Association of diabetes technology use and diabetes distress in adults with type 1 diabetes

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Association of diabetes technology use and diabetes distress in adults with type 1 diabetes

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My greatest aspiration is that my research contributes to a better understanding of the experiences people living with diabetes have.

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ABBREVIATIONS

App	Mobile application
BGM	Blood glucose monitoring
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DKA	Diabetic ketoacidosis
FPG	Fasting plasma glucose
HbA1c	Glycated hemoglobin
IP	Insulin pump
PAID	Problems Areas in Diabetes
PPG	Postprandial plasma glucose
PRO	Patient- reported outcome
RCT	Randomized controlled trial
SMBG	Self-monitoring blood glucose
T1DM	Type 1 diabetes
TAR	Time above range
TBR	Time below range
TIR	Time in range

1. INTRODUCTION

1.1. Type 1 diabetes

Type 1 diabetes mellitus (T1DM) is a chronic condition caused by the autoimmune destruction of insulin-secreting pancreatic β cells, characterized by severe insulin deficiency. T1DM accounts for approximately 5-10% of all cases of diabetes, with a global all-age prevalence of 9.5 per 10 000 and incidence which is estimated to be 15 per 100 000 (1). In 2022, there were 8.75 million (95.0% uncertainty interval 8.4–9.1) individuals worldwide with T1DM and both, the incidence and prevalence of T1DM have been increasing in recent decades (2). Overall annual increase is estimated to be around 3% and is most marked in children under the age of 15 years (3). Although the incidence peaks in puberty, T1DM affects all age groups. T1DM incidence varies around the world with some regions having much higher incidences than others as shown in Figure 1 (3).

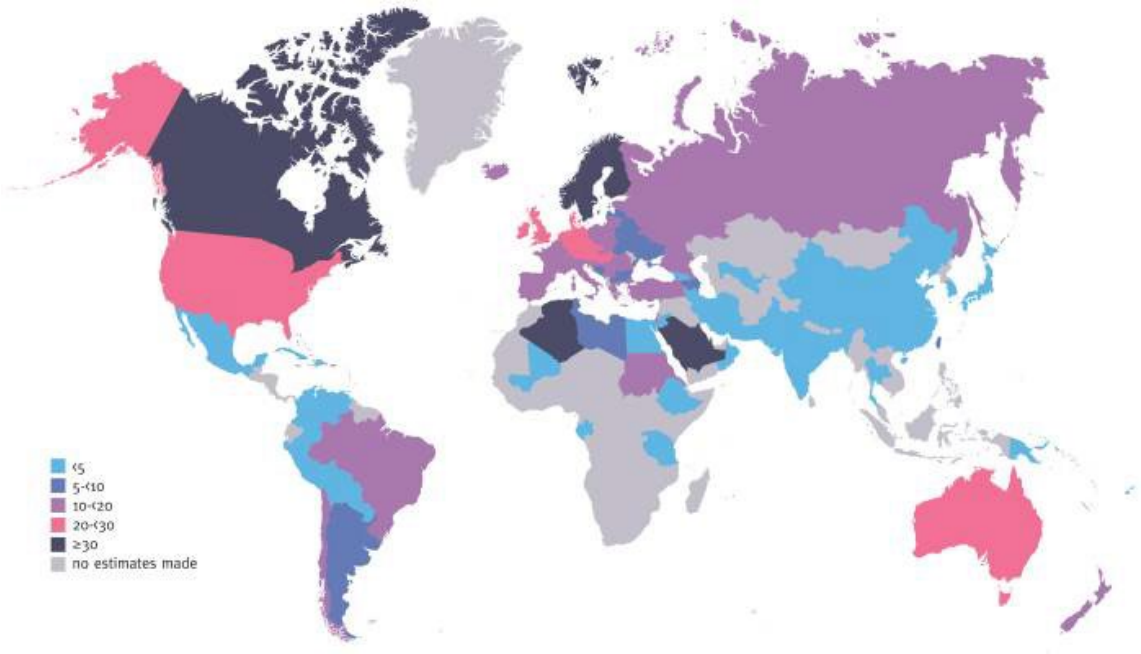


Figure 1. Incidence rates (per 100,000 population per annum) of type 1 diabetes in children and adolescents aged 0–14 years, adapted from IDF Diabetes Atlas, 10th edition

The discovery of insulin in 1922. transformed the lives of many people. The results of the landmark Diabetes Control and Complications Trial (DCCT) trial demonstrated the importance of glycemic management, achieving and maintaining glycemic control (4). The use of intensive insulin therapy that aimed to achieve blood glucose levels close to the people that are not suffering from diabetes, markedly reduces the risk of development and progression of long-term complications. Primary development of retinopathy was reduced by 75% and progression of retinopathy slowed by 54%, the development of microalbuminuria by 39% and clinical neuropathy by 60%. These benefits persisted beyond the end of the trial despite equivalent glucose levels in the two groups (HbA1c ~8% in the post-trial period) (5).

The aim of diabetes care and management is to support people with T1DM to live a long and healthy life (6). The management strategies to achieve this aim include treatments and devices that effectively deliver exogenous insulin as safely as possible. It implies maintaining blood glucose in a near-normal state, while avoiding episodes of hypoglycemia, thus preventing the development and progression of diabetes complications. Moreover, management approaches should minimize the psychosocial burden of living with T1DM and, consequently, diabetes-related distress, while promoting psychological well-being. T1DM is a demanding condition that requires ongoing care that implies the patient's engagement in self-management and adherence to specific dietary and physical activity recommendations (6).

The cornerstone of T1DM therapy is insulin replacement. Most people with T1DM should use regimens that mimic physiology as closely as possible and allow flexibility in terms of mealtimes and activity levels. This is best achieved with either multiple daily injections of subcutaneous basal insulin analogues and mealtime rapid-acting insulin analogues or with continuous subcutaneous insulin infusion (CSII) of a rapid-acting insulin analogue via insulin pump (IP), delivered as continuous basal insulin combined with manual mealtime boluses (6). Despite developments in insulin and its delivery over the last 100 years, many people with T1DM do not reach the glycemic targets necessary to prevent or slow the progression of diabetes complications.

1.1.1. Management and complications of type 1 diabetes

For most adults with type 1 diabetes, an HbA1c goal of <7.0% without significant hypoglycemia is recommended (6). To achieve this HbA1c, a pre-prandial capillary plasma glucose target of 4.4–7.2 mmol/L (80–130 mg/dL) and postprandial capillary plasma glucose of < 10.0 mmol/L (180 mg/dL) is recommended for most people with diabetes. Goals should be individualized and less stringent HbA1c goals (such as <8.0%) may be considered for individuals with limited life expectancy or where the harms of treatment are greater than the benefits. Person's psychosocial needs and a reduction in diabetes distress if elevated should be taken into consideration when setting individual treatment goals. Although HbA1c is a surrogate marker which informs on average blood glucose during the preceding 3 months, it does not provide information on glycemic variability and hypoglycemia. This limitation has recently been overcome by introducing new glycemic control metrics that complement HbA1c and blood glucose measurement assessments from continuous glucose monitoring (CGM) (7).

Hypoglycemia is the main limiting factor in the glycemic management of T1DM. It is the most common acute complication of glucose-lowering therapy and is associated with poor outcomes and quality of life in people living with diabetes. Hypoglycemia in patients with diabetes can be defined as all episodes of an abnormally low plasma glucose concentration, with or without symptoms, that expose the individual to harm. Level 1 hypoglycemia is defined as blood glucose <3.9 mmol/L (70 mg/dL), and level 2 hypoglycemia, defined as blood glucose <3 mmol/L (54 mg/dL) is considered as clinically important hypoglycemia. Level 3, or severe hypoglycemia requires the assistance of another person for recovery. Patients with T1DM report an average of two to five episodes of severe hypoglycemia per year (8). Clinically important hypoglycemia detected with CGM is much more common than prior estimates based on self-reported events or finger-stick glucose assessments (9). More than half of episodes of iatrogenic hypoglycemia, including severe hypoglycemia, occur during the night (10). Risks for hypoglycemia, particularly Level 3 hypoglycemia, include longer duration of diabetes, older age, history of recent Level 3 hypoglycemia, alcohol ingestion, exercise, lower education levels and lower household incomes (11). Recurrent hypoglycemia is a strong risk factor for impaired awareness of hypoglycemia which, in turn, increases the risk of severe hypoglycemia six-fold in people with T1DM (12).

Hypoglycemia causes neurogenic (autonomic) and neuroglycopenic symptoms. The neurogenic symptoms include tremor, palpitations, and anxiety (catecholamine mediated, adrenergic) and

sweating, hunger, and paresthesia (acetylcholine mediated, cholinergic) (10). The neuroglycopenic symptoms include dizziness, weakness, drowsiness, delirium, confusion, and, at lower plasma glucose concentrations, seizure and coma. The extent to which recurrent hypoglycemia causes cognitive impairment is uncertain and may depend on patient age (13).

Hypoglycemia can be a frightening, unpleasant, and potentially lethal complication of diabetes, and therefore, concerns about hypoglycemia are understandable. Fear of hypoglycemia is defined as an excessive worry/discomfort that interferes with diabetes management through behavioral avoidance and distress. Patients who had a frightening episode of severe hypoglycemia in the previous year often became so fearful that they kept their blood glucose excessively high for several months afterwards (14). In turn, fear of hypoglycemia can lead to behaviors that are detrimental to diabetes management (15).

Hypoglycemia, particularly nocturnal or severe episodes, has been associated with reduced health-related quality of life and severe hypoglycemia has been associated with diabetes distress and fear of hypoglycemia(16). Reducing the risk of hypoglycemia involves patient education and empowerment, frequent blood glucose monitoring (BGM) or CGM, individualized glycemic goals, flexible and rational insulin (and other drug) regimens, and ongoing professional guidance and support.

Diabetic ketoacidosis (DKA) is a life-threatening but preventable acute complication of T1DM, characterized by hyperglycemia, metabolic acidosis and ketosis. The underlying cause is insulin deficiency, either absolute (new diagnosis of T1DM or omission of insulin in those with diagnosed disease) or relative (increased counter-regulatory hormones due to infection or other stressors without an adequate increase in insulin doses). The prevalence of DKA is more often in younger children, it can be the initial presentation of diabetes in 15 to 70% of patients. European registry data suggests, adults with T1DM had DKA at a rate of 2.5 per 100 patient-years (17).

Hyperglycemia defines diabetes and is directly related to the incidence of complications. Chronic hyperglycemia is detrimental and while both basal glucose increments and postprandial excursions contribute to the overall glycemic status, the achievement of optimal postprandial glucose control remains another great challenge in patients with T1DM. Postprandial hyperglycemia is the result of many factors, including the characteristics of insulin therapy. It contributes to individual glucose variability and overall glucose control assessed by HbA1c, the

control of postprandial hyperglycemia is a recognized important therapeutic goal in the management of T1DM according to various International Guidelines.

The injurious effects of prolonged hyperglycemia lead to the development of long-term complications: macrovascular (coronary artery disease, peripheral arterial disease, and stroke) and microvascular (diabetic nephropathy, neuropathy, and retinopathy). According to the results of global observational survey, high rates of long-term complications were reported in people with T1DM: microvascular complications in almost 50% and macrovascular complications in 5.9% (18).

Risk of developing microvascular complications is proportional to both the magnitude and duration of hyperglycemia. Retinal endothelial cells, mesangial cells in the glomerulus and Schwann cells in the peripheral nerves are sensitive to elevated glucose concentration, and as a result of chronic hyperglycemia, cell damage occurs with the consequent development of retinopathy, neuropathy and nephropathy. Diabetes increases the likelihood of atherosclerotic plaque formation thus the risk that an individual will develop cardiovascular disease which is the primary cause of death in people with either type of diabetes (19).

Intensive treatment to the lowest safe targets of HbA1c is associated with significantly decreased rates of development and progression of microvascular complications as described previously but also macrovascular complications. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study demonstrated that during 17 years of prospective analysis, intensive treatment of T1DM is associated with a 42% risk reduction in all cardiovascular events and a 57% reduction in the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease (20).

Complications associated with diabetes have a considerable negative impact on patient wellbeing and economic contribution and place a large burden on healthcare and welfare systems. Although new and improved insulins, pumps and monitors have reduced the frequency and severity of diabetes complications, the lack of approved therapies that target the cause of the disease, autoimmunity, rather than the symptom, hyperglycemia, remains an unfortunate gap.

1.2. Diabetes distress

Stress is a natural human response that prompts us to address challenges and threats in our lives (21). Stress responses are normal reactions to environmental or internal perturbations and can be considered adaptive in nature. People living with chronic health conditions face additional stress related to the self-management of the condition.

Diabetes distress reflects the person's emotional response to the burden of living with a largely self- managed chronic disease and its complications (22). The term 'diabetes distress' first entered the psychosocial research in 1995, and since then is being recognized as one of the most common and important psychosocial barriers to effective diabetes care. In people with type 2 diabetes, it is a prominent condition with an overall prevalence of 36%. Some studies indicate that elevated diabetes-related distress was experienced by 20–40% of people with T1DM, suggesting a widespread clinical problem in this population as well (6,23).

Diabetes distress is the personal, often hidden side of diabetes: it reflects the unique emotional burdens and strains that individuals with diabetes may experience as they struggle to keep blood glucose levels within range. Chronically elevated blood glucose levels may lead to persistent fatigue, which can exacerbate depressed mood. Similarly, frequent hypoglycemic episodes can be exhausting, discouraging, and potentially quite frightening. The demands of diabetes care can have a potent impact on mood, both short-term and long-term. People with diabetes may feel hopeless about the possibility of avoiding long-term complications. It can be a difficult, emotional struggle to find a way to include diabetes in one's life (24).

