hypoglycemia is related to a lower health-related quality of life (28).

"Hypoglycemic unawareness" is a condition in which the patient is not able to experience or recognize any symptoms of low blood glucose levels (22, 26). Confusion is usually the first symptom that presents in these affected individuals, and in certain cases the response will not be triggered before the glucose level is in range of neuroglycopenia (27, 29). Women inherently exhibit decreased counterregulatory responses to hypoglycemia, whereas men are more prone to desensitization (29). These patients are depending on others to recognize their symptoms and treat low glucose levels (22, 27).

Impaired awareness of hypoglycemia and defective glucose counterregulation are components of hypoglycemia-associated autonomic failure (HAAF) in diabetes mellitus. The precise mechanisms of what is causing HAAF to occur are not known, but prior exercise, sleep or recent antecedent hypoglycemia are potential factors (28, 29). Increased insulin sensitivity and glucose utilization can contribute to development of exercise-induced hypoglycemia up to 17 hours after cessation of physical activity. However, counterregulatory responses can be reduced by up to 50% during hypoglycemia after a moderately intense exercise (29). CGM is a useful tool that can be used by patients experiencing hypoglycemic unawareness or even nocturnal hypoglycemia (25).

Hypoglycemia can be quantified as the percentage of CGM values that are below a given threshold (<70 mg/dL (3.9 mmol/L) or <54 mg/dL (3.0 mmol/L)) or the number of minutes or hours below these thresholds. Another way to quantify hypoglycemia is by the number of hypoglycemic events that occur over the given CGM reporting period (20).

Conventional risk factors of hypoglycemia in patients with diabetes mellitus include excessive doses of insulin administered, decreased exogenous glucose delivery after intake of low-carbohydrate meal or overnight fast or increased glucose utilization during or shortly after exercise. Sensitivity to insulin increases late after exercise, in the middle of the night and after weight loss, but also potential clinical diagnosis such as renal failure and hypothyroidism are

associated with decreased insulin clearance, and thereby also serve as potential risk factors for development of hypoglycemia (28).

Hypoglycemia is often associated with challenges in both children and adults with diabetes mellitus type 1. In children, challenges are related to variable eating patterns, insulin dosing, physical activity and the limited ability to recognize the symptoms. Insulin resistance is likely to occur during puberty, but as the child is growing, inattention of the diabetes might occur and unequal distribution of activity during the day, are all factors associated with risk for development of hypoglycemia (27).

The physiology of aging, known to impair the responses mediated by glucagon and epinephrine, can lead to dangerous consequences from presenting hypoglycemia in elderly patients (23). Reasons can be partially related to age-related decrease in β -adrenergic receptor function, and symptoms of neuroglycopenia are more common in these patients (27). Acute hypoglycemia is associated with an increased risk of development of cardiovascular events, particularly because it can lead to a prolongation of the QT interval and ventricular arrhythmias (23). When assessing hypoglycemia in clinical care, factors such as weight gain, reduced awareness of subsequent hypoglycemia, fear of hypoglycemia and associated cardiac arrhythmia, confusion, or abnormal or combative behavior need to be considered (20).

For the treatment of hypoglycemia, "the rule of 15" or "15-15 rule" is commonly used. It involves intake of 15g of carbohydrates and a remeasurement of the blood glucose value after 15 minutes, assuming that the plasma glucose level after this period of time will reach a value of 75mg/dL (22). If the hypoglycemia is severe, in the form that the patient is unconscious or not able to help themselves, glucagon injection given either IM, IV or SC needs to be administered (22, 23). In case an IV is available, a solution of 50% dextrose can be given (22).

1.5 Accuracy of Flash Glucose Monitoring

In order to determine the accuracy of interstitial fluid glucose readings, a comparison with blood glucose reading taken at the same time, needs to be done. The matching between the two readings is dependent on accuracy and precision of the interstitial fluid device tested, but also the reference blood glucose device used (31). As the blood and the interstitial fluid present as different physiological compartments, factors such as the lag time it takes the interstitial fluid to reflect the blood glucose levels, should be taken into account. (31, 32). The lag time varies between 4 and 10 minutes, but it can be longer when there are more rapid changes in the glucose concentration (32). Accuracy seems to be lower in lower glucose ranges (6).

The mean absolute relative difference (MARD) is one metric that is commonly used as a routine statement of sensor accuracy (Figure 2). A metric analyzing the concordance of glucose values from two different physiological compartments, measured with different systems (6, 31, 32). MARD of 10% shows the level of accuracy needed for safe use of CGM readings in order to make insulin dosing decisions, without the use of SMBG measurement. Taken into account that the MARD of a SMBG device is between 4.4% and 13.4% (31). The glucose sensor systems have shown a steady improvement in the accuracy with approximately $\pm 10\%$ MARD. With a greater acceptance from both patients and physicians, the users of CGM require a decreased number of measurements of capillary blood glucose. CGM today are considered for nonadjutant use and not an adjutant to SMBG anymore (30). However, during the first day of sensor use the MARD is believed to be higher, potentially explained by inflammatory reaction mediated from inserting the sensor subcutaneously (31, 33).

As the blood glucose falls towards lower levels, MARD is related to larger errors which is important to take into account when considering the accuracy of interstitial fluid glucose readings when patient is in hypoglycemia (31). Sensors used in earlier times are known to have a low accuracy, such as GlucoWatch with a MARD of 22% (34). When comparing MARD of different FGM systems, it has been shown that the overall MARD of FreeStyle Libre is 13.2% with relatively little change in hypoglycemic ($<3.9\text{mmol/L}$) and hyperglycemic ($>10\text{mmol/L}$) range (MARD of 14.6% and 10.1%). In contrast, Dexcom G4 platinum has a MARD of 16.8% and a larger difference of hypoglycemic and hyperglycemic range (MARD of 23.8% and 11.6%) (36). Dexcom G5 Mobile has a MARD of 12.5% (35).

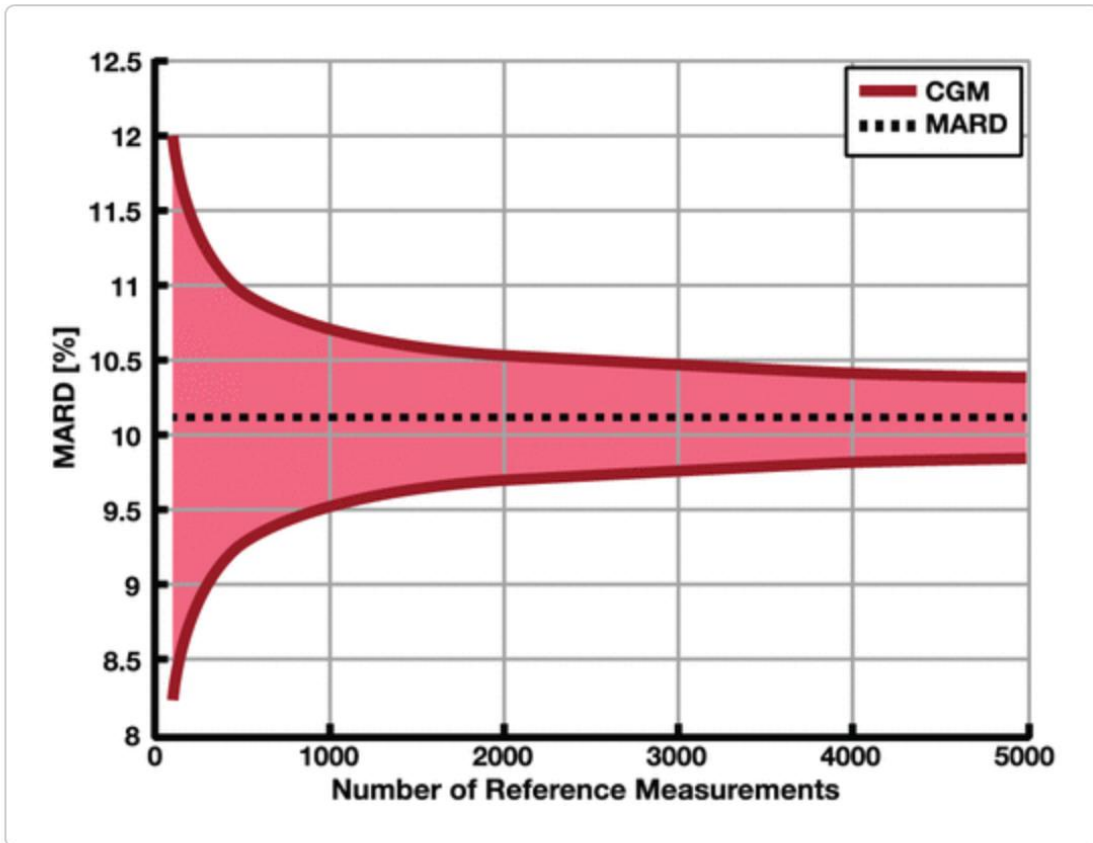


Figure 2. Shows that the degree of uncertainty for a hypothetical MARD becomes tighter as the number of reference measurements increases. On the other side, the larger number of reference samples, the more burden is placed on the patients and the study personal (34).

