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“Modern technologies in glucose monitoring of children and adolescents with Diabetes type 1 – advantages”

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Nowadays type 1 diabetes mellitus (T1DM) is the most frequent type of diabetes in childhood and adolescents, about 95%. In the last decades, the incidence is increasing mainly in the group below 6 years of age. The last international consensus statement postulates that the “gold standard” for treatment of T1DM in childhood is insulin pump therapy (IPT, CSII), and currently sensor-augmented pump therapy (SAP) (ISPAD, 2018). The last one consists of CSII and glucose sensor, which measures interstitial glucose levels constantly (280 times per 24 h.), called also real-time continuous glucose monitoring (rtCGM). Another type of CGM system in patients on basal-bolus regimen with insulin pens (MDI) is professional “blinded” sensor for 7 days on the same principle as SAP. In this case, patient does not see the blood glucose (BG) in real-time, but retrospectively, when the data is downloaded on special software. In the last year, a number of studies have confirmed the benefits and accuracy of the Libra system (measurement of BG in the interstitial fluid without finger pricking for 14 days). The accuracy of blood glucose measurements, recorded by Libre, is comparable to the registered with a glucometer. (Battelino et al., 2016) Main advantages of CGM usage are associated with: decreased in blood glucose variability, reduced episodes of acute complications (hypoglycaemia and DKA), better the quality of life of patients and their families and postponed chronic complications (Shalitin et al., 2011) as well as reducing the incidence of “burnout” syndrome (Lane et al., 2013). CSII and CGM are the basic components of the “closed loop systems” known as „artificial pancreas”. In 2016, FDA approved first “closed loop system” for usage above age of 14 years in U.S. It consists of insulin pump, rtCGM and algorithm, which controls automatically releasing of insulin without a human intervention. (FDA, 2016) In Bulgaria, the main CGM systems are not register yet and reimbursed by national health system but are widely known and used. No published data is available among Bulgarian people with diabetes at the time of project.

Project objectives:

1. Introduction of innovative and modern technologies in the control of T1DM.
2. Comparison between different types of SAP and conventional insulin analog therapy (MDI).
3. Electronic and remote monitoring of patients.
4. Technical training of parents for proper usage of CGM.
5. Assessment of glycemic control by HbA1c and CGM parameters.
6. Assessment of acute complications (hypoglycemia and hyperglycemia).

7. Assessment of quality of life among patients and their families.

Materials and methods: During the prospective study, 20 children and adolescents with type 1 diabetes mellitus (11 boys and 9 girls) were enrolled. We randomized them, by the study protocol, in 3 groups according to the type of insulin therapy. Group 1 consisted of 6 children on SAP with sensor Enlite, II-gr. - 6 children MDIs with Libre and the 3rd gr. – 8 children on CSII with a Libre. The study protocol was approved by the ethical committee of the Medical University of Varna. Parents and participants above 6 years old were enrolled after singing written informed consent. All parents underwent training on the maintenance of a sensor according to the manufacturer requirements. At the 0 and 6th month, all participants performed a physical examination, including: weight, height, waist circumference (WC), BMI, blood pressure (BP), places of insulin applications, pubertal development. Additionally, data for the type of therapy (MDI/pump), sensor type (iPro /Enlite), daily insulin dose and sensor parameters were assessed (0, 3rd and 6th month). If necessary, the therapy settings were adjusted to the individual needs of the patient, by e-mail/Internet contact. At the end of the follow-up, an assessment of the quality of life and satisfaction of the participants was carried out. The data collected was processed by SPSS 18.0.

Results:

1. **Statistical analysis showed no significant difference in following parameters:**
   - ❖ Mean age of children between the groups: Ist: 9.3±3y., IInd gr. 9.9±1.8y., IIIrd gr. 9.0±3.9y.
   - ❖ Mean duration of diabetes: Ist. 5.5±1.2y., II nd. 3.2±2.6y., IIIrd. 4.4±2.3y.
   - ❖ Mean total daily insulin dose:

Insulin dose (IU/kg/d)	**Baseline**	**3rd m.**	**6th m.**	**p**
I gr.	0.66-0.74	0.69-0.75	0.62-0.73	NS
II gr.	0.74-0.79	0.79-0.80	0.74-0.80	NS
III gr.	0.75-0.89	0.75-0.84	0.74-0.85	NS
p	NS	NS	NS	

   - ❖ Height, weight, BMI, WC, BP and puberty stage
   - ❖ Time in range (3.9-10 mmol/l), aim>70%