High diabetes distress is characterized by frustration, feeling overwhelmed, and feeling hopeless and discouraged by the unceasing demands of diabetes. Diabetes-specific stressors for people living with T1DM, includes intensive care demands such as daily blood glucose monitoring, multiple insulin injections, and specific dietary and physical activity recommendations (6). Not understanding all these recommendations and a lack of compliance to treatment leads to poor glycemic control, chronic complications, and disrupted psychological and emotional well-being of patients and their families. In adults with T1DM diabetes distress is associated with suboptimal glycemic control and tends to be higher for women and relatively younger adults (22).

Due to the lack of prospective cohort studies following people with diabetes from diagnosis, focused on psychosocial issues, there are still few data on diabetes distress etiology and

development. Unlike type 2, the onset of T1DM is linked to a younger age and is often associated with stressful life events; psychosocial factors were shown to play a role in both its etiopathogenesis and disease management (25). People with T1DM require complex and lifelong self-management with insulin, dietary restrictions, physical exercise, and blood glucose monitoring. The chronic nature of the disease, constant worry about weight gain, hypoglycemia and the guilt of having poor glycemic control can cause marked emotional distress over the course of time and patients often feel overwhelmed and burned out. This can cause further motivational problems and poor adherence to treatment management (25).

Diabetes distress is conceptually distinct from depression and refers to the often-hidden fears, worries and frustrations that people experience while living with and managing diabetes on a daily basis. Still, prolonged, significant distress in chronic disease like T1DM is further associated with an increased prevalence of depressive symptoms (26).

1.2.1. Patient-reported outcomes and measures

Success of diabetes treatment has been linked to metabolic outcomes but also its impact on patient's satisfaction and quality of life. Patient- reported outcomes (PRO) measures are important in complementing clinical measures of treatment efficacy and safety. These health outcomes are reported directly by patients, generally in the form of a response to validated questionnaires to clinicians and healthcare providers. These responses play a crucial role in assessing patient's perspective for health, treatment satisfaction, or functional status associated with disease or ongoing treatment and care (27).

PRO instruments involve measurement of one or more aspects of a patient's health status based on information gathered directly from the patient, without interpretation by physicians or others. Patients provide information concerning the impact of an intervention or therapy from their perspective. PRO instruments offer a means for capturing how a patient feels or functions with respect to her/his health, condition, or disease (27).

Different concepts captured by patient-reported outcomes measures in clinical studies in people with diabetes are psychological well-being, health status and satisfaction (28). Measurement developed to assess those concepts can be either generic or disease-specific. Generic instruments refer to the patient's sense of his own health and well-being in the broad areas of physical, psychological, and social functioning and enable assessment and comparison across

various conditions but are not disease- or treatment-specific. They generally include many items that may be irrelevant and/or not specific to i.e. diabetes, they often exclude domains that are likely to be of great relevance and would contribute to a more sensitive measure. The evaluation of diabetes-specific instruments involves the assessment of diabetes-specific impairment along the three major dimensions: physical, psychological and social well-being. While diabetes specific instruments do not allow comparison with other conditions, they are likely to be 'more sensitive to change and responsive to subgroup differences than a generic instrument. This is because they have usually been informed by qualitative studies with people with diabetes (29).

For example, domains such as "enjoyment of food" and "dietary freedom" are unlikely to appear in generic measures, which focus usually on common indicators of health and illness, such as pain and mobility. Yet, in diabetes, "food intake" is often most challenging and difficult to manage for patients and clinicians alike (30). Often, clinical studies use a combination of generic and disease-specific measures, although a diabetes-specific measure is preferable in most circumstances (31).

The use of PRO measures continues to expand beyond clinical research in recognition of its potential to transform health care, as well as improve quality and safety by placing the patients at the center of decision making. This increasing usage of PRO measures has culminated in PROs attaining greater credibility amongst regulatory bodies who aim to standardize their use and interpretation in clinical trials. Both the US Food & Drug Administration and the European Medicines Agency have released guidelines that mandate the use of PRO measures to support labeling claims (32,33).

Usually, extensive research and testing process is required for the development of a PRO questionnaire. An instrument needs to be relevant to respondents, the disease and the intervention (34). To ensure that data from the questionnaires are meaningful, it is crucial that they have been validated, i.e. demonstrated to be reliable and valid measures of the specific concepts targeted. An instrument's 'psychometric properties' to be fulfilled are validity- and indicator that the questionnaire measures what it is intended to measure, reliability – an indicator of consistency of scores over time and responsiveness and sensitivity- ability to detect change when used in intervention studies (34).

Scales are also further translated and revalidated if they are not in the language required. The original questionnaire is usually translated into the required language by at least two independent translators working separately to produce two translations. The translators should

be fluent in the original and target languages and cultures and, ideally, one should be a subject expert and the other a language expert to ensure that language complexity as well as subject matter intricacies are not missed. After a single agreed version is created, the accuracy of translation is assured by backward translation into the original language. This should be done by at least two translators not involved in the previous exercise, to avoid the influence of familiarity with the original text. Finally, the backward translation is checked by the experts to ensure that it matches the original text (35).

Psychological well-being, one of the concepts that could be measured in diabetes, is related to quality of life but is specifically focused on aspects of mental health. Researchers frequently considered quality of life to be synonymous with psychological status and half of the ten most frequently used questionnaires to measure the quality of life (QoL) in diabetes since 1995 were measures of psychological well-being (24).

1.2.2. Problem Areas in Diabetes questionnaire

Problem Areas in Diabetes questionnaire (PAID) was introduced in 1995 as the first PRO to assess diabetes distress in adults. Today it is a widely used self-report measure of diabetes distress. This 20-item screening instrument is designed to measure emotional responsiveness specific to diabetes (36). PAID is brief, easy to score questionnaire. Results of this early research carried out on 451 female patients with both type 1 and type 2 diabetes, all of whom required insulin, were later replicated across different samples and cultures. The PAID showed high internal reliability, sound concurrent validity in terms of the pattern of correlations with a number of theoretically related measures (e.g., hypoglycemia fear, psychiatric symptoms), and evidence of predictive validity for adherence to treatment and blood glucose control(37)and could be employed to monitor change following an intervention (38).

While proved to be clinically useful, wider use of the PAID in everyday practice may be limited by its length. This was addressed by developing of shorter forms- five-item PAID for routine clinical and research use and a single-item measure that may be used as a rapid screen for diabetes-related emotional distress. A major strength of the PAID-5 is that it takes less than 1 min to complete, yet it has good ‘diagnostic’ performance. The PAID-1 focuses uniquely on concerns for the future. Both questionnaires were validated and showed good sensitivity and

specificity however additional psychometric testing of the PAID-5 and PAID-1 is suggested (39).

While the production of shorter, more reliable measures may help improve the response rate by decreasing the time and effort required to complete them, the widespread use has still been limited by the time-consuming and costly process of collection, analysis, of those paper format questionnaires. The internet opens many opportunities to help improve the feasibility and cost-effectiveness of collecting and aggregating both PRO measures and patient experience data. The potential to collect data in real-time to uncover poor clinical care and potential areas of excellence is an additional advantage over the infrequently administered paper-based tools. However, internet users are generally younger, of higher economic status, and therefore may not necessarily represent the target group (39).

Today, with several available instruments to measure different concepts, the complexity in usage of PROs marks the need for standardized measures and technology and digitalization in reporting outcome may ease the process and provide further consistent information.

Diabetes distress is prevalent, quantifiable, clinically relevant, does not self-resolve, and is responsive to treatment. There is a plethora of psychological interventions e.g., cognitive behavior therapy based, emotional, motivational, mindful-based interventions, education and counselling programs, coping skills training, and resilience interventions. Effectiveness of those interventions on mental health and quality of life in people living with T1DM were assessed through systematic review and meta-analysis published RCTs psychological interventions. Compared to standard diabetes care and education, psychological interventions were found to significantly improve quality of life and glycemic control albeit no depressive symptoms in people with T1DM (40). Given the fact that diabetes distress is associated with poorer glycemic control which can turn in more long-term diabetes complications, importance of psychological intervention should not be questionable.

Current T1DM guidelines recommend screening and prompt treatment of diabetes distress care (6) but lack specific steps clinicians can and should take. Diabetes distress assessments is often not incorporated into routine care and as such not effectively treated. Clinicians engaged in managing people with diabetes need to understand the psychological issues that may impact diabetes management, recognize diabetes distress and the burdens, fears, and threats that arise from the challenges of living with diabetes, have good communication skills and be able to refer to specialized mental health services where appropriate. This may require additional efforts in

educating health care teams to provide psychosocial care as an integral component of diabetes care as well as changes to current service provision, for example, inviting people with diabetes to complete standardized questionnaires prior to their consultation. Specific diagnostic tools, in a form of validated questionnaires, for screening and assessing diabetes-related distress are being developed and are available in multiple languages guidelines (6).

Recently, a working group from the International Consortium for Health Outcomes Measurement (ICHOM) made recommendations for a standard set of practical and validated psychosocial measures, and PAID scale is recommended for quantifying diabetes distress (41).

Providing approaches, treatments and devices that minimize the psychosocial burden of living with T1DM and, consequently, diabetes-related distress, while promoting psychological wellbeing has been recognized as one of the goals of type 1 management (6).

1.3. Diabetes technology

Diabetes technology is the devices, hardware, and software that persons with diabetes use to help manage blood glucose (42). Such technology includes pens or pumps that administer insulin and meters or continuous glucose monitors that measure blood glucose levels, and, more recently, mobile applications.

Diabetes technology, when coupled with education, has a number of potential benefits and can improve the lives and health of people with diabetes. However, there are barriers to adoption and the optimal use. Some of those are: restricted availability that can reduce access to certain tools, data privacy that can cause people with diabetes to be hesitant to use digital tools, requirement of digital literacy that can limit use in certain populations, cost, sustainability and integration with healthcare systems. The most important component in all of these systems is the person living with diabetes. The type and selection of devices should be individualized based on a person's specific needs, preferences, and skill level (42).

1.3.1. Glucometers

Regular glucose monitoring allows individuals with diabetes to self-control and individually adjust their insulin treatment, to guide their insulin dosage, food intake, while assessing their

glycemic control. Historically, glucose concentration was assessed from the urine detecting only glucose levels when the renal threshold for glucose was reached. The development of glucometers for personal use started in 1980s and nowadays, handheld glucometers are used to measure glucose concentration from capillary. Frequent self-monitoring blood glucose (SMBG) is considered a key component of effective treatment and daily management of individuals on insulin therapy. While increased testing frequency in individuals with T1DM is associated with better glycemic control (lower HbA1c) (43), frequent measurements are often not feasible and can be distressing. Seeing high or low glucose values can evoke feelings of frustration, anxiety and guilt, leading many people with T1DM to measure less often than needed (44).

Apart from the invasiveness and pain of the measurement procedure itself, the disadvantage of this method is that it shows only the current glucose concentration and does not provide insight into the daily oscillations of glycemia. As blood is sampled intermittently, with the usual number of 4-6 measurements a day, SMBG fails to expose ongoing glucose fluctuations. By not having complete insight into glycemic variability, presence of hypoglycemia, asymptomatic and nocturnal, can often remain unrecognized. This drawback is being addressed with the introduction of CGM devices available commercially since 2006 (44).

1.3.2. Continuous glucose monitoring

Nowadays, CGM devices make the management of T1DM much easier. CGM enables monitoring of blood glucose for 24 h, during the night and day, in fasting and postprandial state. Using CGM, patients are aware of their current glucose level and know when to intervene; when to give a correction bolus, and when to prevent hypoglycemia.

Continuous glucose monitoring devices measure glucose levels continuously from interstitial fluid. By measuring glucose levels in the interstitial fluid in real-time with data readouts in real-time or via intermittent scanning, CGM devices can provide a visual representation of blood glucose data in the form of an ambulatory glucose profile for the identification of glycemic trends and patterns. CGM systems consist of a disposable sensor that measures glucose level (usually at intervals of 1–5 min), and a transmitter attached to the sensor that sends or/and stores the sensor values to a display device using Bluetooth. To effectively use CGM data, standardized metrics, graphical visualization (e.g. ambulatory glucose profile) and clear clinical targets are required. Currently, there are two types of CGM devices; real-time CGM provides a

continuous value of current glucose and trends to a receiver, mobile app, smartwatch, or pump. It can be set to hypoglycemia/hyper-glycemia threshold alarms. Intermittently scanned CGM requires the glucose level to be determined by scanning a small reader or smartphone across the transmitter at least every 8 h in order not to lose the glucose data recorded. Real-time CGM can be coupled to an insulin pump allowing insulin therapy management in a closed loop (automatic delivery system or hybrid closed-loop).

All currently available devices can be uploaded to an internet cloud to allow people with diabetes and healthcare professionals to easily view the data at or between clinic visits. The accuracy and precision of the interstitial glucose values reported by these devices is mainly evaluated by the mean absolute relative difference (MARD), i.e., the mean difference between interstitial and blood glucose values, most often over 24 h. It is well accepted that this MARD is variable from one sensor to another, and for the same sensor according to the range of glucose and other factors of variability (calibration, rate of change in glucose, several drugs, site of sensor installation, remaining sensor life) (45).

