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Quality of Life in Children and Adolescents with Chronic Diseases – Neurological Disorders (Epilepsy and Cerebral Palsy) and Diabetes Mellitus

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Contents

1 Abbreviations 6

2 Publication List 7

3 Abstract English 9

4 Abstract German 10

5 Quality of Life and Chronic Diseases 11

5.1 Definitions 11

5.2 Quality of Life in Chronic Diseases 12

5.3 Quality of Life in Children 14

6 Goals of the Studies 15

7 Contributions to the Papers 17

8 Paper 1: Long-term Hb_{A1c}, Physical Fitness, Nerve Conduction Velocities, and Quality of Life in Children with Type 1 Diabetes Mellitus – A Pilot Study 18

9 Paper 2: Accuracy of Flash Glucose Monitoring in a Patient with Dravet Syndrome on a Ketogenic Diet 19

10 Paper 3: Visual Impairment and Functional Classification in Children with Cerebral Palsy 20

11 Conclusion 21

12 References 23

13 Acknowledgment 28

1 Abbreviations

CP	Cerebral Palsy
DS	Dravet Syndrome
KD	Ketogenic Diet
T1DM	Type 1 Diabetes Mellitus
QoL	Quality of Life
WHO	World Health Organization

2 Publication List

Papers published and included in this dissertation:

Paper 1:

Schiller K, Kofler M, Frühwirth M, Kiechl-Kohlendorfer U, Rauchenzauner M. Long-term Hb_{A1c}, Physical Fitness, Nerve Conduction Velocities, and Quality of Life in Children with Type 1 Diabetes mellitus – A Pilot Study. Healthcare (Basel). 2020;8(4).

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Schiller K, Kortas A, Unterholzner G, Rauchenzauner M. Accuracy of Flash Glucose Monitoring in a Patient with Dravet Syndrome on a Ketogenic Diet. Jahrestagung der Deutschen Gesellschaft für Neuropädiatrie, München, 11.-14.09.2019.

Romberg L, **Schiller K**, Unterholzner G, Weber K, Raffler S, Einsle J, Sommer J, Rauchenzauner M. The Importance of 24h-Video-EEG-Monitoring in the Diagnosis of Epilepsy in Children and Youth. Jahrestagung der Deutschen Gesellschaft für Neuropädiatrie, München, 11.-14.09.2019.

Schiller K, Koch M, Seufert T. Wie schafft man es, dass sich der Leser beim Lesen auf den Text konzentriert – Disfluency-Effekt und Lernstrategien. EARLI-SIG 2 Meeting, University Rotterdam, 25.-27.08.2014.

3 Abstract English

Background: Quality of Life (QoL) is a multidimensional concept comprising physical health, psychological state, daily and social functioning and serves as an evaluation tool for medical interventions. Stated as the ultimate goal of health care, QoL is one important target in the treatment of chronic diseases. Compared to healthy controls, QoL in patients with chronic diseases is often reduced. Therefore, the aim of the conducted studies was the improvement of QoL in children with chronic diseases.

Methods: Three studies with different approaches to QoL were performed. Study 1 is about a possible association between long-term metabolic marker and QoL in children with Type 1 Diabetes Mellitus (T1DM). Study 2 focuses on the control of hypoglycemia as side effect of Ketogenic Diet (KD) in patients with Dravet Syndrome (DS). In study 3, visual impairment and functional classification in patients with Cerebral Palsy (CP) were analyzed.

Results: Data showed that i) good metabolic control was associated with enhanced QoL in patients with T1DM and QoL during follow-up might be influenced by Hb_{A1c} values (Study 1). Additionally, ii) hypoglycemia rate was higher in the beginning of KD and declined over time in the treatment of DS (Study 2) and iii) visual impairment was found in almost two-third of children with CP and functional classification was associated with severity of visual impairment (Study 3).

Conclusion: QoL in children with chronic diseases can be influenced in different ways. Herein, it was achieved by i) detecting an association between Hb_{A1c} values and QoL in patients with T1DM (Study 1), ii) using a flash glucose monitoring system in children with DS under KD to control side-effects (Study 2), and iii) considering the possibility of visual impairment affecting the behaviors and participation in social life of children with CP in everyday life (Study 3).

4 Abstract German

Einleitung: Lebensqualität (QoL) stellt sich als multidimensionales Konstrukt dar, das neben der physischen Gesundheit auch den psychischen Zustand sowie Alltagsfunktionen und die soziale Funktionalität des Menschen umfasst. Im klinischen Alltag dient das Konstrukt „Lebensqualität“ häufig der Bewertung von klinischen Interventionen und Therapien. Im Gesundheitswesen wird die Lebensqualität als ein übergeordnetes Ziel statuiert und hat bei der Behandlung von Kindern mit chronischen Erkrankungen einen hohen Stellenwert inne. Im Vergleich zu gesunden Kontrollgruppen ist die Lebensqualität von chronisch Kranken oftmals deutlich reduziert. Das Ziel der vorliegenden Studien bestand darin, durch verschiedene Interventionen eine verbesserte Lebensqualität chronisch kranker Kinder zu erreichen.