	Baseline	3rd m.	6th m.
I gr.	75%	65.8%	68.2%
II gr.	57%	76.5%	70%
III gr.	64%	63.4%	67.6%

2. **Duration of CGM usage**: We found that participants on CSII+Libre and MDI+Libre spent significantly more time with CGM at 6th month compare to baseline as followed: 91% vs. 97%, p=0.0001 and 94% vs. 98%, p=0.001.
3. **Time in hypoglycemia (aim<4%):** No episodes of severe hypoglycemia were registered during the study period. Time in spent in hypoglycemia was consistent for the followed up period. In the end of the study time spent with BG below 3.5 mmol/l was reduced by 50%. Participants on CSII+Enlite spent significantly less time in hypoglycemia <3.5 mmol/l as followed: 3% vs. 0.4%, p=0.02.
4. **Time spent in hyperglycemia above 14 mmol/l (aim<5%):** Mean time spent in hyperglycemia for all participants was reduced by 1.5% (13.5% vs. 12%). Most pronounced improvement is registered in the group using CSII and Libre – 13% vs. 10%, p<0.05. Participants on SAP spent least time with BG above 14 mmol/l compared to all.
5. **Coefficient of variation (CV, aim <36%):** At the final point of the study we found reduced CV by 3% (29% vs. 26%, p=0.03). Most pronounced improvement in this parameter is shown in CSII+Enlite group by 5%, followed by CSII+Libre by 4%.
6. **Metabolic control:** Mean HbA1c is reduced by 0.4% (7.6% vs. 7.2%, p=0.03). We found significant correlations between estimated HbA1c (eHbA1c) and conventional measured from blood samples for the study period. eHbA1c on the 3rd month strongly correlate with final HbA1c (r=0.85, p<0.001), which turn it in new parameter for assessment of diabetes control, eliminating the need for taking blood samples. In that way we could reduce the burden in patients and medical staff.
7. **Quality of life** assessed by Kidscreen 27 questionnaire, version children 8-18 years and version parents. (Max. score135 p.). There is child-parent agreement it total score (105.7±0.9 vs. 103.2±18.8 p., p>0.05). Parents gave significantly higher score compared to their children in sections: school, friend, family relations and free time.

Conclusions:

1. The metabolic control among children and adolescents with T1DM is improved, six months after the introduction of the routine use of CGMs
2. Estimated HbA1c significantly correlates with conventionally measured HbA1c for the whole period of the study.
3. Coefficient of variation remains permanently below 36% during the continuous usage of CGM. TIR show negative correlation to HbA1c level and does not depend on the duration of sensor use, remaining permanently above the target 70% in all patients with a sensor in the study group.
4. Time spent in hypoglycemia (3.9 mmol/l) is steadily around the postulated international target of 4%. At the end of the observation, the duration of episodes with BG<3.5 mmol/l was reduced by 50%.
5. Time spent in hyperglycemia (>14 mmol/l) is still above 5% and significantly prevails over the time spent in hypoglycemia. Hyperglycemia directly and significantly affects HbA1c levels throughout the follow-up without increasing the risk of DKA.

6. Strong significant association is shown between CGM parameters and metabolic control. That identifies them as suitable for including them in additional panel for assessment in diabetes control for patients on constant usage of CGM. Most important parameters affecting glycemic control are: estimated HbA1c, time in range, coefficient of variation and time spent in hyperglycemia.

Project contributions:

1. For the first time in Bulgaria are evaluated the benefits of constant use of CGM systems among Bulgarian children and adolescents. The role of new sensor parameters as “time in range”, “time in hypoglycemia”, “time in hyperglycemia” is established among Bulgarian patients, as well as is specified the most urgent target for improvement in control and reduction of future complications - time in hyperglycemia above 14 mmol/l.
2. For the first time are proposed changes in routine monitoring of children with diabetes using new technologies in their diabetes treatment.
3. For the first time in Bulgaria, the quality of life of patients with T1DM below 18 years is assessed. The KidScreen 27 questionnaire is translated and accessible for future research.

The project is a part of a the dissertation work “Innovations for improving the successes in the treatment of children and adolescents with diabetes” for the acquisition of a scientific and educational degree “PhD” by Dr. Yulia Bazdarska on, successfully defended on 29.05.2020, as well as in several publications and participations, incl. international meetings. The project contributed to the development of skills and knowledge in the field of new technologies in type 1 diabetes mellitus and for the scientific and clinical data needed in order to improve the diabetes treatment and prognosis.