CGM reveals new parameters seen in an ambulatory glucose profile report. Those parameters are the proportion of time spent on the specific blood glucose ranges like time-in-range (TIR), time below range (TBR) and time above range (TAR), parameters of glucose variability like the coefficient of variation (% CV) and standard deviation (SD), a glucose management indicator (GMI) and average sensor glucose. One of the most used parameters is TIR, a metric that complements HbA1c in glycemic assessment (6).

TIR is defined as 3.9-10 mmol/l (70-180 mg/dL) in most adults TBR as below 3.9 mmol/l (70 mg/dL). TIR correlates well with HbA1c(46). An international consensus recommends for most adults with T1DM, a target TIR above 70% with TBR less than 4% (with <1% <3.0 mmol/l) and TAR <25% (<5% measurements >13.9 mmol/l) (7).

CGM devices are increasingly popular, affordable, reliable in improving HbA1c, and overcome many of the glucometers' limitations. CGM-derived metrics are now incorporated into the management of patients with diabetes (7). CGM devices are recommended for diabetes management in adults and youth on multiple daily injections, subcutaneous insulin infusion or basal insulin (47). T1D Exchange Registry data informed that about 30% of people with T1DM in the US (age 1-93) use CGM (48). Although there are geographical disparities in adoption in clinical practice, CGM has become a standard for glucose monitoring for most adults with T1DM.

Using CGM without confirmatory SMBG measurements is as safe and effective as using CGM adjunctive to SMBG (49). Large randomized studies have shown an improvement in HbA1c, reduced time spent in hypoglycemia and hyperglycemia, and a reduction in the number of moderate and severe hypoglycemia in adults with T1DM using CGM as compared to conventional self-monitoring of blood glucose, irrespective of insulin regimen (9,50). The beneficial effect is particularly visible in people with impaired hypoglycemia awareness (51).

Recent evidence supports an association between CGM-derived TIR and microvascular complications among patients with T2DM. However, CGM still lacks solid direct evidence for its relation to the chronic complications of diabetes (52).

1.3.3. Insulin pumps

The administration of insulin with an insulin pump (continuous subcutaneous insulin infusion [CSII]) was introduced 40 years ago (53). The CSII infuses a short-acting, rapid acting, or ultrarapid-acting insulin analogue to subcutaneous tissue via self-inserted catheters at slow and variable basal rates to match the individual's needs, and additional bolus doses to cover meals and correct hyperglycemia (54). The pump is a battery-powered programmable device that holds multiple settings that can be tailored to each individual specifically (Figure 2).

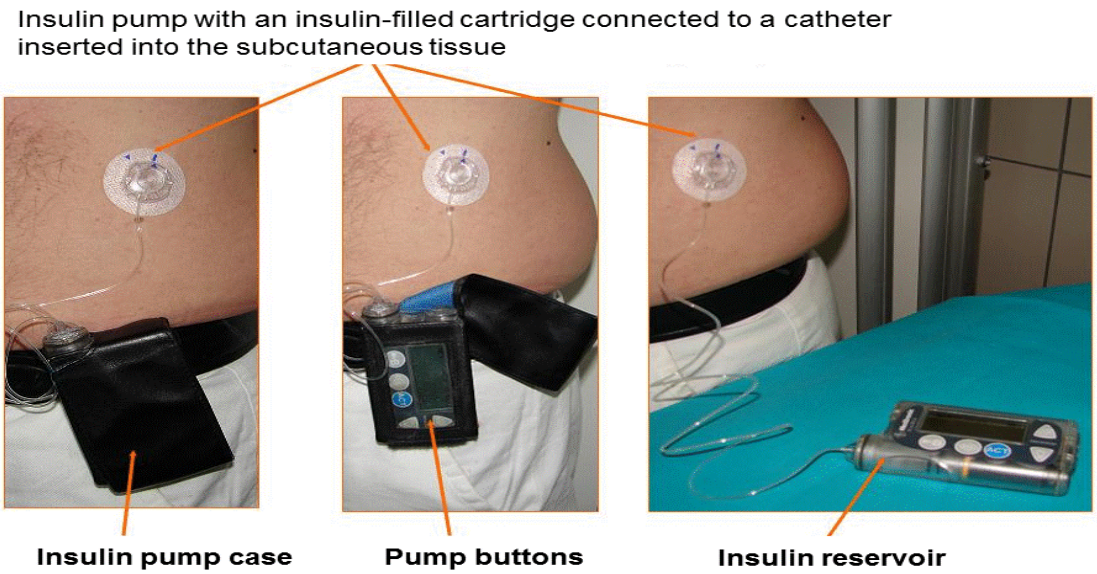


Figure 2. Insulin pump
Photos courtesy of Assist. Prof. Maja Baretić

Advances in insulin pump technology have led to the development of more user-friendly and efficient devices. These advancements include features like CGM integration, automated insulin delivery (closed-loop systems), smartphone connectivity, and data-sharing capabilities. These features enhance convenience, accuracy, and overall patient experience. Sensor Augmented Pumps are devices that integrate two independent technologies into one system, an insulin pump and a real-time CGM system (55). More recently, control algorithms were incorporated in sensor-augmented pumps, allowing the discontinuation of insulin delivery in the event of hypoglycemia ("low-suspend") or when hypoglycemia is predicted by the algorithm (predictive low-glucose insulin suspend). In randomized controlled trials (RCT)s, it has been demonstrated that the utilization of predictive low-glucose insulin suspend system technology reduces exposure to hypoglycemia (56).

Insulin pump therapy in people with T1DM offers the potential to improve glycemic control and may help to reduce long-term diabetes complications as well as the risk of acute complications, such as severe hypoglycemia and diabetic ketoacidosis (57). Systematic review of clinical trials and observational studies indicates that adults on pump therapy have reduced fear of hypoglycemia, enjoy greater flexibility in lifestyle and report better quality of life, when compared to multiple daily injections (58).

Complications of the pump can be caused by issues with infusion sets (occlusion), which place individuals at risk for ketosis and DKA. Other pump skin issues included lipohypertrophy or, less frequently, lipoatrophy and pump site infection. Common barriers to pump therapy adoption in children and adolescents are concerns regarding the physical interference of the device, discomfort with the idea of having a device on the body, therapeutic effectiveness, and financial burden (59).

An insulin pump is considered a safe and effective treatment option, whose adoption in practice is rising due to the development of new, more advanced devices (60). Recent data from a large registry including almost 100 000 individuals with T1DM reported an increase from 1% to 53% in a 20-year observational period (61). Insulin pump therapy alone with or without sensor-augmented pump low glucose suspend feature should be offered for diabetes management to youth and adults on multiple daily injections with T1DM who are capable of using the device safely (42). The choice of multiple daily injections or an insulin pump is often based on the characteristics of the person with diabetes and which method is most likely to benefit them (42).

1.3.4. Digital health applications

Digital diabetes technology, which includes mobile health applications (mHealth apps), can aid self-care and thereby improve the lives of people with diabetes (47). As we continue to move through the digital age, there is increasing recognition of the potential use of technology to support healthcare. In recent years, diabetes management has continued to evolve into digital space, with a range of apps with different functions such as self-monitoring diaries, reminders for measuring glycemia and insulin administration, physical activity apps, apps for counting carbohydrates, and bolus calculators being released. Commercial applications with complex advanced algorithms are also being developed. Based on the analysis of a large amount of collected data (insulin dose, glycemia, meals), those should give recommendations for the correction of insulin therapy. Applications are available on smartphones and computers, and their integration with glucometers, insulin pumps, smart pens and CGM devices is possible (62).

Across the US and Europe, mobile apps intended to manage health and wellness are largely unregulated unless they meet the definition of medical devices for therapeutic and/or diagnostic purposes. Despite the availability of numerous mobile health apps for download, longer-term clinical evidence is needed to assess more accurately the effectiveness of diabetes apps.

A 2017 meta-analysis of 13 studies on mobile apps for diabetes suggested overall efficacy in reducing HbA1c, with a mean 0.44% (95% CI 0.29%, 0.59%) decrease in intervention compared with control, as well as increased perception of self-care among mobile application users (63). By using an app, patients become more self-confident in dealing with their diabetes, mainly by reducing their fear of not knowing how to deal with potential hypoglycemic episodes that may occur (63). Nevertheless, a discrepancy between the intended use of mHealth apps and people's real-world experiences exists, as indicated by the results of observational longitudinal study - people living with diabetes do not adhere to mHealth app use with reports of participant engagement decreasing with long-term use (64). Reported barriers to App use were lack of awareness of existing mHealth apps and features, technical literacy barriers, lack of recommendation to use by health care providers lack of motivation, unfriendly App designs, and cost (65).

1.4. Diabetes technology use and diabetes distress

Although technology provides many useful aids, it could also potentially add to distress due to access, cost, maintenance, and other issues. Having a CGM, for example, means that blood glucose levels are only a glance away—which could foster distress through simple availability.

Collectively, research on diabetes-related stress among people living with T1D is modest, mainly focused on children and adolescents and in adults' population yet to be explored (23). PROs are mainly studied as secondary outcomes in individuals with T1DM using technology. Several studies showed mixed results in terms of psychosocial outcomes, from a moderate reduction in diabetes distress in individuals using CGM (50,66) and pumps (67) to no difference in distress levels, in CGM vs non-CGM users (58).

The DIAMOND RCT compared CGM with SMBG in adults with T1DM using multiple daily injections and demonstrated a greater increase in confidence in managing hypoglycemia in the CGM arm and moderate improvement in diabetes distress compared with the SMBG group over 24 weeks (50).

The GOLD study, a crossover RCT of CGM versus SMBG in people with T1DM on multiple daily injections, demonstrated improved general emotional well-being and confidence in managing hypoglycemia in the CGM group at 6 months (66).

A single-arm observational study of 60 adults with T1DM participants were sent a link to complete multiple PRO questionnaires, including PAID, online just before real time CGM device start and six months later. Results showed that glycemic control and diabetes-specific worries improved, while hypoglycemia rate and more general distress did not change with use of real-time CGM (68).

More suboptimal scores at baseline were related to meaningful improvements in HbA1c, predefined as difference ≥0.9%, and PROs predefined as difference ≥0.5 SD. Compared with studies examining similar measures in people on multiple daily injections (50,66), in this observational study, the effect size for measures of diabetes-distress was stronger on insulin pump therapy. The authors speculated that pump users are more technology-oriented and potentially better prepared for the increase in information and actions CGM technology brings, while this increase is more likely to be perceived as overwhelming in individuals on injection therapy. People with more suboptimal PROs at baseline were most likely to benefit from real-time CGM use. The same pattern was found for glycemic control as measured with HbA1c.

This may suggest that psychological problems or vulnerabilities may not by definition an obstacle for real-time CGM start (68).

Results of U.K. real-world experience on intermittent CGM, with analyzed data for 10 370 FreeStyle Libre flash glucose-monitoring users (97% with T1DM), showed that use of intermittent CGM was associated with a reduction in diabetes distress ($P < 0.0001$) (69).

Results of prospective, observational, one-center study in people with T1DM and pump therapy showed early improvement in glycemic control, rates of hypoglycemia along with improvements with diabetes-specific emotional distress. Remarkable improvement in PAID scores from 29.8 ± 18.5 to 17.2 ± 14.0 ($p = 0.0002$) at 3– 6 months and to 12.8 ± 11.7 ($p < 0.00001$) at 6–12 months could indicate that patients integrate pump therapy into their daily lives with greater ease and motivation and they experience less emotional distress. Pump therapy offers greater flexibility of insulin delivery and therefore patients could potentially make better emotional adjustments (67).

In a cross-sectional, singe center study in adults with T1DM and pump therapy, Khan et al. used the two-item diabetes distress screening instrument, the DDS-2, and discovered that insulin pump wearers with higher diabetes distress scores had significantly higher HbA1c levels and there was 1% difference in HbA1c between the low and the high diabetes distress group (70).

While use of apps has been shown to positively affect outcomes, such as HbA1c and hypoglycemia incidence, studies evaluating app-based interventions are limited with no meaningful improvement in diabetes distress reported (71). One study reported a statistically significant decrease in mean diabetes-related emotional problems, which is one of the subscales of the instrument measuring diabetes distress (72). However, mHealth app use was not found to significantly improve quality of life (73,74), diabetes self-efficacy and hypoglycemia fear (72), diabetes self-care activity (75), and diabetes distress as a whole (72,73). Recent results of a multi-center randomized controlled trial, revealed that the use of the mySugr App led to a significant improvement in diabetes distress after 3 months compared to the treatment-as-usual control group with PAID scores at follow-up significantly lower than in the control group (Δ -2.20, 95% CI: -4.02 to -0.38) (76).

2. OBJECTIVES AND HYPOTHESIS OF THE STUDY

2.1. Hypothesis

The hypothesis of the study was that the usage of diabetes technology (CGM, insulin pumps, mobile application) in the treatment and management of T1DM is associated with less diabetes distress.

2.2. Objectives of the study

The primary objective was to study the association between diabetes technology use (CGM, insulin pump, and smartphone applications) and diabetes distress in adults with T1DM in Southeast Europe.

The secondary objectives were to study:

- The proportion of participants with high diabetes distress and differences between countries in diabetes distress scores
- Predictors for diabetes distress: age, gender, duration of T1DM diabetes, presence of microvascular complications, hypoglycemia occurrence, and HbA1c
- Difference in diabetes distress scores in participants using a different type of technology.