Methoden: Es wurden drei Studien mit unterschiedlichen Ansätzen zur Erhöhung der Lebensqualität durchgeführt. Studie 1 untersucht eine potenzielle Verbindung zwischen der langfristigen Blutzuckerkontrolle und Lebensqualität bei Patienten mit Typ 1 Diabetes mellitus (T1DM). Studie 2 fokussiert auf eine Optimierung der Lebensqualität von Kindern mit Dravet-Syndrom (DS) durch Kontrolle von Hypoglykämien als Nebeneffekt der ketogenen Diät (KD). In Studie 3 werden visuelle Einschränkungen und die Klassifikation von Grob- und Feinmotorik bei Kindern mit Zerebralparese (CP) analysiert.

Ergebnisse: Die Auswertung der Daten ergab, dass i) eine bessere Blutzuckerkontrolle mit erhöhten Werten der Lebensqualität einherging und frühe Hb_{A1c}–Werte mit QoL der Patienten im Verlauf assoziiert waren (Studie 1). In der zweiten Studie war ii) die Hypoglykämie-Rate zu Beginn der KD von Patienten mit DS höher und nahm im Verlauf der Beobachtungsperiode signifikant ab (Studie 2). Schließlich konnten iii) visuelle Einschränkungen bei etwa zwei Drittel der Patienten mit CP registriert und ein Zusammenhang von der Schwere der visuellen Einschränkung mit dem funktionellen Klassifikationssystem aufgedeckt werden (Studie 3).

Zusammenfassung: Die Lebensqualität von Kindern mit chronischen Erkrankungen kann auf unterschiedliche Arten beeinflusst werden. Im vorliegenden Fall wurde dies durch i) die Aufdeckung eines Zusammenhangs von Hb_{A1c}–Werten und Lebensqualität bei Kindern mit T1DM (Studie 1), ii) durch den Einsatz eines kontinuierlichen Blutzuckermessgeräts bei Kindern mit DS unter KD zur Kontrolle von Hypoglykämien als Nebenwirkung (Studie 2) und iii) durch die Beachtung des möglichen Einflusses von visuellen Einschränkungen bei Kindern mit CP auf die alltäglichen Fähigkeiten und Teilnahme am sozialen Leben (Studie 3), erreicht.

5 Quality of Life and Chronic Diseases

5.1 Definitions

By the World Health Organization (WHO) *„Quality of life is defined as an individual's perception of his/her position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment"*(1). Following this definition, Quality of Life (QoL) is a multidimensional concept and is influenced by different factors. To evaluate medical interventions today, measurements often focus on the last part of the definition and therefore assess physical health, psychological state, everyday functioning, and social embedment (2).

The term "chronic disease" is used differently within professional communities (3). The WHO stated the definition that "*Noncommunicable diseases, also known as chronic diseases, are not passed from person to person. They are of long duration and generally slow progression. The four main types of noncommunicable diseases are cardiovascular diseases (like heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructed pulmonary disease and asthma) and diabetes."*[1] Medicine.Net defines chronic disease as "*one lasting 3 months or more, by the definition of the U.S. National Center for Health Statistics. Chronic diseases generally cannot be prevented by vaccines or cured by medication, nor do they just disappear*"[2]. New reports suggest not to define a certain list of diseases as well as a specified length of the disease to match the criteria for "chronic". They postulated a more practical definition in which "chronic" stands for a disease that is "permanently or recuring again for a long period of time" (3). This suggestion will be followed when defining chronic diseases in this dissertation.

QoL is one important part in the treatment of chronic diseases and often stated as the ultimate goal of health care in these patients (4). In the next chapter, QoL in chronic diseases and especially in children will be discussed.

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[1] http://origin.who.int/topics/noncommunicable_diseases/en/ (12/2020)

[2] https://www.medicinenet.com/script/main/art.asp?articlekey=33490 (12/2020)

5.2 Quality of Life in Chronic Diseases

QoL is an important outcome measure evaluating the perspective of patients and their social environment (5). The goal is the improvement of treatment efficiency and care of patients by focusing on their QoL (6). The multidimensional concept QoL concentrates on the well-being of patients which is influenced by health status, health care, and the social network (7). Additionally, QoL encompasses the amount of symptoms, the occurrence of side effects due to treatments and the general rating of the own health status and contentment in life (8). It is therefore one important factor in the management of chronic diseases (6).