When users read a low glucose value (below 3.9mmol/L) from the FGM device, this is noted as hypoglycemia and continues usually with corrective actions. However, corrective actions might be unnecessary if the blood glucose concentration, showed by SMBG is higher. The lag time between the interstitial glucose levels and the blood glucose values might be an explanation for the difference and creates unwanted risks. Unwanted risks both for unnecessary correction of hypoglycemia, but also when more experienced users pay less attention to interstitial fluid low glucose readings and take no immediate action (31).

Clark error grid (CEG) serves for additional accuracy reporting of FGM. It is comparing reference blood glucose readings to glucose reading of device being tested and plots the results on a grid (5, 31). The grid is further divided into zones A-E, where readings that are positioned into zones A and B can be used for making clinical decisions, see Figure 3 (31, 35). When compared to a blood glucose meter, the percentage of results within zones A and B is 99.7% for the Freestyle Libre system and 98.6% for the Dexcom G4 (35).

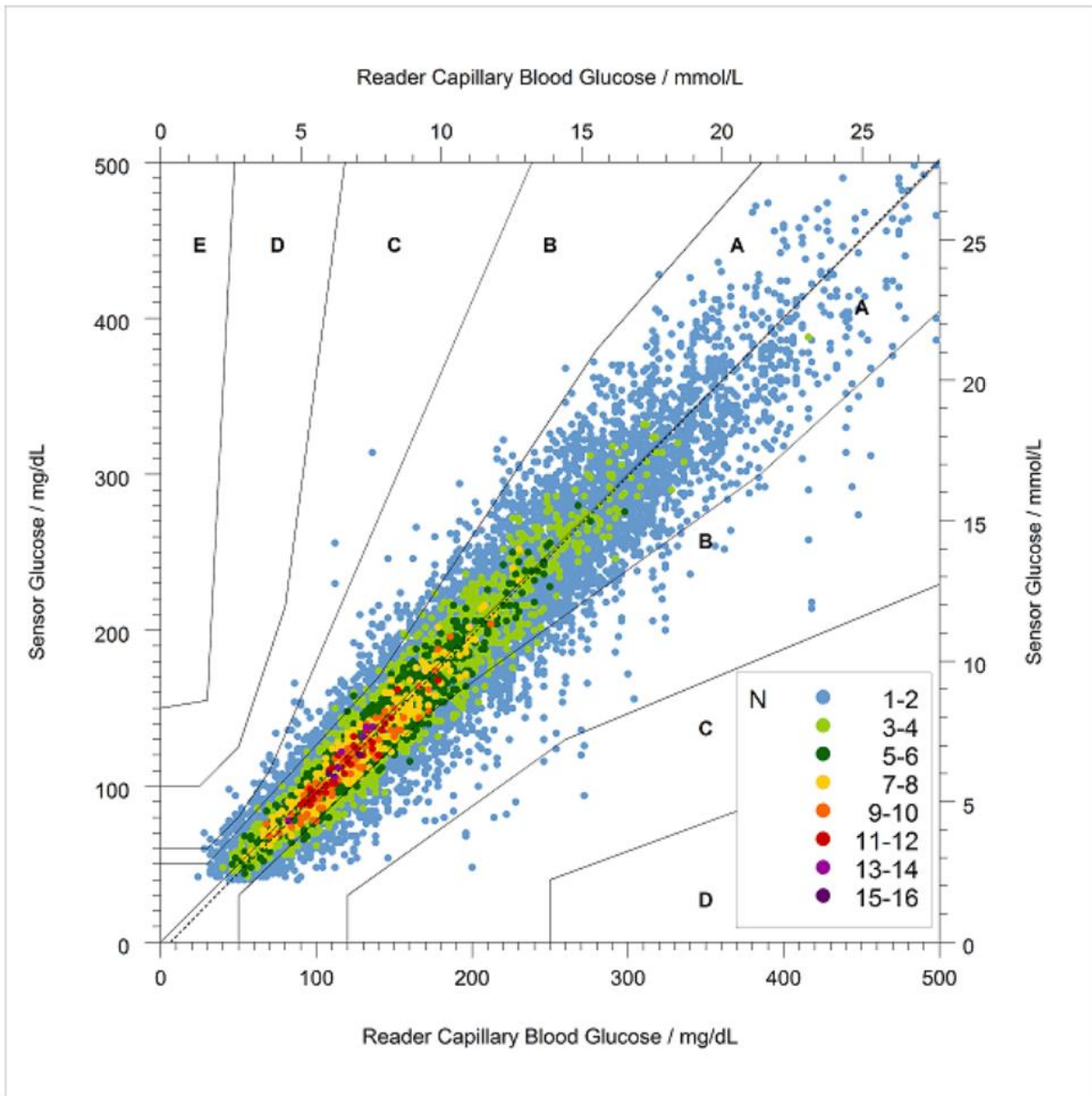


Figure 3. The Error Grids have zones from zone A to zone E. Results in zones A and B are considered to be clinically acceptable, while the results outside of these zones have a negative clinical outcome. The higher the percentage of results in zones A and B, the more clinically accurate the glucose system is (35).

1.6 Fear of hypoglycemia

Hypoglycemia can be experienced as discomfort by patients, but symptoms of anxiety and concerns can also be evident when the hypoglycemia occurs unpredictably (26). In patients with diabetes mellitus, symptoms of anxiety relating to hypoglycemia can lead to disruption in everyday activities, reduced glycemic control, negative consequences for emotional well-being and impaired quality of life (26, 28, 29). Symptoms of hypoglycemia can create a fear for future hypoglycemic events not only in the patients who are experiencing them, but also family members and nondiabetic spouses (26, 28, 29).

Potential hypoglycemic episodes can provoke stress and marital conflict regarding the management of diabetes mellitus, which can further raise the glucose levels. Affected individuals can make an effort to avoid the hypoglycemic episodes by changing their behavior towards the treatment of the disease, leading to maintenance of higher-than-desirable plasma glucose levels by performing actions such as reducing insulin dosage or consuming high-glycemic index food (28, 29).

Nocturnal hypoglycemia can lead to changes in sleep, whereas recurrent hypoglycemia can be associated with chronic mood disorders (27). Severe hypoglycemic episodes can occur during sleep, associated with diminished ability to recognize counterregulatory responses and thereby depriving individuals of the adequate stimulus to counteract hypoglycemia. Asymptomatic nocturnal hypoglycemia can affect both children and adults, can potentially last up to several hours and is suspected to contribute to the "dead-in-bed-syndrome" (29).

Neuroglycopenic symptoms of hypoglycemia, like cognitive disorientation and fatigue, or adrenergic symptoms like anxiety and tremor, can be experienced as uncomfortable by the patient and interfere with their working abilities or participation in everyday activities. These symptoms can be linked to the fear of hypoglycemia and reduced ability to trust their own instincts, particularly when the patients have some kind of responsibilities, like when driving a car or taking care of other individuals (21, 22, 24, 27, 29). There may be a connection between fear of hypoglycemia and failure to recognize hypoglycemic episodes both during the day and night. The failure to recognize hypoglycemic episode can be explained by desensitization, meaning that there are decreased neuroendocrine responses to hypoglycemia that dampen symptomatic responses (29).