3. SUBJECTS AND METHODS

3.1. Subjects

This cross-sectional study was carried out in countries of Southern Eastern Europe, including Croatia, Bulgaria and Serbia. Included participants fulfilled the eligibility criteria defined by the study protocol: they were diagnosed with T1DM for ≥ 1 year, aged ≥ 26 years, with recent HbA1c available within the 30 days preceding the study visit. Exclusion criteria were diabetes other than T1DM, change in insulin therapy within three months preceding the study, and non-insulin treatment at any time since T1DM diagnosis. Participants who fulfilled inclusion criteria, signed informed consent and were asked to self-complete a validated questionnaire. A screening log form was completed by the physician to document the site's selection process of the study patients.

3.2. Ethics

All study procedures were performed in accordance with relevant guidelines and regulations. The study was approved by the Institutional Review Board/Institutional Ethics Committee at each site according to local practice. The Agency for Medicinal Products and Medical Devices of Croatia's Central Ethics Committee's approval was obtained.

3.3. Data collection

Data were collected between January - December 2018 from medical records and interviews during a single study visit at hospital centers. To secure a representative sample, participating physicians were selected randomly (computer-generated randomization) from the preestablished list of all endocrinologists and diabetologists who treat adults with T1DM. The potential investigators/ participating physicians were contacted by phone in ascending order from the randomized list and selected for the study if they agreed to participate. The process continued until a target number of eligible physicians was reached. The reasons for non-participation were: physicians were not reachable by phone in three attempts, physicians refused to participate due to disinterest, and physicians were engaged with other studies with the same

population. These refusals were recorded in the call log. Once a physician agreed to participate, they recruited the first 20 eligible patients consecutively within a two-month period. The physician completed a screening log form was completed to document the site's selection process of the study patients. The country sample size was determined proportionally to the best estimation of the total number of T1DM patients in each country (n=100 in Croatia, n=200 in Bulgaria and Serbia).

During the single visit at the time of the study, data were collected from patients' records and interviews. Data collected were age, gender, level of education, type of household (single-person or non-single-person), duration of the T1DM, presence of chronic complications, HbA1c value, fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) (last available laboratory or SMBG value). hypoglycemia occurrence, data on technology use (finger-stick blood glucometer, continuous glucose meter, insulin pump, and mobile applications). The physicians, using the patient's medical records, completed a case report form. The number of documented symptomatic hypoglycemic episodes (blood glucose ≤ 3.9 mmol/L and blood glucose ≤ 3.0 mmol/L) during the last three months were recorded. After data collection, participants were asked to complete the PAID questionnaires, which were afterward collected by the project staff.

3.4. Questionnaire

The PAID questionnaire, regarded as the first PRO to assess diabetes distress in adults, is a 20-item screening instrument designed to measure emotional responsiveness specific to diabetes and to provide information on emotional adjustment related to a wide range of diabetes management situations (36). The items are rated on a 5-point Likert scale and respondents self-indicate the degree to which each of the items is currently a problem for them; 0 (not a problem), 1 (minor problem), 2 (moderate problem), 3 (somewhat serious problem), 4 (a serious problem). The scores for each item are summed, then multiplied by 1.25 to generate a total score out of 100. A higher total score indicates higher distress. A total PAID ≥ 40 is considered as high diabetes-related distress (77). PAID scale covers a great variety of emotional concerns, has been validated in research and clinical settings, and is available in 17 languages (78). Translated and validated versions of PAID questionnaires for Bulgaria, Croatia and Serbia were used in the study. Sample of PAID questionnaire used in study, English version is in appendix 1.

3.5. Statistical analysis

GPower 3.1 was used to calculate *a priori* power and the needed sample size. To analyze the differences in the main outcome, diabetes distress, assuming a medium expected sample size (0.25-0.39) with two-tailed significance level, and power of statistical tests above 0.90, for multivariate analysis like ANCOVA, requires a total sample size of 400 was estimated. The inclusion of 500 would be sufficient to achieve post hoc analysis power >0.80. Data was analyzed using the statistical software SPSS (IBM, V 25.0).

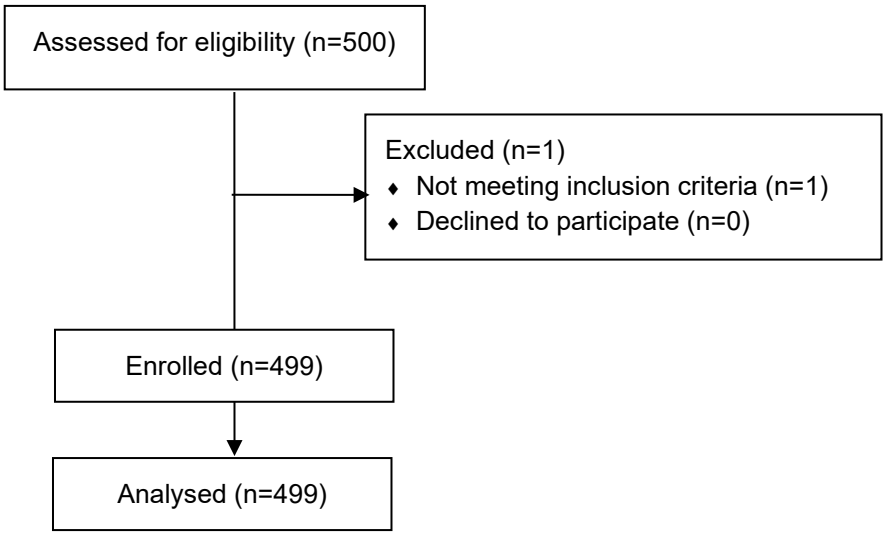
The normality of distribution for continuous variables was verified using the Kolmogorov-Smirnov test. Univariate statistical methods were used to compare the groups on all the independent variables, such as comparing the differences between countries: one-way ANOVA for normally distributed data and/or homogenous variance between groups, or data Kruskal-Wallis test for quantitative data that are not normally distributed or show non-homogeneity. Chi-square test was used for categorical data, or Fisher's exact for 2x2 tables. New technology users were predefined as those who used at least one of the following: continuous glucose meter, insulin pump, and mobile applications. The association of diabetes distress and diabetes technology use (new technology users vs blood glucometer users) was explored using correlation coefficients and analysis of covariance (ANCOVA) for analyzing the effects of the type of technology used on diabetes distress level, controlling for age and gender, as well as duration of diabetes, complications, number of severe hypoglycemia and HbA1c levels (multiple comparisons were always done using Bonferroni correction). Also, diabetes distress was further explored by using binary logistic regression with binarized diabetes distress as a dependent variable, and technology used as an independent factor, adjusted for age and gender. A multiple regression model was also considered, using a stepwise selection of factors, with an entry-level of 0.10 and a removal level of 0.05. Statistical significance $p<0.05$ was used.

4. RESULTS

4.1. Participants' characteristics

In the total sample of Southeast Europe, 499 participants were included, flow diagram shown at Figure 3.

Figure 3. Flow Diagram



Participants' characteristics are shown in Table 1.

Table 1. Participants characteristics

		N	(%)
Sex	Male	231	(46.3)
	Female	268	(53.7)
Total		499	(100.0)
Age (years)	≤ 40	163	(32.7)
	41-60	215	(43.1)
	≥ 61	121	(24.2)
Total		499	(100.0)
Duration T1DM	<10 years	98	(19.6)
	≥10 years	401	(80.4)
Total		499	(100.0)
Education level	Primary	35	(7.1)
	Secondary	257	(51.8)
	University/Higher Education	204	(41.1)
Total		496	(100.0)
Living conditions	Alone	45	(9.0)
	With another adult	453	(90.8)
	In an institution	1	(0.2)
Total		499	(100.0)
Macrovascular diabetes	No	427	(86.6)
complication	Yes	66	(13.4)
Total		493	(100.0)
Microvascular diabetes	No	145	(29.4)
complication	Yes	348	(70.6)
Total		493	(100.0)
Country	Bulgaria	200	(40.1)
	Croatia	100	(20.0)
	Serbia	199	(39.9)
Total		499	(100.0)

Our study participants had mean age of 49.11 (13.99) years, mean HbA1c 7.9 (1.46) and mean PAID total score of 29.19 (19.51) as shown in Table 2.

Table 2. Baseline characteristics, descriptive parameters

	Mean	SD	Median	1st quartile	3rd quartile	Minimum	Maximum	N	*P**
Age	49.11	13.99	48.00	38.00	60.00	84.00	60.00	499	<0.001
BMI	25.24	4.54	24.68	22.06	27.68	47.18	27.68	499	<0.001
HbA1c (%)	7.90	1.46	7.73	6.80	8.87	16.80	8.87	499	<0.001
FPG (mmol/L)	7.06	3.38	6.80	5.30	8.70	26.00	8.70	499	<0.001
PPG (mmol/L)	7.53	4.13	8.00	5.80	10.00	20.82	10.00	499	<0.001
PAID Total Score	29.19	19.51	25.63	13.75	41.25	85.00	41.25	496	<0.001

Descriptive parameters shown as mean values ± standard deviation, SD. All variables differ significantly from normal Gauss distribution. However, median and mean aligned for most variables
*Kolmogorov-Smirnov test
Acronyms: BMI= Body mass index, HbA1c= Glycated hemoglobin, FPG= Fasting Plasma Glucose, PPG= Postprandial Plasma Glucose, PAID= Problems areas in diabetes

4.2. Diabetes distress prevalence and response to individual PAID answers

The results indicated that 29.2% of participants had diabetes distress as per predefined cut-of PAID total score of ≥40 (Figure 4).

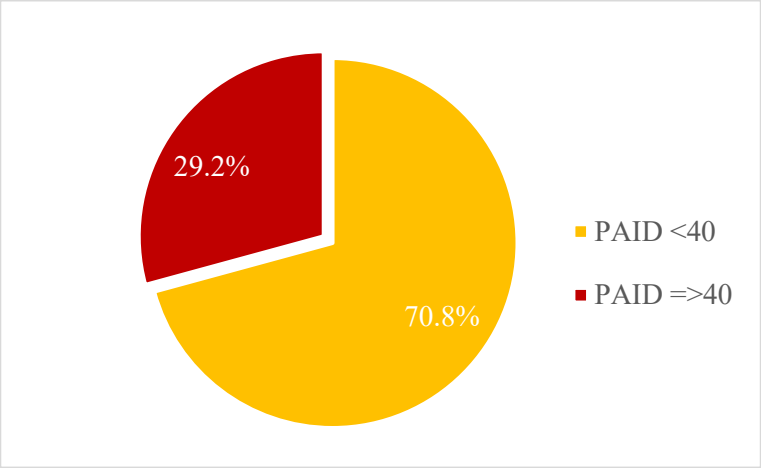


Figure 4. Percentage of patients with high diabetes distress
PAID= Problem Areas in Diabetes

Response rates to individual PAID items, as shown in Figure 5, indicated items that most of the participants perceived as distressing, i.e. items scored „somewhat serious“ and „serious“. Those were item 12 “Worrying about the future and complications” (40.9% of participants) and item 19 „Coping with complications of diabetes“ (25.3% of participants), item 13 „Feelings of guilt or anxiety when you get off track with your diabetes management“ (21.8% of participants) and item 9 „Worrying about low blood sugar reactions“ (20% of participants). Items scored by most participants with 0 (“not a problem”) are as follows: item 1 „Not having clear and concrete goals for your diabetes care“ (43.7%), item 2 „Feeling discouraged with your diabetes treatment plan“ (45.9%), item 10 „Feeling angry when you think about living with diabetes“ (41.5%), item 14 „Not accepting your diabetes“ (52.4%), item 15 „Feeling unsatisfied with your diabetes physician“ (81.5%), item 17„Feeling alone with your diabetes“ (54.7%), item 18 „Feeling that your friends and family are not supportive of your diabetes management efforts (65.5%).