Several studies pointed to an impaired QoL in patients fulfilling the criteria of a chronic disease when they were compared to a healthy control group (9-13). The burden of chronic diseases seems to have a negative effect not only on QoL of the patient but also on the general health status (14, 15). Additionally, QoL was shown to significantly impact the compliance of the patients (16). This is of importance especially in the treatment of Diabetes Mellitus because the diabetes management has a substantial effect on the course of the disease (17).

In this thesis, the focus was on QoL in children and adolescents in different chronic diseases, i) Type 1 Diabetes Mellitus (T1DM), ii) Dravet Syndrome (DS), and iii) Cerebral Palsy (CP). These chronic diseases are explained in the following sections.

i) Type 1 Diabetes Mellitus (T1DM)

T1DM is an autoimmune disorder described by the damage of pancreatic cells which generate insulin resulting in an altered metabolism (18). The autoimmunity process in T1DM arises early and lasts for years (19). Determinants of the process are genetic polymorphism, environmental factors and infectious agents (20-22). Managing T1DM is multifaceted and requires a high amount of responsibility and self-discipline to accomplish and maintain a satisfactory metabolism (23). Especially in childhood and youth during puberty, hormonal and psychological changes occur and make diabetes management more difficult (24, 25). Therefore, a multidisciplinary team of pediatricians, psychologists, social workers and nutritionists for teaching and controlling diabetes management is part of the treatment of T1DM (23).

QoL in patients with T1DM has been shown to be associated with metabolic control (26, 27). Glycated haemoglobin values (Hb_{A1c}) serve as marker for metabolic control and a positive association between better lower Hb_{A1c}, which indicates a better metabolic control, was connected to higher QoL in children and adolescents with T1DM (27). Furthermore, sociodemographic factors also seem to have an effect on QoL in patients with T1DM. These involve for example gender, age of children, family status, family income or social status (28). In detail, female gender, higher age, single-parent families and low social status resulted in worse QoL (28).

ii) Dravet Syndrome (DS)

The Dravet Syndrome (DS) is an intractable epilepsy described as Severe Myoclonic Epilepsy of Infancy with a typical seizure onset within the first year of an infant (29, 30). Therein, generalized and unilateralized tonic-clonic or just clonic febrile or afebrile seizures can be observed (30). Afterwards, it comes to various seizures which are often connected to interruption in the development of the children, behavioral problems as well as cognitive impairment (29, 30). Charlottes Dravet described the DS the first time in 1978, but diagnosis as well as management of DS are still difficult to this day (29). Pharmacoresistance often requires multiple modifications of the anticonvulsive treatment (31). Most of the children with DS are not seizure-free and the Ketogenic Diet (KD) as a non-pharmaceutic option already revealed significant improvement up to seizure freedom (31, 32). The KD was developed in the 1920s and amended the treatment of several forms of drug resistant epilepsy syndromes such as DS (31, 33-35). Consisting of a high amount of fat, adequate proteins and less carbohydrates in a certain proportion, one potential side effect of the KD are hypoglycemia (36). Hypoglycemia can be acute and severe or chronic and non-severe and due to the risk of damaging effects for example on cognition, hypoglycemia should be well controlled when starting a KD (36). Frequently, hypoglycemia are not observed during the treatment of KD, but the implementation of a flash glucose monitoring system would be an easy and practical method to control the hypoglycemia as side effects and enhance QoL of patients with DS.

iii) Cerebral Palsy (CP)

CP is defined as a group of permanent disorders affecting the development of movement and posture (37). Generated in the fetal or infant brain, activity limitation is one main symptom. Two to three children of 1000 newborns are diagnosed with CP and the rate is increased in neonates with low birth weight from 40 to 100 children of 1000 newborns (38). It is the most frequent motor disability during childhood, and difficulties frequently appear before the age of

18 months (39). Treatment of CP is not only a challenge to the children and their families, but also to clinical institutions. Frequent concomitants of CP such as pathological alterations of sensation, perception, cognition as well as behavioral abnormalities, epilepsy, and derivative musculoskeletal problems calling for a multimodal approach (39). Due to the huge number of comorbidities and different degrees of impairment, the evaluation and enhancement of QoL is essential in these patients.

5.3 Quality of Life in Children

Considering the past years, QoL research has become more important, but most of the published studies and measurements concentrated on adults (2). Assessing QoL in children is different and chronic health problems are not only a burden to the children but also to their families (40). For a long time, the main part of QoL research in children were the ratings of their parents or physicians and only few studies focused on the children's perception (41-44). Additionally, measurements for younger children under 12 years were sparse (2).

In recent years, a lot of validated questionnaires matching a broad age-spectrum with adequate reliabilities have been developed and were applied in clinical research (45-50). Following the criteria of the WHO, measurements assessing QoL should be child-centered, assessable in self-reports, dependent on age and developmental stage of the children, intercultural, comprise a general score with specific elements as well as more positive than negative parts of QoL (51). Another debate was about at which age children are able to communicate about their QoL. The majority of experts agreed that QoL in younger children can be assessed when their abilities are respected, i.e. child's language is used and the children are not overstrained as measured by their stage of development (52).