Patients with diabetes mellitus can experience difficulties talking to other people about their hypoglycemic issues, which can have a negative influence on their work life, but also be linked to reduced reproductivity (27). To avoid hypoglycemia or fear of hypoglycemia, patients can intentionally aim for higher glucose levels, which is one strategy particularly used in work

life where demands and job-related stress can compete with the task of diabetes self-management (38).

The management of diabetes mellitus during childhood and adolescence places burden on the youth and their family, and requires a constant ongoing assessment of psychosocial status, social determinants of health and diabetes distress in patient and the caregiver (37). Caregivers and family members can experience fear of hypoglycemia when patients in this age-group take part in everyday activities that have influence on the glycemic control, such as school performance and sport activities (29, 37). The young patients rely on observations made by their caregivers to recognize when they are experiencing hypoglycemic events, with changes in behavior being the symptom most commonly noticed. However, both children with diabetes mellitus type 1 and their parents fail to recognize up to 40-50% of hypoglycemic episodes (28).

Considerations about the impact of diabetes mellitus on quality of life, fear of hypoglycemia, development of mental health problems related to diabetic distress, symptoms of anxiety or depression and disordered eating behaviors are important to emphasize in this age group (28, 37). The management of diabetes mellitus requires ongoing parental involvement throughout childhood and development of a family teamwork in order to prevent deterioration in glycemic control and maintain adherence (37).

1.7 Safety and Side Effects of Flash Glucose Monitoring (FGM)

Mild to severe adverse reactions related to sensor-wear reactions are reported. Adverse events related to the use of sensor reported in adult population are itching, rash, allergic reactions, erythema, edema, induration, bleeding, bruising and minor infections at the insertion site. In the pediatric age group on the other hand, adverse reactions like mild pain, irritation at the sensor insertion site, itching, erythema and swelling are reported (6). Frequent related problems with the device can be related to early loss of sensor and low confidence in reported sensor values triggered by well-known lower accuracy during the first 24 hours after sensor insertion (39). Other frequently reported safety issues related to the sensor devices are the ease to pull them off, they can peel off due to sweat or there may be transmission issues at night (40).

Contact dermatitis, both allergic and irritant types, can occur with the devices attached to the skin. This can potentially be explained by the presence of isobornyl acrylate, a skin sensitizer that has the capability to cause an additional spreading allergic reaction. (6, 39, 40).

2. OBJECTIVES

The aim of the study is to compare the fear of hypoglycemia in patients with diabetes mellitus type 1 on self-monitoring of blood glucose (SMBG) and flash glucose monitoring (FGM). Different attitudes that patients might experience during episodes of hypoglycemia, both from an aspect of behavior and worry, were investigated.

Following variables were considered:

1. The type of glucose measurement used by the patients, SMBG or FGM in form of FreeStyle Libre sensor;
2. Gender of the patients;
3. Duration of the disease.

Our hypotheses were:

1. Fear of hypoglycemia in patients with diabetes mellitus type 1 is lower for the ones using FGM than for the ones on SMBG;
2. There is a smaller difference in fear of hypoglycemia between females and males with diabetes mellitus type 1 using FGM than the ones on SMBG;
3. The fear of hypoglycemia is bigger in patients with diabetes mellitus type 1 for a longer period of disease duration (T1DM).

3. MATERIALS AND METHODS

Subjects

This prospective observational study was carried out among patients with diabetes mellitus type 1 treated at the KBC Split. The inclusion criteria were type 1 diabetes mellitus diagnosed for more than 3 months, subjects aged 18 years or older. No specific exclusion criteria was implemented except pregnancy. The questionnaires were conducted during a period of two months, from May to June 2020. A total of 200 patients were asked to participate in the study, 100 patients that use SMBG, and 100 patient that use FGM, FreeStyle Libre sensor respectively. The response rate for the patients that use SMBG was 80.0%, whereas the response rate for the patients on FGM, FreeStyle Libre sensor was 77.0%.

A total of 80 patients, 44 females and 36 males on SMBG were conducted in the study. For the patients that use FGM FreeStyle Libre sensor, a total number of 77, 44 females and 33 males were included.

This study was approved by the University of Split School of Medicine Ethical committee, Approval number: 500-03/21-01/94. The research has been conducted in full accordance with the World Medical Association Declaration of Helsinki.

Questionnaire

Our questionnaire is based on The Hypoglycemia Fear Survey (HFS), first published in 1987. The original (HFS-I) and the revised version (HFS II) are composed of two main parts, the Behavior (HFS-B) and Worry (HFS-W). HFS-B consist of questions that describe behaviors that the patients might have in order to avoid hypoglycemic episode and its negative following consequences (e.g., making sure that they are never alone, limiting exercise and physical activity, measuring their blood glucose levels more frequently before gatherings/meetings). HFS-W consist of questions that are directed to describe the concerns that patients might have during an episode of hypoglycemia (e.g., having an accident, judgement from co-workers, loss of control when taking care of other people) (41). This questionnaire (see Supplement 1) was translated to Croatian language and used before our study. The patients gave answers to the questions by use of numbers. (0- never, 1- rarely, 2- sometimes, 3- often, 4- always).

The questionnaire was voluntary and anonymous, performed through phone calls with the participating patients. We conducted the questionnaires through phone calls mainly because of the pandemic of COVID-19, beginning each phone call with an oral explanation about the background and aim of the research.

The age of the patients and the total duration of the disease were gathered from the patient records.

Methods

Elementary statistics considering means, quartiles and standard deviations were calculated for continuous variables. For testing difference we used t-test for dependent samples and ANOVA test. Chi-square test was used for testing dependence between two categorical variables. Correlation analysis was performed using Pearson test. Conclusion is made on significant level of $P < 0.05$. Data was analyzed using STATISTICA, version 12.0 (TIBCO Software Inc. Palo Alto, CA, USA; 2013).

4. RESULTS

Descriptive statistics

There is no statistical significant difference in total number of patients using SMBG (N=80) and FGM (N=77) ($P=0.810$), see Table 1.

Table 1. Descriptive statistics for total number of patients with T1DM using SMBG and FGM

| | N | % | χ^2 | P^* |
|-------------|----|-------|----------|-------|
| SMBG | 80 | 50.96 | | |
| FGM | 77 | 49.04 | 0.058 | 0.810 |

SMBG- self-monitoring of blood glucose, FGM- flash glucose monitoring;

*Chi-square test

There is no statistically significant difference between males (N=36) and females (N=44) using SMBG and males (N=33) and females (N=43) using FGM ($P=0.787$), see Table 2.

Table 2. Descriptive statistics for gender distribution between users of SMBG and FGM

| | Male N (%) | Female N (%) | P^* |
|-------------|------------|--------------|-------|
| SMBG | 36 (45.00) | 44 (55.00) | |
| FGM | 33 (42.86) | 43 (55.84) | 0.787 |

SMBG- self-monitoring of blood glucose, FGM- flash glucose monitoring;

* Chi-square test

Patients using FGM are on average 5 years older than the patients using SMBG, but there is no statistical significant difference between the groups ($P=0.385$), see Table 3.

Table 3. Descriptive statistics for age of patient using SMBG and FGM

| | Age (years) | | | | T | P^* |
|-------------|-------------|-------|--------|---------------|------|-------|
| | Mean | SD | Median | IQR | | |
| SMBG | 41.84 | 13.04 | 44.00 | (29.00-52.00) | | |
| FGM | 43.62 | 12.46 | 45.00 | (33.00-52.00) | 0.87 | 0.385 |

SMBG- self-monitoring of blood glucose, FGM- flash glucose monitoring, SD- standard deviation, IQR- interquartile range;

*T-test

Patients using SMBG have on average 4 years longer duration of the disease than the patients using FGM, but there is no statistical significant difference between the groups ($P=0.094$), see Table 4.