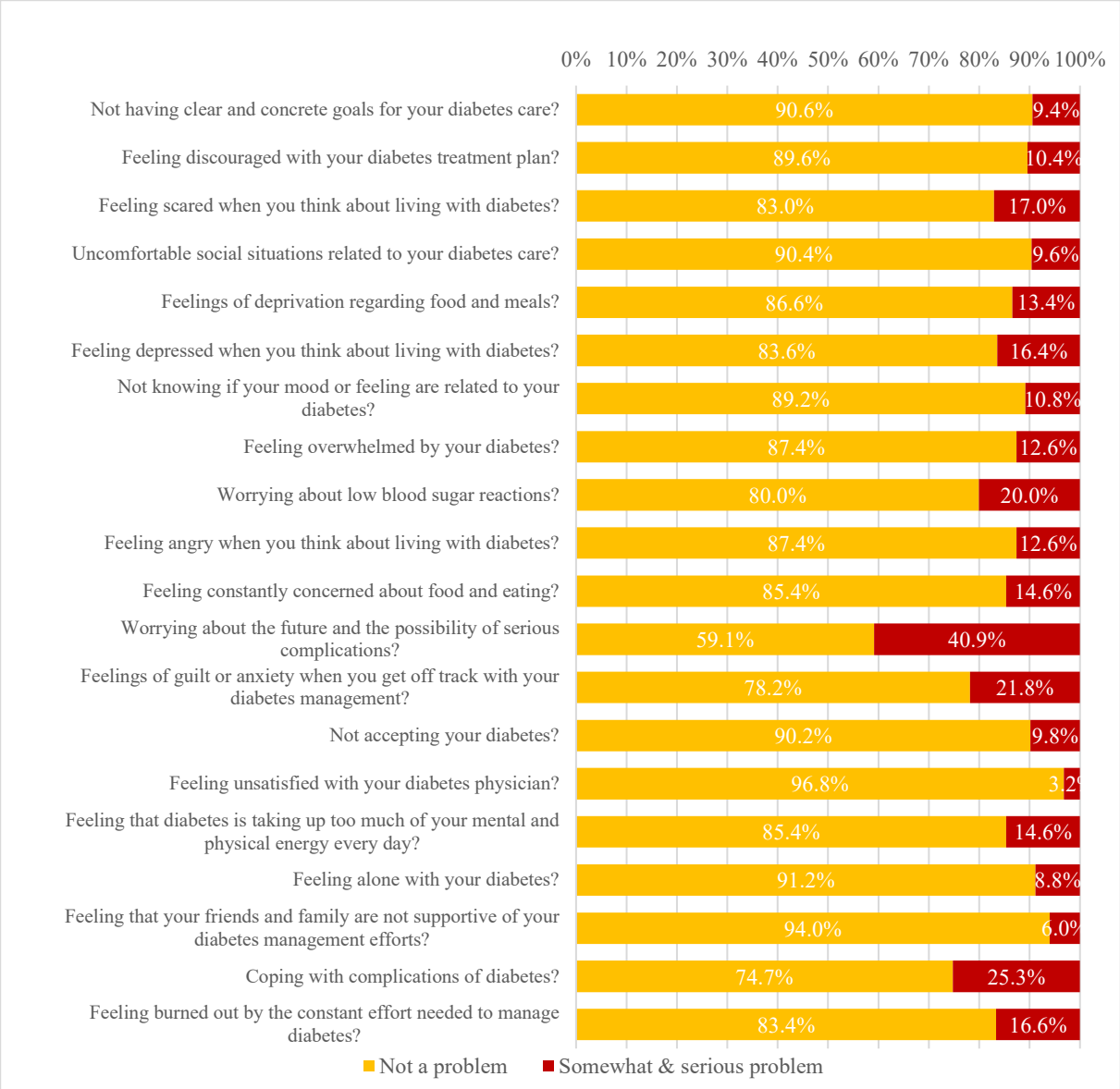


Figure 5. Rates of responses to individual PAID items
Acronym: PAID= Problem Areas in Diabetes

There were 56% of participants that reported elevated distress (answers somewhat serious or serious) from at least one of the individual items in the PAID questionnaire. Very high Cronbach alpha (0.94) showed strong internal consistency of PAID items.

4.3. Technology use

Finger-stick blood glucose meters were used by most participants (99.0%) and a new technology, with or without concomitant BGM use, was used by 20% of participants. When looking into a particular type of new technology, CGM was used by 5.8%, insulin pumps by 7.9% and apps in 6.3%. The use of apps, including those to monitor diet/provide carbohydrate counting, to remind users to take their diabetes medication, to assist with insulin dose adjustment, and to manage weight, was generally low, mostly recommended by the health care professionals. The proportion of participants using different types of technology is shown in Table 3. Only 99 (20%) participants used new technologies.

Table 3. Proportion of patients using different types of technology

		N	%
Diabetes technology use	CGM	29	(5.8)
	IP	39	(7.9)
	App	31	(6.3)
	BGM	397	(80.0)
Total		496	(100.0)

Subgroups were predefined: CGM subgroup include participants using CGM with or without mobile App users. Insulin pump subgroup include participants using IP with or without CGM with or without mobile App users. Mobile applications group include App users only.
Acronyms: CGM= Continuous glucose monitoring, IP= Insulin pump, App= Mobile application, BGM= Blood glucose monitoring

4.4. Association between technology use and diabetes distress

Participants who used the new technologies were compared to BGM users to investigate association of technology use and diabetes distress determined by PAID total score ≥40. Mean PAID total scores among the groups are shown in Table 4.

Table 4. Problem Areas in Diabetes (PAID) total scores

	Mean	**SD**	**SE**	**95% CI for Mean**		**N**	***P****
BGM	29.57	20.22	0.975	27.792	31.624	388	0.293
New technology use[a]	27.92	16.27	1.961	23.530	31.235	99	

*$F_{(1,487)}$=1.109
[a]CGM, Insulin Pump, mobile application
Acronym: BGM= Blood glucose monitoring

When comparing new technology users vs. BGM users, HbA1c and age significantly influence distress. After controlling for possible effects of age, sex, duration of diabetes, HbA1c, number of severe hypoglycemia, and microvascular complications, we found no statistically significant association between technology use and diabetes distress.

We found no significant difference in the proportion of patients with high PAID between the users of new technologies and BGM users, as shown in Figure 6.

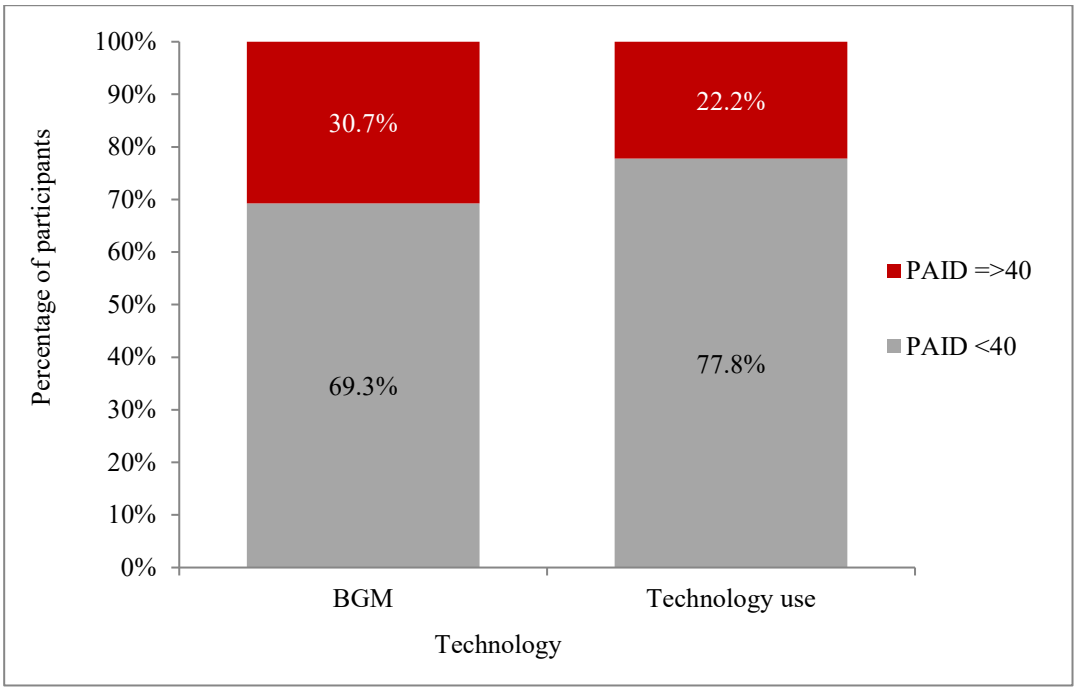


Figure 6. Proportion of participants with PAID ≥40 according to technology use
P=0.108 *Fisher's exact
Acronym: PAID= Problems areas in diabetes, BGM= Blood glucose monitoring

4.5. Predictors for diabetes distress

Sex, body mass index (BMI) and HbA1c were significant predictors of high diabetes distress, as shown in Table 5. Being male reduces the odds for high diabetes distress by 46% compared to women (OR=0.543, 95%CI: 0.359-0.821, p=0.004). The increase in HbA1c by 1% increases the chance of high diabetes distress by 16%. (OR=1.162, p=0.034, CI=1.012-1.334). Also, an increase in one BMI unit increases the chance of high diabetes distress by 5% (OR=1.5052, 95%CI: 1.004-1.102, p=0.033).

After controlling for sex, HbA1c and BMI, technology use remains a significant predictor of high distress: OR=0.576, 95%CI: 0.333-0.996, p=0.049, suggesting that T1DM patients using new technology have 42% less chance to have high diabetes distress, compared to BGM users.

Table 5. Predictors of high diabetes distress

	P*	OR	95% CI
Sex (male)	**0.004**	0.543	0.359 – 0.821
Age	0.374		
Age (41-60 years)	0.889	0.967	0.600 – 1.557
Age (61- years)	0.205	0.686	0.384 – 1.228
Microvascular complications	0.303	1.294	0.793 – 2.112
Duration T1DM (≥10 years)	0.678	1.123	0.650 – 1.942
HbA1c (%)	**0.034**	1.162	1.012 – 1.334
[a]Hypoglycemia<3.9	0.326	1.331	0.752 – 2.358
[a]Hypoglycemia<3.0	0.281	1.296	0.809 – 2.077
Technology use	**0.049**	0.576	0.333 – 0.996
BMI	**0.033**	1.052	1.004 – 1.102
Constant	0.000	.030	

*Logistic regression with binarized diabetes distress
[a]Documented symptomatic hypoglycemic episode within last 3 months
Acronym: HbA1c= Glycated hemoglobin, BMI= body mass index

4.6. Difference in diabetes distress using different type of technology

We found no statistical difference in total PAID scores among different technology users, as shown in Table 6.

Table 6. Problem Area in Diabetes (PAID) scores among technology subgroups

		Mean	SD	SE	95% CI for Mean	N	*P**
PAID Total Score	CGM	22.11	9.67	1.796	18.433 – 25.791	29	0.212
	IP	29.01	17.76	2.844	23.250 – 34.763	39	
	App	31.98	18.07	3.245	25.349 – 38.603	31	
	BGM	29.37	20.16	1.015	27.372 – 31.365	394	

After controlling for confounding factors (duration of DM, hypoglycemia, microvascular complications, HbA1c, sex and gender), ANCOVA didn't find significant differences in mean total PAID score between users of different kind of technology $F(3,487)=2.032$, $P=0.109$
Acronyms: PAID= Problem Areas in Diabetes, CGM= Continuous glucose monitoring, IP= insulin pump, App= mobile application, BGM= Blood glucose monitoring

No statistically significant difference was found, in proportion of participants with high diabetes distress using different type of technology in but level of significance was close to p<0.05, Figure 7.

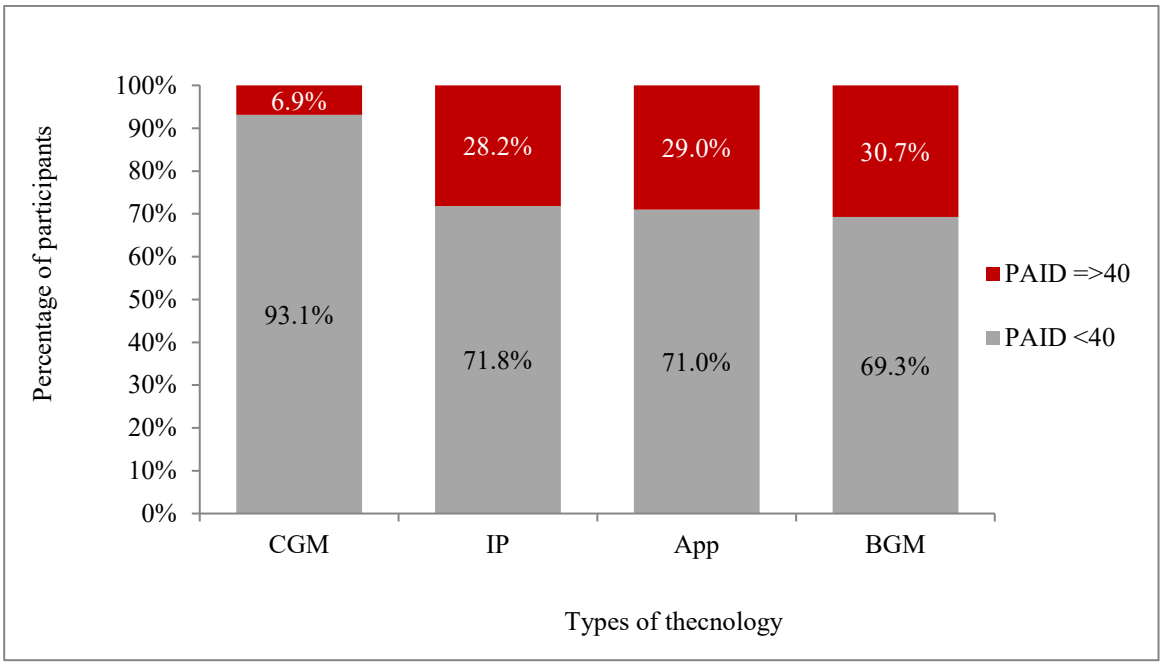


Figure 7. Proportion of participants with high diabetes distress using different type of technology
P=0.059, *χ2=7.452, df=3
Acronyms: CGM=Continuous glucose monitoring, IP=insulin pump, App=mobile application, BGM= Blood glucose monitoring

Descriptive data between different technology users are shown in Table 7.

Table 7. Technology subgroups characteristics

		CGM		IP		App		BGM		
		N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	***P****
Sex	Male	11	(37.9)	8	(20.5)	17	(54.8)	194	(48.9)	**0.004**
	Female	18	(62.1)	31	(79.5)	14	(45.2)	203	(51.1)	
Total		29	(100.0)	39	(100.0)	31	(100.0)	397	(100.0)	
Age (years)	≤ 40	8	(27.6)	18	(46.2)	17	(54.8)	120	(30.2)	**0.001**
	41-60	12	(41.4)	20	(51.3)	12	(38.7)	169	(42.6)	
	≥ 61	9	(31.0)	1	(2.6)	2	(6.5)	108	(27.2)	
Total		29	(100.0)	39	(100.0)	31	(100.0)	397	(100.0)	
Duration T1DM (years)	< 10	9	(31.0)	3	(7.7)	9	(29.0)	77	(19.4)	0.055
	≥ 10	20	(69.0)	36	(92.3)	22	(71.0)	320	(80.6)	
Total		29	(100.0)	39	(100.0)	31	(100.0)	397	(100.0)	
Macrovascular complication	No	27	(93.1)	38	(97.4)	30	(96.8)	330	(84.4)	**0.024**
	Yes	2	(6.9)	1	(2.6)	1	(3.2)	61	(15.6)	
Total		29	(100.0)	39	(100.0)	31	(100.0)	391	(100.0)	
Microvascular complication	No	4	(13.8)	18	(46.2)	19	(61.3)	104	(26.6)	**<0.001**
	Yes	25	(86.2)	21	(53.8)	12	(38.7)	287	(73.4)	
Total		29	(100.0)	39	(100.0)	31	(100.0)	391	(100.0)	
Symptomatic hypoglycemia (mmol/L)	None	19	(65.5)	7	(17.9)	3	(9.7)	95	(23.9)	**<0.001**
	≤ 3.9	10	(34.5)	32	(82.1)	28	(90.3)	302	(76.1)	
Total		29	(100.0)	39	(100.0)	31	(100.0)	397	(100.0)	
Symptomatic hypoglycemia mmol/L	None	21	(72.4)	14	(35.9)	12	(38.7)	215	(54.2)	**0.008**
	< 3.0	8	(27.6)	25	(64.1)	19	(61.3)	182	(45.8)	
Total		29	(100.0)	39	(100.0)	31	(100.0)	397	(100.0)	

* chi-square tests
[a]Documented symptomatic hypoglycemic episode within last 3 months
Acronyms: CGM=Continuous glucose monitoring, IP=insulin pump, App=mobile application, BGM= Blood glucose monitoring

We found in the study significant differences among different technology types' users. Female patients used more frequently insulin pumps and CGM than males (p=0.004). Most apps users were in the youngest age group, while older patients mostly used (p=0.001). Most macrovascular complications are found among patients using BGM (p=0.024). Most microvascular complications are found among patients using CGM, and the least among App users (p<0.001). Finally, proportions of participants without hypoglycemia episodes (both <3.9 and <3.0 mmol/L) were the highest among CGM users (p<0.001, p=0.008, respectively).

4.7. Technology use and glycemic regulation

Further analysis on differences between predefined subgroups showed differences in postprandial values being at significant level among insulin pumps and BGM users as shown in Table 8.

Table 8. Glycemic parameters among technology subgroups

		Mean	SD	SE	95% CI for Mean	N	*P**
HbA1c (%)	CGM	8.39	1.57	0.291	7.793 – 8.985	29	0.147
	IP	7.59	1.35	0.215	7.151 – 8.023	39	
	App	8.03	1.54	0.276	7.462 – 8.590	31	
	BGM	7.88	1.45	0.073	7.735 – 8.022	397	
FPG (mmol/L)	CGM	6.98	3.15	0.584	5.781 – 8.174	29	0.389
	IP	6.29	2.48	0.397	5.486 – 7.093	39	
	App	6.62	2.68	0.481	5.633 – 7.598	31	
	BGM	7.17	3.52	0.177	6.827 – 7.521	397	
PPG (mmol/L)	CGM	8.01	3.49	0.649	6.682 – 9.340	29	**0.024**
	IP	5.69	3.83	0.614	4.447 – 6.932	39	
	App	8.33	4.20	0.754	6.789 – 9.869	31	
	BGM	7.61	4.17	0.209	7.199 – 8.022	397	

Postprandial Glucose values statistically differ among predefined technology subgroups.
*one-way ANOVA, (Levene's test didn't show significant difference in homogeneity of variances)
† Scheffe's post hoc test showed insulin pumps have significantly lower PPG vs BGM *P*=0.05
Acronyms: HbA1c=Glycated hemoglobin, FPG= Fasting Plasma Glucose, PPG= Postprandial Plasma Glucose, CGM= Continuous glucose monitoring, IP= Insulin pump, App= Mobile application, BGM= Blood glucose monitoring

Additional analysis was carried out to look for association between different technology use and glycemic control. Insulin pump use was associated with reaching lower PPG values albeit no differences were found for FPG and HbA1c values (Figure 8).

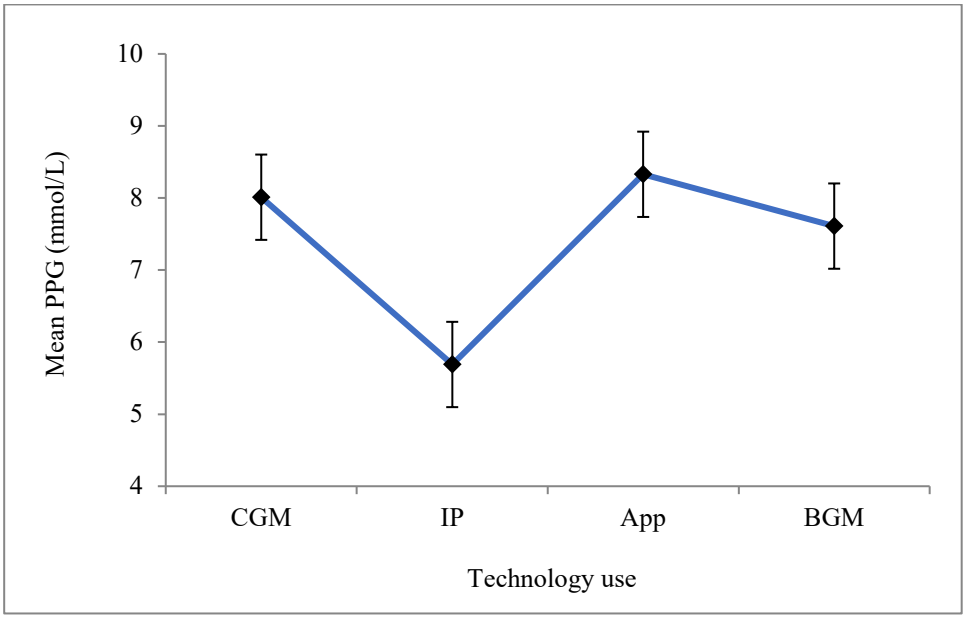


Figure 8. Mean Postprandial glucose among subgroups
P=0.023 *ANCOVA analysis F(2,99)=3.203
†Scheffe's post hoc *P*=0.044 for IP vs Apps users and P=0.025 for IP vs BGM users.
Acronyms: PPG=Postprandial Plasma Glucose, CGM=Continuous glucose monitoring, IP=insulin pump, App=mobile application, BGM= Blood glucose monitoring

4.8. Differences between countries

Participant's baseline characteristics per country are shown in Table 9. Groups across the countries differed in several variables differs: duration of T1DM was significantly longer in Serbia compared to the other two countries (χ^2=10.545, df=2, p=0.005), percentage of patients with microvascular complications was smallest in Croatia (χ^2=54.027, df=2, p<0.001), while the percentage of patients reporting symptomatic hypoglycemic episodes <3.9 mmol/L and <3.0 mmol/L was the smallest in Bulgaria (χ^2=26.802, df=2, p<0.001, and χ^2=24.279, df=2, p<0.001, respectively).

The use of BGM was more frequent in Bulgaria than in the other two countries. More BGM users and fewer new technology users were found in Bulgaria compared to the other 2 countries (χ^2=7.016, df=2, p=0.030).

Looking at new technologies, Bulgaria patient used more CGMs and fewer insulin pumps compared to the other 2 countries, while participants in Serbia uses Apps more than others (χ^2=49.862, df=4, p<0.001).

Table 9. Countries' baseline characteristics

		Bulgaria		Croatia		Serbia		
		N	(%)	N	(%)	N	(%)	*P**
Sex	Male	92	(46.0)	52	(52.0)	87	(43.7)	
	Female	108	(54.0)	48	(48.0)	112	(56.3)	0.397
Total		200	(100.0)	100	(100.0)	199	(100.0)	
Age (years)	≤ 40	58	(29.0)	39	(39.0)	66	(33.2)	
	41-60	99	(49.5)	36	(36.0)	80	(40.2)	0.156
	≥ 61	43	(21.5)	25	(25.0)	53	(26.6)	
Total		200	(100.0)	100	(100.0)	199	(100.0)	
Duration T1DM	< 10 years	48	(24.0)	25	(25.0)	25	(12.6)	**0.005**
	≥ 10 years	152	(76.0)	75	(75.0)	174	(87.4)	
Total		200	(100.0)	100	(100.0)	199	(100.0)	
Education	Primary	14	(7.0)	4	(4.1)	17	(8.5)	
	Secondary	110	(55.0)	50	(51.5)	97	(48.7)	0.493
	University/Higher Education	76	(38.0)	43	(44.3)	85	(42.7)	
Total		200	(100.0)	97	(100.0)	199	(100.0)	
Living[a]	Alone	17	(8.5)	6	(6.0)	22	(11.1)	0.328
	With another adult	183	(91.5)	94	(94.0)	176	(88.9)	
Total		200	(100.0)	100	(100.0)	198	(100.0)	
Macrovascular complication	No	175	(87.9)	88	(88.9)	164	(84.1)	
	Yes	24	(12.1)	11	(11.1)	31	(15.9)	0.406
Total		199	(100.0)	99	(100.0)	195	(100.0)	
Microvascular complication	No	29	(14.6)	55	(55.6)	61	(31.3)	
	Yes	170	(85.4)	44	(44.4)	134	(68.7)	**<0.001**
Total		199	(100.0)	99	(100.0)	195	(100.0)	
Symptomatic hypoglycemia	None	73	(36.5)	24	(24.0)	28	(14.1)	
	≤ 3.9 mmol/L	127	(63.5)	76	(76.0)	171	(85.9)	**<0.001**
Total		200	(100.0)	100	(100.0)	199	(100.0)	
Symptomatic hypoglycemia	None	132	(66.0)	47	(47.0)	84	(42.2)	
	<3.0 mmol/L	68	(34.0)	53	(53.0)	115	(57.8)	**<0.001**
Total		200	(100.0)	100	(100.0)	199	(100.0)	
Technology types	CGM	21	(10.6)	6	(6.1)	2	(1.0)	
	IP	2	(1.0)	14	(14.1)	23	(11.6)	**<0.001**
	App	5	(2.5)	3	(3.0)	23	(11.6)	
	BGM	170	(85.9)	76	(76.8)	151	(75.9)	
Total		198	(100.0)	99	(100.0)	199	(100.0)	

*Chi-square tests, Fisher's exact

[a]Institutionalized coded as missing

[b]Documented symptomatic hypoglycemic episode within last 3 months

Acronyms: CGM=Continuous glucose monitoring, IP=insulin pump, App=mobile application, BGM= Blood glucose monitoring

After controlling for effects of confounding variables that influence or could have potentially influenced diabetes distress, we found a statistically significant difference in mean total PAID score between countries, with post hoc test showing this difference being significant between Serbia and Croatia, with diabetes distress being lower in Serbia (Figure 9).

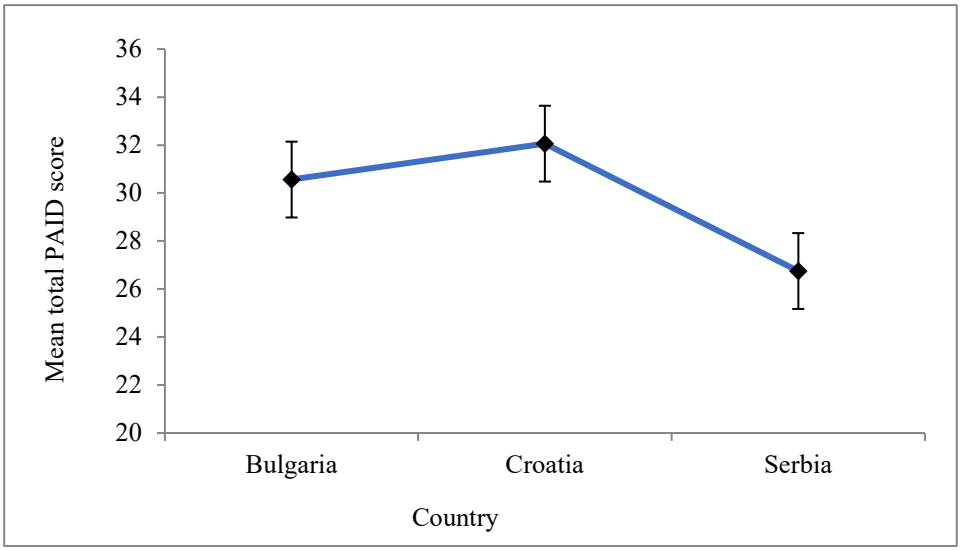


Figure 9. Mean total Problem Areas in Diabetes (PAID) scores between countries
ANCOVA was used to control for the confounding factors: duration of DM, hypoglycemia, microvascular complications, HbA1c, sex and gender, $F(2,490)=7.065$, $P=0.001$
Scheffe's post hoc test, $P<0.05$
Acronym: PAID=Problem Areas in Diabetes

Proportion of participants having diabetes distress in Bulgaria, Croatia and Serbia was 29.9% vs 36.0% vs 25.1%, with no statistical difference among countries (Figure 10).