Table 4. Descriptive statistics for duration of the disease between the patients using SMBG and FGM

| | Duration of T1DM (years) | | | | | T | P* |
|-------------|--------------------------|------|--------|-------------|------|-------|----|
| | Mean | SD | Median | IQR | | | |
| SMBG | 24.94 | 9.91 | 27.00 | 18.00-32.25 | | | |
| FGM | 22.25 | 9.98 | 23.00 | 15.00-30.00 | 1.68 | 0.094 | |

SMBG- self-monitoring of blood glucose, FGM- flash glucose monitoring, SD- standard deviation, IQR- interquartile range;

*T-test

Behavior

Behavior is measured by answers given by the patients on the first 10 question in the questionnaire. Table 5 shows the difference in behavior between patients on SMBG and FGM. On average, patients using FGM have 4.54 points higher results than the ones using SMBG. There is a statistical significant difference in behavior between patients on SMBG and FGM ($P<0.001$), see Table 6.

Table 5. Descriptive statistics for behavior between patients on SMBG and FGM according to answers from the questionnaire

| | Behavior | | | | | | | | | |
|-----------------|----------|-------------|-----------|---------------|------------|----------|-------------|-----------|---------------|------------|
| | SMBG | | | | | FGM | | | | |
| | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 |
| Q1 | 13 | 28 | 22 | 15 | 2 | 38 | 13 | 14 | 8 | 4 |
| | 16.25 | 35.00 | 27.50 | 18.75 | 2.50 | 49.35 | 16.88 | 18.18 | 10.39 | 5.19 |
| Q2 | 35 | 23 | 14 | 4 | 4 | 34 | 10 | 14 | 5 | 14 |
| | 43.75 | 28.75 | 17.50 | 5.00 | 5.00 | 44.16 | 12.99 | 18.18 | 6.49 | 18.18 |
| Q3 | 41 | 12 | 10 | 11 | 6 | 13 | 9 | 17 | 23 | 15 |
| | 51.25 | 15.00 | 12.50 | 13.75 | 7.50 | 16.88 | 11.69 | 22.08 | 29.87 | 19.48 |
| Q4 | 41 | 14 | 13 | 9 | 3 | 43 | 7 | 10 | 10 | 7 |
| | 51.25 | 17.50 | 16.25 | 11.25 | 3.75 | 55.84 | 9.09 | 12.99 | 12.99 | 9.09 |
| Q5 | 0 | 0 | 5 | 28 | 47 | 2 | 3 | 5 | 12 | 55 |
| | 0.00 | 0.00 | 6.25 | 35.00 | 58.75 | 2.60 | 3.90 | 6.49 | 15.58 | 71.43 |
| Q6 | 4 | 5 | 21 | 25 | 25 | 5 | 2 | 9 | 7 | 54 |
| | 5.00 | 6.25 | 26.25 | 31.25 | 31.25 | 6.49 | 2.60 | 11.69 | 9.09 | 70.13 |
| Q7 | 33 | 18 | 17 | 8 | 4 | 28 | 4 | 13 | 18 | 14 |
| | 41.25 | 22.50 | 21.25 | 10.00 | 5.00 | 36.36 | 5.19 | 16.88 | 23.38 | 18.18 |
| Q8 | 0 | 1 | 0 | 20 | 59 | 2 | 0 | 3 | 3 | 69 |
| | 0.00 | 1.25 | 0.00 | 25.00 | 73.75 | 2.60 | 0.00 | 3.90 | 3.90 | 89.61 |
| Q9 | 1 | 3 | 13 | 23 | 40 | 5 | 3 | 7 | 14 | 48 |
| | 1.25 | 3.75 | 16.25 | 28.75 | 50.00 | 6.49 | 3.90 | 9.09 | 18.18 | 62.34 |
| Q10 | 32 | 22 | 5 | 13 | 8 | 7 | 1 | 4 | 9 | 56 |
| | 40.00 | 27.50 | 6.25 | 16.25 | 10.00 | 9.09 | 1.30 | 5.19 | 11.69 | 72.73 |
| | N | Mean | SD | Median | IQR | N | Mean | SD | Median | IQR |
| Behavior | 80 | 20.33 | 5.80 | 19.00 | 16-24 | 77 | 24.87 | 5.46 | 25.00 | 22-29 |

SMBG- self-monitoring of blood glucose, FGM- flash glucose monitoring, SD- standard deviation, IQR- interquartile range

Table 6. Descriptive statistics for behavior between patients using SMBG and FGM

| | Behavior | | | | T | P* |
|-------------|----------|------|--------|-------------|------|--------|
| | Mean | SD | Median | IQR | | |
| SMBG | 20.33 | 5.80 | 19.00 | 16.00-24.50 | | |
| FGM | 24.87 | 5.46 | 25.00 | 22.00-29.00 | 5.01 | <0.001 |

SMBG- self-monitoring of blood glucose, FGM- flash glucose monitoring, SD- standard deviation, IQR- interquartile range;

*T-test

There is a statistical significant difference in behavior between patients using SMBG and FGM ($P<0.001$). There is no statistical significant difference in level of behavior between males and females according to which type of glucose monitoring system they use ($P=0.549$) and ($P=0.093$), see Table 7. "

Table 7. Descriptive statistics for behavior between males and females using SMBG and FGM

| Type of Glucose Monitoring/Gender | N | Mean | SD | F | P* |
|-----------------------------------|----|-------|------|-------|--------|
| SMBG | 80 | 20.33 | 5.84 | | |
| FGM | 77 | 24.87 | 5.50 | 23.09 | <0.001 |
| Female | 88 | 22.34 | 6.39 | | |
| Male | 69 | 22.83 | 5.75 | 0.36 | 0.549 |
| SMBG/Female | 44 | 19.39 | 5.67 | | |
| SMBG/Male | 36 | 21.47 | 5.92 | | |
| FGM/Female | 44 | 25.30 | 5.70 | | |
| FGM/Male | 33 | 24.30 | 5.25 | 2.86 | 0.093 |

SMBG- self-monitoring of blood glucose, FGM- flash glucose monitoring, SD- standard deviation;

*ANOVA test

Correlation between behavior and duration of disease is negative, but significant ($P=0.038$), see Table 8 and Figure 4

Table 8. Correlation between behavior and duration of T1DM

| Duration of T1DM (years) and behavior | |
|---------------------------------------|-------|
| R | -0.17 |
| P* | 0.038 |

T1DM- type 1 diabetes mellitus;

* Chi-square test

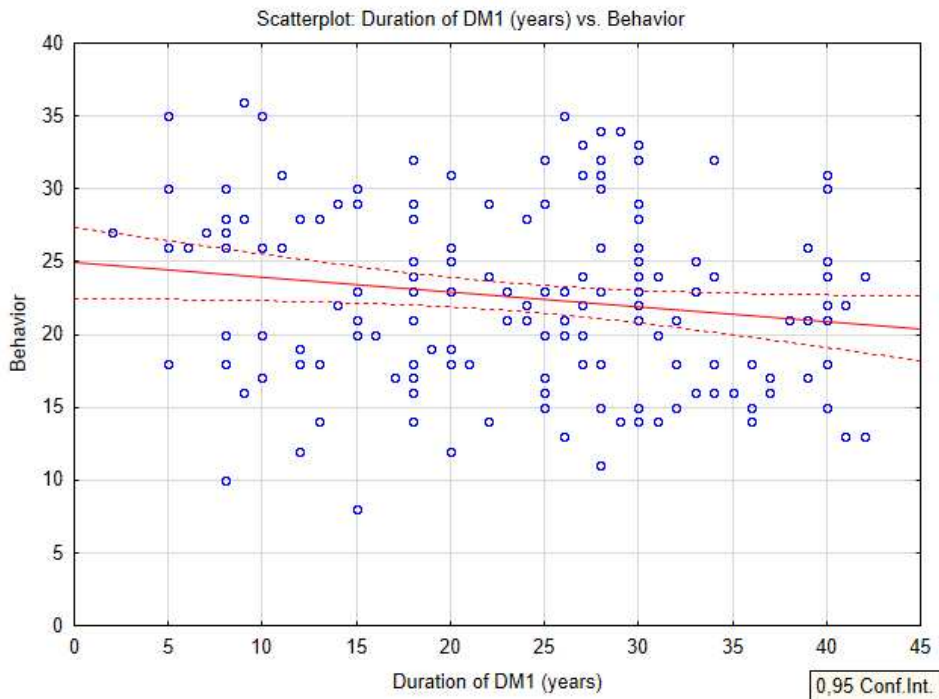


Figure 4. Duration of T1DM vs. behavior

Worry

Worry is measured by answers given by the patients on the last 16 questions in the questionnaire. Table 9 shows the difference in worry between patients on SMBG and FGM. On average, patients using SMBG have 0.97 points higher results than the ones using FGM. There is no statistical significant difference in worry for patients on SMBG and FGM ($P=0.664$), see Figure 5 and Table 10.

Table 9. Descriptive statistics for worry between patients on SMBG and FGM according to answers from the questionnaire

| | SMBG | | | | | FGM | | | | |
|--------------|----------|---------------|-----------|---------------|------------|----------|---------------|-----------|---------------|------------|
| | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 |
| Q11 | 40 | 16 | 12 | 6 | 6 | 43 | 9 | 12 | 7 | 6 |
| | 50.00 | 20.00 | 15.00 | 7.50 | 7.50 | 55.84 | 11.69 | 15.58 | 9.09 | 7.79 |
| Q12 | 36 | 24 | 9 | 5 | 6 | 44 | 6 | 10 | 7 | 10 |
| | 45.00 | 30.00 | 11.25 | 6.25 | 7.50 | 57.14 | 7.79 | 12.99 | 9.09 | 12.99 |
| Q13 | 44 | 18 | 11 | 5 | 2 | 51 | 10 | 8 | 5 | 3 |
| | 55.00 | 22.50 | 13.75 | 6.25 | 2.50 | 66.23 | 12.99 | 10.39 | 6.49 | 3.90 |
| Q14 | 34 | 29 | 13 | 3 | 1 | 65 | 5 | 3 | 2 | 2 |
| | 42.50 | 36.25 | 16.25 | 3.75 | 1.25 | 84.42 | 6.49 | 3.90 | 2.60 | 2.60 |
| Q15 | 27 | 29 | 8 | 9 | 7 | 41 | 12 | 10 | 3 | 11 |
| | 33.75 | 36.25 | 10.00 | 11.25 | 8.75 | 53.25 | 15.58 | 12.99 | 3.90 | 14.29 |
| Q16 | 53 | 9 | 10 | 6 | 2 | 60 | 5 | 5 | 3 | 4 |
| | 66.25 | 11.25 | 12.50 | 7.50 | 2.50 | 77.92 | 6.49 | 6.49 | 3.90 | 5.19 |
| Q17 | 42 | 17 | 10 | 6 | 5 | 48 | 10 | 9 | 3 | 7 |
| | 52.50 | 21.25 | 12.50 | 7.50 | 6.25 | 62.34 | 12.99 | 11.69 | 3.90 | 9.09 |
| Q18 | 29 | 29 | 8 | 7 | 7 | 39 | 14 | 10 | 5 | 9 |
| | 36.25 | 36.25 | 10.00 | 8.75 | 8.75 | 50.65 | 18.18 | 12.99 | 6.49 | 11.69 |
| Q19 | 27 | 31 | 11 | 10 | 1 | 46 | 6 | 10 | 4 | 11 |
| | 33.75 | 38.75 | 13.75 | 12.50 | 1.25 | 59.74 | 7.79 | 12.99 | 5.19 | 14.29 |
| Q20 | 30 | 28 | 10 | 11 | 1 | 56 | 3 | 7 | 5 | 6 |
| | 37.50 | 35.00 | 12.50 | 13.75 | 1.25 | 72.73 | 3.90 | 9.09 | 6.49 | 7.79 |
| Q21 | 35 | 30 | 9 | 4 | 2 | 57 | 6 | 6 | 4 | 3 |
| | 43.75 | 37.50 | 11.25 | 5.00 | 2.50 | 75.00 | 7.89 | 7.89 | 5.26 | 3.95 |
| Q22 | 35 | 26 | 11 | 7 | 1 | 30 | 10 | 9 | 8 | 20 |
| | 43.75 | 32.50 | 13.75 | 8.75 | 1.25 | 38.96 | 12.99 | 11.69 | 10.39 | 25.97 |
| Q23 | 25 | 29 | 15 | 9 | 2 | 37 | 11 | 11 | 5 | 13 |
| | 31.25 | 36.25 | 18.75 | 11.25 | 2.50 | 48.05 | 14.29 | 14.29 | 6.49 | 16.88 |
| Q24 | 46 | 16 | 9 | 7 | 2 | 54 | 9 | 5 | 3 | 6 |
| | 57.50 | 20.00 | 11.25 | 8.75 | 2.50 | 70.13 | 11.69 | 6.49 | 3.90 | 7.79 |
| Q25 | 26 | 23 | 21 | 7 | 3 | 44 | 12 | 8 | 4 | 9 |
| | 32.50 | 28.75 | 26.25 | 8.75 | 3.75 | 57.14 | 15.58 | 10.39 | 5.19 | 11.69 |
| Q26 | 13 | 35 | 19 | 8 | 5 | 30 | 15 | 9 | 12 | 11 |
| | 16.25 | 43.75 | 23.75 | 10.00 | 6.25 | 38.96 | 19.48 | 11.69 | 15.58 | 14.29 |
| | N | Median | SD | Median | IQR | N | Median | SD | Median | IQR |
| Worry | 80 | 16.29 | 14.06 | 12.0 | 6-21 | 77 | 15.32 | 13.48 | 12.00 | 4-25 |

SMBG- self-monitoring of blood glucose, FGM- flash glucose monitoring, SD- standard deviation, IQR- interquartile range

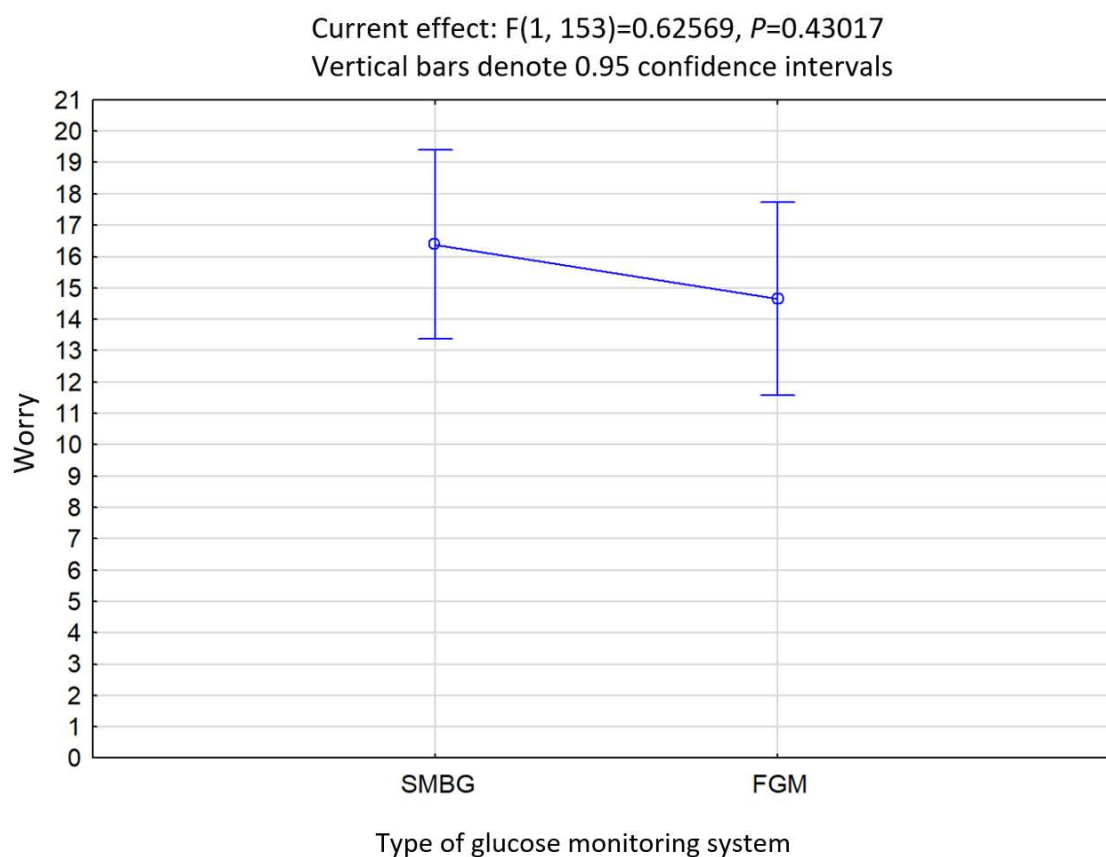


Figure 5. Worry according to type of glucose monitoring system used (SMBG and FGM)