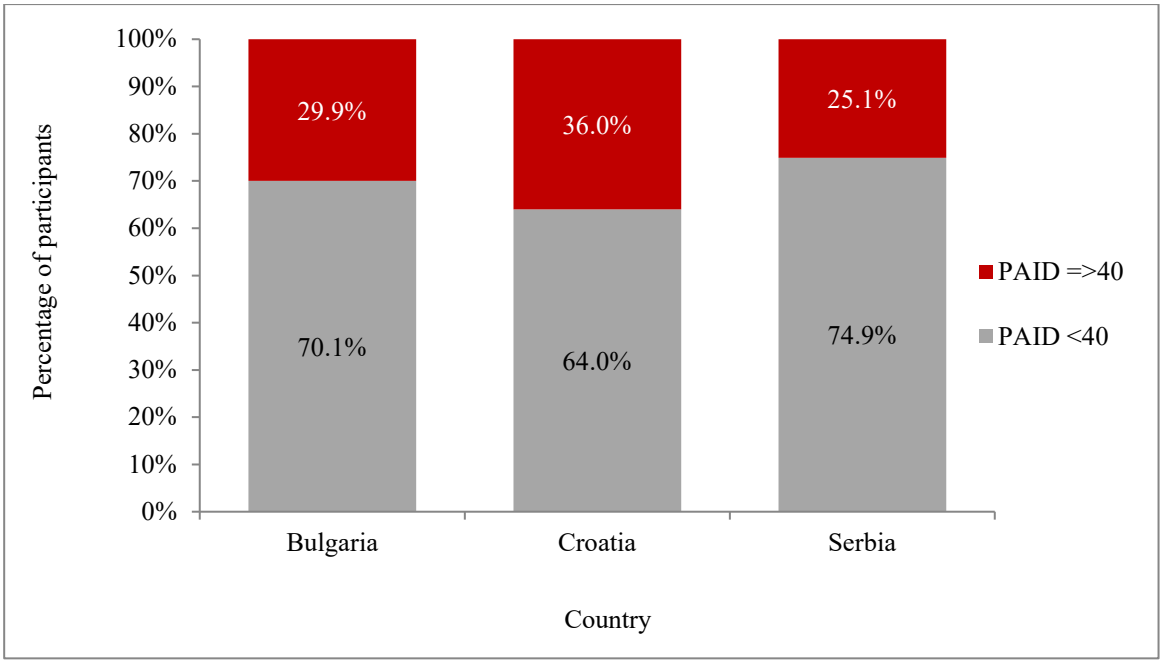


Figure 10. Proportion of participants with high diabetes distress per country
P=0.143 *χ^2=3.885, df=2

5. DISCUSSION

We found that almost one-third of our study sample suffered from substantial diabetes-related distress, which is in line with the results of previous studies showing that elevated diabetes-related distress affects 20–40% of people with T1DM (6).

No statistical association between the use of new technologies and diabetes distress was found, suggesting that use of one or more new technology does not add additional emotional burden in people living with T1DM. Furthermore, it has been shown that new technology use predicts independently lower diabetes distress at a statistically significant level. It is to note that only 20 % of our study participants used at least one of the new technologies, with the usage rate of using CGM, pumps and mobile apps being slightly lower compared to global usage reported in the SAGE study (5.8%, 7.9% and 6.3% vs 23%, 20% and 11.3% respectively) (79).

Differences in access to healthcare, treatment and support as well as healthcare system-related factors may considerably contribute to the usage of diabetes technology which varied considerably across the regions and countries: the proportion who used CGM (23.2% globally) varied from 46.4% in Western Europe to 2.5% in the Middle East, insulin pump use (19.5% overall) ranged from 42.3% in Western Europe to 2.7% in the Middle East(79). We also observed differences in diabetes technology use when looking into countries' differences- the proportion of participants using CGM ranged from 10.6% in Bulgaria to 6.1 % in Croatia and 1.0% in Serbia. The proportion of participants using insulin pumps ranged from 14.1% in Croatia to 11.6% in Serbia and 1.0% in Bulgaria. Previous studies have shown that technology usage by patients with T1DM has increased in recent years; during 2016–2018 in T1D Exchange study in the US, pumps and CGM were used by 63% and 30% of participants, respectively. Technology usage potentially reflects differences in insurance coverage or physician training, and we believe that percentage of new technology users in our study sample would be relevantly increased today with new technologies being more available, affordable and endorsed by local clinical practice and policies.

Another point is that CGM users in our study were all using real-time CGM. Intermittent CGM FreeStyle Libre was namely launched in 2017 and became commercially available later in 2018 (80).

Our study revealed relatively low levels of diabetes distress reported by patients, which is in concordance with to the results of the SAGE study (79).

Earlier research showed that the PAID questionnaire had high internal reliability (coefficient alpha = 0.95) and support for construct validity from factor analyses (37). The reliability analysis of the PAID questionnaire in our study showed a Cronbach alpha coefficient of 0.94, confirming already existing evidence that the scale is internally consistent and that the scores may be a true representation of the results.

Clinically, the PAID total score should be used as an overall measure of the emotional burden of diabetes or "diabetes burnout". However, the pattern of individual PAID items scores could help identify the specific sources of diabetes distress with which the patient is struggling. Individual items endorsed strongly by the patient can represent clinical „red flags“ that could be the focus of further patient-clinician discussion and potential psychological treatment.

The original 20-item PAID questionnaire that we used in our study enabled us to explore responses to individual items in four known instrument dimensions measuring negative emotions (12 questions), treatment-related problems (three questions), food-related problems (three questions), and social support-related problems (two questions).

In general, our results show that roughly 30% of our sample reported elevated total distress, but twice as many of participants experienced elevated distress from at least one of the individual items in the PAID questionnaire.

The items that were highly scored by the majority of the studied population, pointing to moderate or severe distress regarding a particular topic were worrying about the future and complications, coping with complications of diabetes and feeling guilty when off-track with diabetes management were the most prominent concerns. These findings reflected the enormous emotional impact (i.e. worry, fear, guilt) of living with diabetes and were in concordance with previous results of the Croatian study. Interestingly, all those 3 items are included in the negative emotions subdimension of the PAID questionnaire (38). Similar results were shown in Welch et al. study in which the PAID questionnaire was completed by 256 volunteer outpatient people with diabetes - worry about the future and the possibility of serious complications was most highly endorsed as a serious problem among the 45% of T1DM group (37).

Other issues endorsed as serious by at least 20% of T1DM patients included being scared about living with diabetes, feeling discouraged with diabetes treatment, worrying about low blood glucose reactions, being burned-out by the constant effort to manage diabetes, coping with complications, and feeling that diabetes is taking up too much mental and physical energy.

Likewise, diabetes distress appears to be common, with serious concerns being reported for at least one PAID item in 60% of the study participants in the very first Polonsky study. Worries about the possible development of long-term complications and feelings of guilt and anxiety regarding poor adherence to the diabetes regimen were the most prominent of these concerns(36). Feeling burned out by the constant effort to manage diabetes, the physical and emotional energy expended, and apprehension associated with complications was all highly endorsed as a serious problem (37).

We found that items perceived by the vast majority of participants as no problem were feeling unsatisfied with your diabetes physician“ (81.5%), the item that belongs to the subdimension of treatment-related problems and indirectly informs about treatment satisfaction. Of note, the PAID questionnaires were completed in a clinic setting, during the patients' visits immediately after data collection. It would be interesting to examine whether more patients might report strong concerns about their physicians if these data were collected in other settings. Other items being not a scope of concern for majority of patients were feeling alone with your diabetes (54.7%) and feeling that your friends and family are not supportive of your diabetes management efforts (65.5%). The last two items are included in social support–related problems subdimension.

There are three major ways in which diabetes can negatively affect physical well-being. The most potent factor is the development of long-term complications. The second factor is short-term complications. Chronically elevated blood glucose levels may lead to increased fatigue, sleep problems, more frequent infections, and other associated problems. Tight glycemic control may lead to unwanted weight gain, more frequent hypoglycemia, and/or loss of hypoglycemic warning signs. The third major factor concerns physical symptoms and lifestyle changes resulting from the demands of the diabetes regimen. Finally, when patients are forced (or believe that they are forced) to limit their activities in order to manage their diabetes effectively, the quality of life is likely to be affected (24).

The demands of diabetes care can have a potent impact on mood, both short-term and long-term. Many patients may become chronically frustrated, discouraged, and/or enraged with a disease that often does not seem to respond to their best efforts (24).

Furthermore, the mere presence of diabetes can affect the quantity and quality of a patient's relationships. Lack of social support or feeling ‘policed’ by family, friends or co-workers also evokes emotional distress in individuals with T1DM (81). Social support can influence

individual's mental health, motivation, and capacity to engage in self-management practices, increasing the risk for elevated HbA1c and complications. Research shows that people with diabetes, both type 1 and type 2, feel isolated, alone, and sometimes judged by their healthcare providers (82).

Often, communication gaps leave people with diabetes lost while looking for information. Data from another survey illustrates that people with diabetes (N=478) want to talk about things that matter to them since 74% of participants felt that being asked about mental health during a routine visit would be a huge improvement to their care. Despite this demonstrated interest, clinicians are not routinely assessing and monitoring for mental health and research shows that health care professionals feel uncomfortable and feared that asking about them will make things worse (83).

"The clinician-patient relationship is the least explored complication of diabetes", W.Polonsky. One of the reasons could be health care professionals lack training and resources on implementing patient reported outcomes.

The results of our study indicate that female gender, higher HbA1c and higher BMI were significant predictors of high diabetes distress. This is concordant with the results of the T1 Exchange Clinic Registry, which demonstrated that diabetes-related stress among people with T1D occurs at higher levels among female with higher HbA1c (84). Gender differences in emotional experience and expressivity have been reported previously (85). While men and women may experience similar emotional experiences, women may display higher emotional expressivity and usually experience more frequent and stronger negative emotions (86).

Weight gain is associated with intensive insulin therapy. Overweight and obese weight status in individuals with T1D is higher than the general population and a variety of demographic (e.g., female sex), clinical (e.g., greater insulin needs), environmental (e.g., skipping meals), and psychosocial (e.g., depression, stress) factors are associated with overweight/obese weight status in T1D (87). Higher stress, lower quality of life, low social support, and negative body image were found to be associated with higher BMI and/or overweight and/or obese weight status (88,89). Higher BMI in people living with T1DM is further linked with lower engagement with physical activity, which creates a vicious cycle (90). While associations between diabetes-related distress and decreased age and diabetes duration were demonstrated elsewhere, our study findings yield no difference in the level of diabetes-related distress among age groups. A

possible explanation could be the higher mean age of our study sample, which was 49.11 (13.99) vs 37.64 (16.33) in T1 Exchange Clinic Registry.

Another finding from this Registry of 10 821 adults with T1DM informs that the treatment-related variables, i.e. use of injections/pen (alone or in combination with the pump), were associated with heightened stress relative to the pump, and the use of a CGM along with the frequency of blood glucose checking was associated with higher reported stress, albeit only when adjusting for all other variables. In our study, we did not find such an association.

Along with differences in participants' characteristics and methodology already elaborated, it is to note that in the T1 Exchange Registry, diabetes distress was assessed by a single self-report question ‘‘In general, how often do you feel stressed because of your diabetes” to which participants responded using a 5-point scale (1 = ‘‘Never”; 5 = ‘‘Very often”). While a one item self-report used to screen for diabetes distress has been demonstrated to be psychometrically sound, it has been shown that individual items in any given questionnaire have lower reliability than composite measures comprised of a number of similar items for each domain. Diabetes stress is a multi-dimensional construct, and each dimension may have unique correlates (37). The 20-item scale used in our research allows for comprehensive and potentially multi-dimensional measurement of diabetes distress in a diverse multicounty sample of adults with T1D seen in everyday practice.

A recent systematic review identified four instruments with appropriate psychometric properties, which have been used to measure diabetes distress among adults with T1DM, including the PAID questionnaire (91) Partially based on the PAID, the more recently developed Diabetes Distress Scale comprises 17 items assessing diabetes-specific problems (78). As regards to psychometrics, both scales feature high reliability. Although the two scales are similar, the main differences include: the PAID covers a greater variety of emotional concerns (including diabetes related emotional burn-out and diabetes non-acceptance), which is supported by its higher associations with depressive symptoms and undesirable coping styles. Furthermore, it has a stronger focus on diet and diabetes complications. The diabetes distress scale has a stronger focus on motivational and behavioral problems associated with diabetes self-management, as confirmed by its stronger associations with self-care activities and metabolic outcomes.

T1-diabetes distress scale, a version of the DDS specifically designed for people with T1DM, is currently available only in English, French, German, Portuguese, and Spanish translated and validated versions (92)therefore, we did not consider using it in our research.

The advantages and disadvantages of shorter PAID forms were discussed before and PAID-11 has also been listed among four instruments for screening and measuring diabetes distress in adults with T1DM.

The complexity in the usage of PROs marks the need for standardized measures, and technology and digitalization in reporting outcomes may ease the process and provide further consistent information in the future.

The results of our previous single-country analysis were only partially aligned, showing that elevated HbA1c and the presence of microvascular complications are significant predictors of diabetes distress (93).

While we used the same method (binary logistic regression) with the main variable being categorized as either above cut-off score or below, a possible explanation for those different findings might be differences in the sample size but also in the characteristics of the studied population. Compared to the Southeast Europe sample, Croatian participants had better glycemic regulation as measured by HbA1c 7.29 (1.28) vs 7.9 (1.46), a lower proportion of included females (48% vs 53%), a slightly lower proportion of participants with long duration of diabetes (75% vs 80%). Moreover, the proportion of patients with microvascular complications in Croatia was smaller than in the total multi-country sample, 44.4% vs 70.6% respectively.