Table 10. Descriptive statistics for worry between patients using SMBG and FGM

| | Worry | | | | | |
|-------------|-------|-------|--------|------|------|------------|
| | Mean | SD | Median | IQR | T | <i>P</i> * |
| SMBG | 16.29 | 14.06 | 12.00 | 6-21 | | |
| FGM | 15.32 | 13.48 | 12.00 | 4-25 | 0.43 | 0.664 |

SMBG- self-monitoring of blood glucose, FGM- flash glucose monitoring, SD- standard deviation, IQR- interquartile range;

*T-test

When comparing worry related to the type of glucose monitoring system the patient is using ($P=0.430$) and gender ($P=0.098$), no statistical significant difference can be found, see Table 11. However, females using FGM reported the highest incidence of worry (Mean=19.30), (SD=13.98), while males using FGM have the lowest values (Mean=10.03), (SD=11.13), see Table 11 and Figure 6. There is a statistical significant difference between the groups ($P=0.010$).

Table 11. Descriptive statistics for worry between males and females using SMBG and FGM

| Type of Glucose Monitoring/Gender | N | Mean | SD | F | P* |
|-----------------------------------|----|-------|-------|------|-------|
| SMBG | 80 | 16.29 | 14.15 | | |
| FGM | 77 | 15.32 | 13.57 | 0.63 | 0.430 |
| F | 88 | 17.34 | 14.15 | | |
| M | 69 | 13.87 | 13.26 | 2.77 | 0.098 |
| SMBG/Female | 44 | 15.39 | 14.20 | | |
| SMBG/Male | 36 | 17.39 | 14.21 | | |
| FGM/Female | 44 | 19.30 | 13.98 | | |
| FGM/Male | 33 | 10.03 | 11.13 | 6.68 | 0.010 |

SMBG- self-monitoring of blood glucose, FGM- flash glucose monitoring, SD- standard deviation;

*ANOVA test

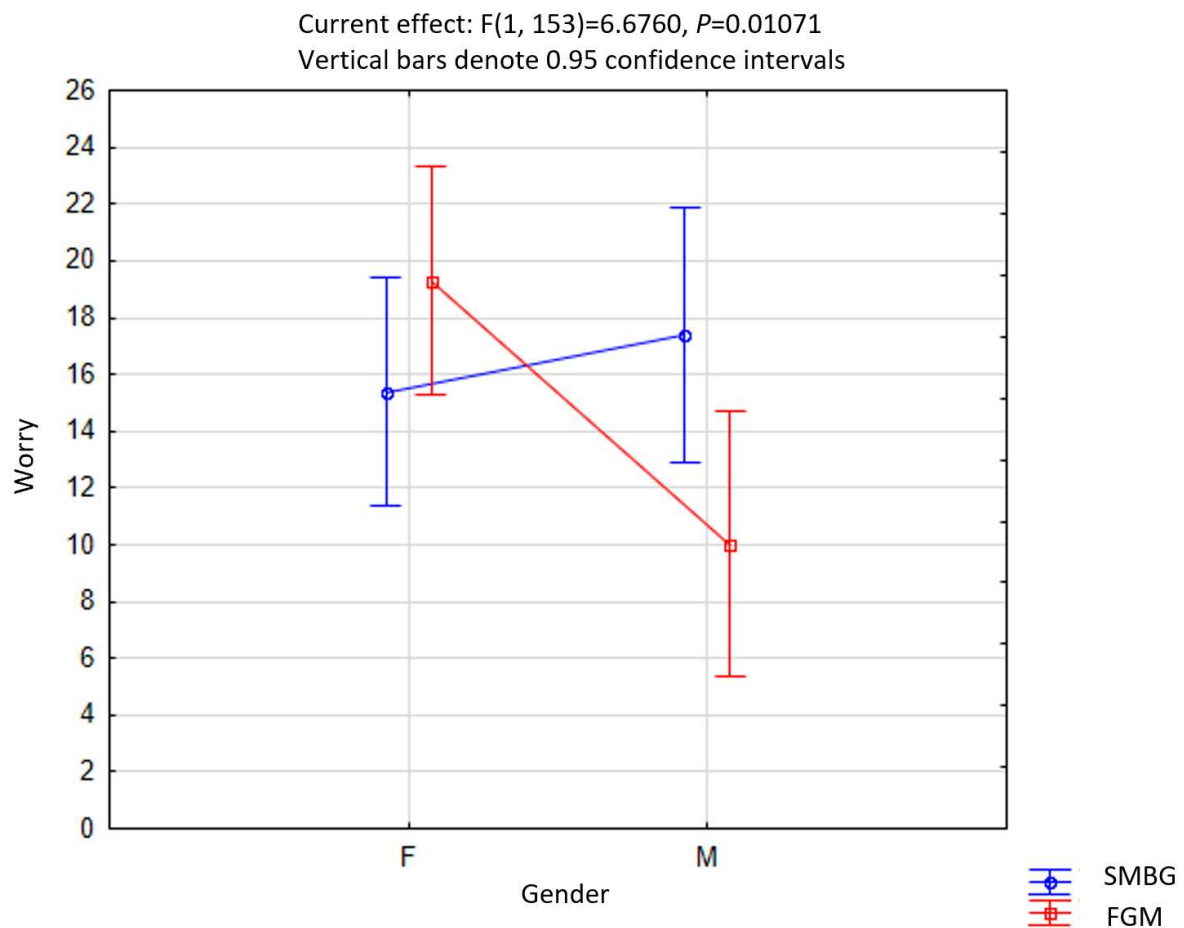


Figure 6. Worry between males and females using SMBG and FGM

There is no correlation between worry and the duration of the disease and there is no statistical significant difference ($P=0.203$), see Figure 7 and Table 12.

Table 12. Correlation between worry and duration of T1DM

| Duration of T1DM (years) and Worry | |
|------------------------------------|-------|
| R | -0.10 |
| P* | 0.203 |

T1DM- type 1 diabetes mellitus;

*Chi-square test

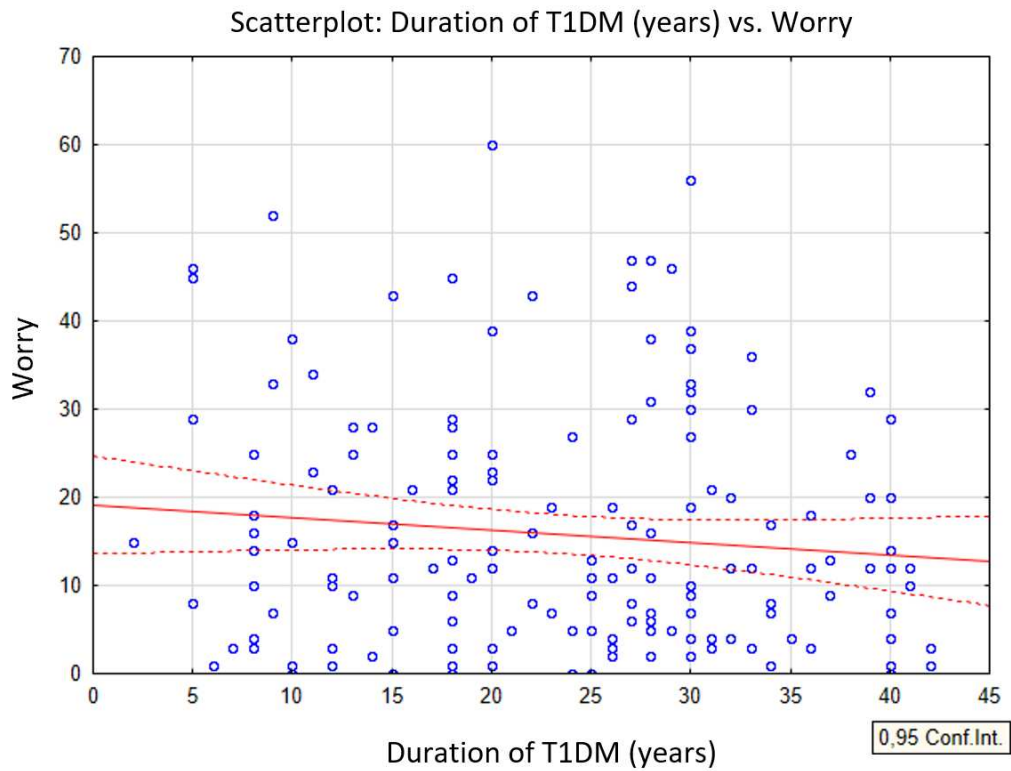


Figure 7. Duration of T1DM vs. worry

5. DISCUSSION

Hypoglycemia can lead to a wide range of symptomatic, cognitive, physiological and social consequences, but also development of possible phobic avoidance behavior (42). There have been some studies quantifying the fear of hypoglycemia, similar to the quantification of metabolic control through HbA1c, and thereby making a definition of abnormally elevated or suppressed fear (42, 43, 50).

In our study we see that there is no statistical significant difference in total number of patients using SMBG and FGM, as well as no statistical significant difference between males and females in these groups. This is to be expected, and important, it indicates that there is no significant difference in the number of patients and gender distribution according to type of blood glucose monitoring system used. We also see that our two groups (SMBG and FGM) show no statistical significant difference in age of the patient and total duration of the disease. They represent homogenous population of type 1 diabetics.

Further, we found that there is a statistical significant difference in level of behavior between the patients using SMBG and FGM. Patients using FGM answered to the questions related to behavior with higher points than the patients using SMBG. These findings were not expected, but can reflect upon how the level of behavior was measured. Since we measured the level of behavior by questions related to how patients behave in everyday activities; like checking their blood glucose level more frequently before participating in meetings, always consuming carbohydrates when first sign of hypoglycemia is felt, etc. These findings can potentially be explained by the fact that patients using FGM have a higher level of motivation for achieving minimal daily glycemic variability. The results can be affected by the patient's personality, compliance and expectations (43). Patients that use FGM have both an easier and faster way to confirm their blood glucose levels at any time in comparison to the patients using SMBG (6, 16, 18).

In a prospective observational study by Rouhard S *et al.* they evaluated the medium-term impact of flash glucose monitoring system (FGM) in a type 1 diabetic population. 248 patients were included, and they switched from conventional glucose monitoring to FGM. The patients filled in two questionnaires where one was based on the Hypoglycemia Fear Survey. "Behavior" score regarding hypoglycemia decreased from 5.7 ± 4.1 to 4.4 ± 3.6 points ($P < 0.001$) (44). These findings are different from the ones in our study.

In our study we found no statistical significant difference to level of behavior between males and females according to which type of glucose monitoring system they use. We did not expect these findings as males and females have different attitudes and behaviors related to

diabetic care. Females have a greater concern and interest for diabetes mellitus, but they are also more likely to perceive symptoms (45).

Further, we found that the correlation between behavior and total duration of T1DM is negative, but significant. This is a finding that was surprising to see, and indicates that the longer duration of the disease, the less care about the level of behavior is taken by the patient. Diabetes mellitus as a chronic disease is emotionally stressful in many aspects, and can potentially lead to physical and psychological fatigue. Lifestyle modifications and burnout symptoms might occur, and the severity of these symptoms is influenced by the duration of the disease (46).

However, patients with T1DM for a longer period of time are better educated and known with their own symptoms that appear in an episode of hypoglycemia. Over time, a pattern will be created, where the patient will take no immediate action as they might potentially know exactly which symptoms they are likely to experience at a specific blood glucose level, but also the consequences of these events (31). In a study by McCarthy MM *et al.* they found that in young adults (age 25 to <45 years) the number of reported episodes of severe hypoglycemia in past 3 months, and more reported daily blood glucose checks, were two factors associated with lower odds of HbA1c $\geq 7\%$. They reported that adults with diabetes mellitus type 1 across different developmental stages differ in their diabetes self-management behaviors and glycemic control. A number of developmental stage groups had similar predictors of poor glycemic control, the frequency of blood glucose checks, exercise and missed insulin doses. Since remaining predictors of poor glycemic control were distinct for each group, they stated that there is a need to take the patient's developmental stage into consideration when adjusting diabetes self-management education (47).

In our study we found no statistical significant difference for worry between the patients using SMBG and FGM. However, patients using SMBG answered to these questions with slightly higher points than the patients using FGM. These results can reflect upon potential limitation of our study. Our study groups might be too small size, but also other potential bias needs to be considered. The fact that we conducted the questionnaires during the pandemic of Covid-19 over phone calls with the patients, should be taken into consideration. Even though all information was explained carefully to each patient, performance of the questionnaires in paper format could have given different results.

However, when we compared worry related to the type of glucose monitoring system used by the patients and gender, we found no statistical significant difference. On the other hand, females using FGM reported the highest incidence of worry, while men using FGM have the lowest values, and we found a statistical significant difference.

A cross-sectional study by Liu J *et al.* investigated factors associated with behavioral and emotional aspects of fear of hypoglycemia among adults living with T1DM. 494 participants, with a total of 63% males were included in the study. The Hypoglycemia Fear Survey II-short form was used to assess the fear of hypoglycemia. Their findings showed that a past experience with severe hypoglycemia was associated with higher level of worry ($P<0.01$). Their regression models did not show consistent gender differences in fear of hypoglycemia. However, their results based on the HFS-II worry subscale, showed that females may be more worried about hypoglycemia than males. They found no significant difference in total fear of hypoglycemia scores by gender (48). This is different from our findings. However, another study by Gjerløw E *et al.* reported that women expressed more concerns about hypoglycemia than men. The highest mean scores were shown in the worry items like "become hypoglycemic while sleeping" in both males and females. However, the largest gender differences in mean scores, where women scored the highest, was shown in items like self-esteem (49).

We did not find any correlation between worry and the total duration of the disease, as well as there is no statistical significant difference. These are somewhat unexpected findings, especially since patients with diabetes mellitus are under stressful conditions and glycemic control throughout their lives. Diabetes mellitus can be linked to stress related to development of complications in the future, and a life living with a chronic disease (46).

In a study by Polonsky WH *et al.* with similarities to ours, no significant group differences in well-being, health status or hypoglycemic fear were observed. Further, no significant group differences were observed in hypoglycemic worry. However, they also included glycemic changes and its association with reduction in diabetes distress and hypoglycemic fear. They divided their subject sample according to type of glucose monitoring used by the patients, CGM (N=102) and SMBG (N=53). The participants were aged between 26-73 years, 45% were females and duration of the disease was 12 ± 14 years (50).

In another study by Boucher ES *et al.* they had a total of 64 participants, aged between 13-20 years. Participants were equipped with isCGM (N=33) or continued the use of SMBG (N=31). They measured the fear of hypoglycemia by the use Hypoglycemic Fear Survey (HFS), but again other variables were included, like HbA1c. After a period of six months, they found

no significant difference between the study groups on the fear of hypoglycemia. However, the users of isCGM facilitated more frequent glucose monitoring compared to SMBG (51). This is similar to our findings.

Considerations for future investigations could be to include more subjects to get a larger sample size. Research where comparing level of behavior and worry of patients using SMBG and FGM during a specific period of time, could be interesting to investigate, as well as including parameters like HbA1c and micro- and macrovascular complications of the disease. By including more variables, one can see whether a better glycemic variability can be obtained at the same time as detecting the fear of hypoglycemia. We recommend daily routine work incorporation of questionnaires about fear hypoglycemia in order to achieve better care of type 1 patient.

6. CONCLUSIONS

1. This study failed to show that the fear of hypoglycemia is smaller for patients with diabetes mellitus type 1 using FGM than the ones using SMBG, from an aspect of behavior. However, when worry is taken into account, we see that the level of fear is smaller for the patients using FGM than the ones using SMBG;
2. When considering the behavioral part of fear of hypoglycemia in patients with diabetes mellitus type 1, there is a smaller difference between males and females using FGM than the ones on SMBG, However, when worry is taken into account, there is a larger difference between males and females using FGM than the ones using SMBG;
3. The fear of hypoglycemia, from a behavioral perspective is smaller for patients having diabetes mellitus type 1 for a longer period of time. However, we were not able to detect any correlation between worry and duration of the disease in this study.