While technology provides many wonderful aids, it could also potentially add to distress due to access, cost, maintenance, and other issues. Having a CGM, for example, means that blood glucose levels are only a glance away, which could foster distress through simple availability. Findings of our study indicate that CGM users reported the lowest total PAID score and the proportion of participants having diabetes distress was the lowest among CGM users. Although no statistical difference was found among different technology users. Level of significance close to $p<0.05$ for the proportion of participants experiencing diabetes distress., suggests that with a larger sample size in new technology user subgroups (i.e. CGM sample size is n=29 compared to BGM sample size is n=397) statistical significance at $p<0.05$ level could be reached. Taking into account progressive adoption of newer technology in clinical practice, we

can speculate that more recent replication of our study may yield affirmative results for using such technology potentially showing its association with lower diabetes distress in people with T1DM.

In our study sample, more female patients used pump and CGM than males (p=0.004) and most App users were in the youngest age group (p=0.001), the last finding being in concordance with the global results demonstrating that younger participants were more likely to use apps than older participants (e.g. 14.3% of the youngest and 5.5% of the oldest subgroups used apps). We believe that those numbers would be relevantly increased today with new technologies available, affordable and endorsed by local clinical practice and policies. Subgroup analysis per country, with all differences reported being purely descriptive, showed diabetes distress being significantly lower in Serbia compared to Croatia. Looking into differences in patients' characteristics, the study population in Serbia used more apps and insulin pump users, with significant longer duration of T1DM.

Use of CGM in individuals with T1DM has the potential to avoid hypoglycemia through the availability of low-glucose alarms and the use of trend information. In our study, we observed the lowest proportions of participants with documented hypoglycemia episodes (both <3.9 and <3.0 mmol/L) among CGM users and those findings are in concordance with available evidence about the benefits of reduced frequency of hypoglycemic events in individuals with type 1 diabetes using CGM while treated by multiple daily injections (9). The use of different types of technology was associated with glycemic parameters, albeit only with postprandial glucose levels being significantly lower in insulin pump users compared to both, BGM and Apps users. While significant HbA1c improvements could be expected, as shown elsewhere, in adults with T1DM using real-time CGM (42), we didn't confirm this finding in our study. Possible explanation is smaller sample size of patient using new technology which disabled such effect to be detected.

This study has several strengths, including collecting data from a larger population of adults living with T1DM in a real-world setting. All potentially eligible patients at a study site were consecutively offered participation in the study in order to minimize patient selection bias. Participating investigators were selected randomly. Furthermore, we used a well-validated and comprehensive measure of diabetes distress.

Limitations of the study include the use of cross-sectional design, which disabled assessing for causal relationship. Retrospective collection and self-reported of i.e. hypoglycemia may

underestimate the true incidence and rates of hypoglycemic events. Participants on newer technology may be early adopters or have a higher socioeconomic status that may facilitate better glycemic outcomes. In the dynamic diabetes technology market, the percentage of new technology users might be substantially increased since data collection.

As we look to the future of digital in diabetes care, we should strive to ensure that the full potential of technology in diabetes can be reached. Simply having a device or application does not change outcomes unless the human being engages with it. This underscores the need for the health care team to assist people with diabetes in device and program selection and to support its use through ongoing education and training.

6. CONCLUSION

Diabetes is unique among chronic diseases because of the extent to which clinical outcomes are controlled by the patient. Achieving and maintaining control of diabetes requires people with T1DM to deal with a wide range of behaviors and conditions. Our study provides insights into diabetes distress and its relationship with the use of diabetes technology in a large international population of adults with T1DM. The results of the study did not confirm the hypothesis since no association at statistically significant level between new technologies' use and diabetes distress was found. Our finding suggests though that use of one or more new technology does not add additional emotional burden in people living with T1DM. Even more, the usage of new technology use predicts independently lower diabetes distress at a statistically significant level.

Given the high prevalence and impact of psychosocial problems in diabetes, our results imply importance of integrating psychological care into routine care for adults with T1DM aiming to further improve outcomes. Areas to address include providing education and training to healthcare professionals to improve the identification and management of diabetes distress and increase resources for implementing such programs.

7. LITERATURE

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8. SAŽETAK

Povezanost upotrebe tehnologije u liječenu osoba sa šećernom bolešću tipa 1 i distresa uzrokovanog šećernom bolešću.

Uvod: Šećerna bolest tipa 1 (T1DM) je kronična bolest kod koje je neminovna doživotna terapija inzulinom i svakodnevna samokontrola glikemije. T1DM smanjuje kvalitetu života oboljelih te kroz emocionalni odgovor na specifičan stil života može dovesti do distresa uzorkovanog šećernom bolešću. Unatoč tome što je razvoj tehnologije olakšao liječenje T1DM, korištenje tehnologije nekada predstavlja izazov te dodatno opterećenje radi težeg prihvaćanja novih uređaja.

Ciljevi: Primarni cilj bio je istražiti odnos između upotrebe tehnologije u liječenju odralsih osoba s T1DM te distresa vezanog uz šećernu bolest. Sekundarni ciljevi uključivali su procjenu prevalencije distresa vezanog uz šećernu bolesti i identifikaciju njegovih prediktora.

Ispitanici i metode: Radilo se o multicentričnoj, presječnoj studiji koja je provedena je u nekoliko zemalja jugoistočne Europe. Uključeno je 499 sudionika kojima je dijagnosticiran T1DM unazad najmanje godinu dana, koji su imali 26 godina ili više te kod kojih je bio dostupan podatak vrijednosti HbA1c. Ispitanici su samostalno ispunili Upitnik o problematičnim područjima šećernoj bolesti (engl. Problem Areas in Diabetes Questionnaire, PAID) od 20 čestica. Ukupan PAID rezultat od 40 ili više ukazuje na značajan distres vezan uz šećernu bolest.

Rezultati: Srednja dob ispitanika bila je 49,11 (SD 13,99) godina, srednji HbA1c 7,9% (SD 1,46) i srednj ukupni rezultat PAID-a 29,19 (SD 19,51). Distres uzrokovan šećernom bolešću je nađen kod 29,2% sudionika. Ukupno 20% sudionika koristilo je u liječenju T1DM nove tehnologije, uključujući kontinuirano mjerenje glukoze, inzulinske crpke te mobilne aplikacije. Nije nađena statistički značajna povezanost između upotrebe tehnologije u liječenju T1DM i distresa uzorkovanog šećernom bolešću. Izdvojeni su i prediktori distresa uzrokovanog šećernom bolešću; spol, indeks tjelesne mase (ITM) i HbA1c. Osobe muškog spola imale su 46% manji rizik za pojavu distresa uzorkovanog šećernom bolešću, povećanje ITM-a za 1 kg/m^2 dovelo je do 5% veće vjerojatnosti od navedenog distresa, a svaki je porast HbA1c od 1% povećao izglede za distres za 16%. Nakon anuliranja utjecanja navedenih prediktora, sama

uporaba tehnologije ostala je značajan čimbenik te se pokazalo da bolesnici s T1DM koji su koristili novu tehnologiju imaju 42% manju vjerojatnost da će doživjeti distres uzrokovanog šećernom bolešću u usporedbi s onima koji koriste samo glukometre. Zasebno se izdvojeni uzroci nelagode koji najviše dopridonose distresu uzorkovanom šećernom bolešću; zabrinutost za budućnost, tjeskoba zbog kroničnih komplikacija, suočavanje s postojećim problemima povezanim s dijabetesom i krivnja koja nastaje radi loše regulacije T1DM.

Zaključak: U studiji odraslih osoba s T1DM nađena je visoka prevalencija distresa uzrokovanog šećernom bolešću. Nije pronađena statistička povezanost između korištenja tehnologije u T1DM i distresa uzrokovanog šećernom bolešću, što sugerira da korištenje jedne ili više novih tehnologija dodatno emocionalno ne opterećuje pojedince s T1DM. Spol, ITM i HbA1c bili su značajni prediktori distresa uzrokovanog šećernom bolešću, a uporaba nove tehnologije neovisno o navedenim prediktorima predviđa niži distres uzorkovan šećernom bolešću u ispitivanoj populaciji. Rezultati upućuju na potrebu individualnog pristupa svakom bolesniku s T1DM uzimajući u obzir kako korištenje novih tehnologija tako i psihosocijalnu podršku za poboljšanje kvalitete života.

9. SUMMARY

Background: Type 1 diabetes (T1DM) is a chronic disease requiring lifelong insulin therapy and rigorous self-management. As it negatively impacts the affected individuals' quality of life, it may eventually lead to diabetes distress, the emotional response to living with diabetes. While technology has enhanced diabetes management, there can also be subjective burdens and barriers to uptake.

Objectives: The primary goal of this study was to investigate the relationship between the use of diabetes technology and diabetes distress among adults with T1DM. Secondary objectives included assessing the prevalence and predictors of diabetes distress.

Material and methods: The research encompassed a multicenter, cross-sectional approach across several countries in South Eastern Europe. A total of 499 participants who fulfilled the eligibility criteria (diagnosed with T1DM for at least a year, aged 26 or older, with recent HbA1c data) were included in the study. They self-completed 20-item Problem Area in Diabetes (PAID) Questionnaire. A total PAID score of 40 or higher indicated significant diabetes distress.

Results: The mean age of participants was 49.11 (SD 13.99) years, mean HbA1c 7.9% (SD 1.46) and mean PAID total score of 29.19 (SD 19.51). Diabetes distress was found in 29.2% of the participants. About 20% of participants adopted new diabetes technologies, including continuous glucose monitors, insulin pumps, and mobile applications. The study did not reveal a statistically significant association between the use of diabetes technology and diabetes distress. Significant predictors of diabetes distress did emerge; gender, body mass index (BMI), and HbA1c. Being male reduced odds of high diabetes distress by 46% . Each 1 kg/m^2 increase in BMI led to a 5% increase in the likelihood of high distress, while every 1% increase in HbA1c raised the odds by 16%. After accounting for these predictors, technology use remained a significant factor and T1DM patients who embraced new technology exhibited a 42% lower chance of experiencing high diabetes distress, compared to those using traditional blood glucometers. The study also highlighted specific aspects contributing to distress. Concerns about the future, anxiety about chronic complications, coping with existing diabetes-related problems, and guilt stemming from deviations in diabetes management were identified as key drivers of distress.

Conclusion: We found high prevalence of diabetes distress in the population of patients having T1DM. No statistical association between new technology use and diabetes distress was found, suggesting that the use of one or more new technologies does not add additional emotional burden in people living with T1DM. Sex, BMI and HbA1c were significant predictors of high diabetes distress, and new technology use predicts independently lower diabetes distress in such patients. The findings emphasize the need for personalized approaches that consider both technological interventions and psychosocial support to enhance the quality of life for individuals living with T1DM.

10. APPENDIX

Problem Areas in Diabetes (PAID) questionnaire, English Version - Mapi

Problem Areas In Diabetes (PAID) Questionnaire

INSTRUCTIONS: Which of the following diabetes issues are currently a problem for you?
Circle the number that gives the best answer for you. Please provide an answer for each question.

	Not a problem ▼	Minor problem ▼	Moderate problem ▼	Somewhat serious problem ▼	Serious problem ▼
1. Not having clear and concrete goals for your diabetes care?	0	1	2	3	4
2. Feeling discouraged with your diabetes treatment plan?	0	1	2	3	4
3. Feeling scared when you think about living with diabetes?	0	1	2	3	4
4. Uncomfortable social situations related to your diabetes care (e.g., people telling you what to eat)?	0	1	2	3	4
5. Feelings of deprivation regarding food and meals?	0	1	2	3	4
6. Feeling depressed when you think about living with diabetes?	0	1	2	3	4
7. Not knowing if your mood or feelings are related to your diabetes?	0	1	2	3	4
8. Feeling overwhelmed by your diabetes?	0	1	2	3	4
9. Worrying about low blood sugar reactions?	0	1	2	3	4
10. Feeling angry when you think about living with diabetes?	0	1	2	3	4
11. Feeling constantly concerned about food and eating?	0	1	2	3	4
12. Worrying about the future and the possibility of serious complications?	0	1	2	3	4
13. Feelings of guilt or anxiety when you get off track with your diabetes management?	0	1	2	3	4
14. Not "accepting" your diabetes?	0	1	2	3	4
15. Feeling unsatisfied with your diabetes physician?	0	1	2	3	4
16. Feeling that diabetes is taking up too much of your mental and physical energy every day?	0	1	2	3	4
17. Feeling alone with your diabetes?	0	1	2	3	4
18. Feeling that your friends and family are not supportive of your diabetes management efforts?	0	1	2	3	4
19. Coping with complications of diabetes?	0	1	2	3	4
20. Feeling "burned out" by the constant effort needed to manage diabetes?	0	1	2	3	4

PAID - United States/English - Mapi.
PAID_AU1.0_eng-USori.doc

11. CURRICULUM VITAE

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2020 - present Ph.D. programme Translational Research in Biomedicine,
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2021 - present	Global Medical Lead Insulins, Sanofi Paris
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2008 - 2014	Medical Advisor for cardiometabolic diseases
2006 - 2008	Medical Affairs Clinical Operations Head, Sanofi Croatia
2001 - 2006	Clinical Research Associate (R&D) Aventis
1998 - 2001	Medical Representative, Servier
1996 - 1998	General practitioner, Public Health Center, Zagreb

Relevant trainings:

Data generation, Study designs, publications, Vienna, Austria

One week course in Diabetes Centre, University of Perugia, Italy

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