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8. SUMMARY

Objectives: The aim of the study is to compare the fear of hypoglycemia in patients with diabetes mellitus type 1 on self-monitoring of blood glucose (SMBG) and flash glucose monitoring (FGM). Different attitudes during episodes of hypoglycemia, both from an aspect perspective of behavior and worry, were investigated.

Materials and methods: This prospective observational study was carried out among patients with diabetes mellitus type 1 controlled at the University Hospital of Split. The questionnaires were conducted by phone from May to June 2020. The participation was anonymous and voluntary. 80 patients, 44 females and 36 males on SMBG were included. We also included 77 patients using FGM FreeStyle Libre sensor, 44 females and 33 males.

Results: We found no statistical significant difference in total number of patients using SMBG and FGM ($P=0.810$) nor between males and females ($P=0.787$). Patients using FGM are on average 5 years older and have 4 years less disease duration than the patients using SMBG, but this is not statistically significant ($P=0.385$) and ($P=0.094$). We found a statistical significant difference in behavior between patients on SMBG and FGM ($P<0.001$), but we did not find statistical significant difference in level of behavior between males and females according to which type of glucose monitoring system they use ($P=0.549$) and ($P=0.093$). Correlation between behavior and duration of disease is negative, but significant ($P=0.038$). We found no statistical significant difference in worry for patients on SMBG and FGM ($P=0.664$). When we compared worry related to the type of glucose monitoring system used ($P=0.430$), and gender ($P=0.098$), we could not find a statistical significant difference. Females using FGM reported the highest incidence of worry, while males using FGM have the lowest values. We found a statistical significant difference between the groups ($P=0.010$). In this study we were not able to find a correlation between worry and the duration of the disease, there is no statistical significant difference ($P=0.203$).

Conclusion: The fear of hypoglycemia, from an aspect of behavior, is bigger in the patients using FGM than for the ones using SMBG. However, from a perspective of worry, the fear of hypoglycemia is smaller in the patients using FGM than for the ones using SMBG. There is a smaller difference between males and females using FGM than the ones using SMBG, when considering the behavioral part about the fear of hypoglycemia. From a perspective of worry, there is a bigger difference between males and females using FGM than for the ones using SMBG. The fear of hypoglycemia, when considering behavior, is smaller for patient having diabetes mellitus type 1 for a longer period of time. We were not able to detect any correlation between worry and the duration of the disease in this study.

9. CROATIAN SUMMARY

Ciljevi: Cilj istraživanja je usporediti strah od hipoglikemije u bolesnika sa šećernom bolesti tipa 1 koji provode samokontrolu glukoze u krvi putem samomjerača (SMBG) i onih koji koriste senzor FreeStyle Libre (FGM). Planirano je istražiti različite stavove koje pacijenti iskazuju tijekom epizoda hipoglikemije iz aspekta ponašanja i brige.

Materijali i metode: Ovo prospektivno opservacijsko istraživanje provedeno je među oboljelima od šećerne bolesti tipa 1 liječenih u KBC-u Split. Upitnici su provedeni putem telefonskih poziva u razdoblju od svibnja do lipnja 2020. Sudjelovanje je bilo anonimno i dobrovoljno. U istraživanju je sudjelovalo ukupno 80 pacijenata, 44 žene i 36 muškaraca na SMBG-u, dok je za pacijente koji koriste FGM FreeStyle Libre senzor uključen ukupan broj od 77, 44 žene i 33 muškarca.

Rezultati: Nije utvrđena statistička značajna razlika u ukupnom broju bolesnika koji su koristili SMBG i FGM ($P=0,810$) niti između muškaraca i žena ($P=0,787$). Bolesnici koji koriste FGM u prosjeku su stariji od 5 godina i imaju 4 godine manje trajanja bolesti od bolesnika koji koriste SMBG, ali to nije statistički značajno ($P=0,385$) i ($P=0,094$). Utvrđena je statistička značajna razlika u ponašanju između bolesnika na SMBG i FGM ($P<0.001$), ali nismo pronašli statističku značajnu razliku u razini ponašanja između muškaraca i žena prema kojoj vrsti sustava praćenja glukoze koriste ($P=0.549$) i ($P=0.093$). Korelacija između ponašanja i trajanja bolesti je negativna, ali značajna ($P=0,038$). Nije utvrđena statistička značajna razlika u zabrinutosti za bolesnike na SMBG-u i FGM-u ($P=0,664$). Kada smo usporedili zabrinutost povezanu s vrstom korištenog sustava za praćenje glukoze ($P=0,430$) i spolom ($P=0,098$), nismo mogli pronaći statističku značajnu razliku. Žene koje koriste FGM pokazale su najveći stupanj zabrinutosti, dok muškarci imaju najnižu zabrinutost. Utvrđena je statistička značajna razlika između skupina ($P=0,010$). U ovoj studiji nismo uspjeli pronaći korelaciju između brige i trajanja šećerne bolesti ($P=0,203$).

Zaključak: Strah od hipoglikemije, iz perspektive ponašanja, veći je u bolesnika koji koriste FGM nego kod onih koji koriste SMBG. Međutim, iz perspektive brige, strah od hipoglikemije je manji u bolesnika koji koriste FGM nego kod onih koji koriste SMBG. Postoji manja razlika između muškaraca i žena koji koriste FGM od onih koji koriste SMBG, kada se razmatra dio ponašanja u strahu od hipoglikemije. Iz perspektive brige, postoji veća razlika između muškaraca i žena koji koriste FGM nego kod onih koji koriste SMBG. Strah od hipoglikemije, kada se razmatra ponašanje, manji je za pacijenta koji ima šećernu bolest tipa 1 duže vrijeme. U ovoj studiji nismo uspjeli otkriti nikakvu povezanost između zabrinutosti i trajanja bolesti.

10. CURRICULUM VITAE

Personal information

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Education

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2015-2021 University of Split School of Medicine

Internship

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Language skills

Norwegian (mother tongue)

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Croatian (fluent)

11. SUPPLEMENTS

Supplement 1

NIKAD 0 – RIJETKO 1 – PONEKAD 2 – ČESTO 3 – UVIJEK 4

Ponašanje

1. Jedem veliki obrok pred spavanje
2. Izbjegavam samoću kada mi se čini da mi šećer pada
3. Kada mjerim šećer držim da je sigurnije kada je malo veći
4. Kada znam da ću neko vrijeme biti sam održavam šećer višim
5. Odmah pojedem nešto kada osjetim prvi znak niskog šećera
6. Kada mi je šećer niži smanjim dozu inzulina
7. Održavam šećer višim kada planiram sudjelovati na dužem sastanku ili zabavi
8. Nosim uvijek sa sobom šećer (kockicu i sl.)
9. Izbjegavam tjelovježbu kada mislim da mi je šećer nizak
10. Češće mjerim šećer kada planiram sudjelovati na dužem sastanku ili zabavi

NIKAD 0 – RIJETKO 1 – PONEKAD 2 – ČESTO 3 – UVIJEK 4

Brinem se

11. Da neću znati prepoznati niski šećer
12. Da neću imati pri sebi hranu, voće ili sok
13. Da ću pasti na javnom mjestu
14. Da ću sebe ili prijatelje u društvu osramotiti
15. Da ću imati epizodu hipoglikemije kada sam sam
16. Da ću izgledati lud ili pijan
17. Da ću izgubiti kontrolu
18. Da nikoga neće biti u blizini da mi pomogne u hipoglikemijskoj epizodi
19. Da ću imati hipoglikemiju kada vozim automobil
20. Da ću pogriješiti ili skriviti nesreću

21. Da će o meni loše govoriti i kritizirati me na poslu
22. Da ću imati teškoću jasno misliti kada sam u situaciji odgovoran za druge osobe
23. Da ću se osjećati prazne glave ili vrtoglavicu
24. Da ću slučajno ozlijediti sebe ili druge
25. Da ću trajno ozlijediti sebe ili narušiti svoje zdravlje
26. Da niski šećer utječe na važne poslove koje obavljam