There are different methods to assess QoL: One validated questionnaire which was also used in one of the present studies is the KINDL-R (48, 49). Three versions of different age groups (4-7 years = age group 1, 8-12 years = age group 2, 13-17 years = age group 3) as well as disease specific modules are available. For the parent rating, there are two versions for children aged 4-6 years and 7-17 years. The KINDL-R is a paper-pencil questionnaire containing 24 items. Therein, the following six subscales can be extracted: Physical well-being, emotional well-being, self-esteem, family, friends and school. Each of the 24 items targets to quantify the average feelings and experiences from the previous week and are measured on a five-point Likert-scale (from 1 = "never" to 5 = "always"). The mean score of each of the six subscales as well as the total QoL score are computed by adding up the answers and the final score can be transformed into a normalized score with higher numbers representing higher overall QoL. The KINDL-R has adequate reliability and validity and was already successfully used in several studies to assess QoL in childhood and youth (53, 54).

Besides validated questionnaires as KINDL-R (48, 49), it is possible to measure differences in physical health or evaluate implications for everyday functioning. These different methods to influence QoL were also used in the following studies.

6 Goals of the Studies

The three studies lay focus on different parts of QoL in children with chronic diseases. As defined in 6.1, QoL is a multidimensional construct comprising physical health, psychological well-being, everyday functioning and social embedment (1). The parts of QoL addressed in the different studies are illustrated in *Figure 1*.

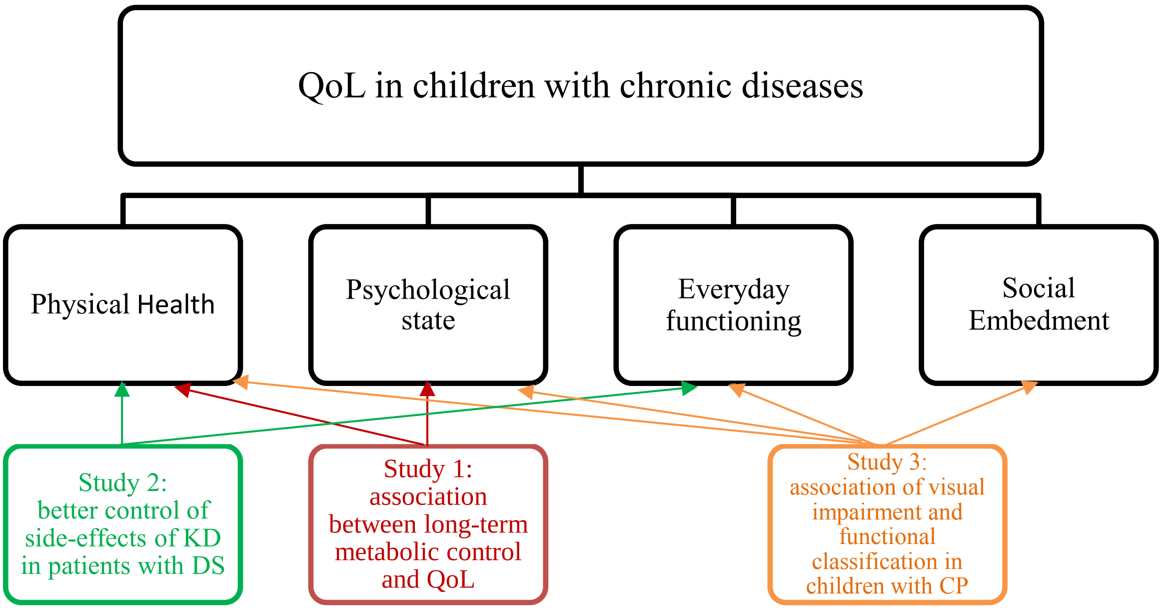

Figure 1. QoL as a multidimensional construct following the definition of WHO (1) and its connection to the studies of this thesis.

It becomes clear, that all components of QoL could be covered by the three studies: The first study referred to physical health and psychological state of T1DM patients. The second study addresses the part of physical health as reducing side effects resulting in a better QoL in patients with DS as well as the everyday functioning. In the third study, effects on everyday functioning and social embedment were examined with visual impairment and functional classification in patients with CP. Due to the better understanding of different comorbidities, a tailored treatment for patients with CP can be obtained and therefore QoL can be increased.

Paper 1: Long-term Hb_{A1c}, Physical Fitness, Nerve Conduction Velocities and Quality of Life in Children with Type 1 Diabetes mellitus – a pilot study

The goal of this study was to find a potential relation of QoL, Hb_{A1c} as a marker for metabolic control, physical fitness, and nerve conduction velocities in patients with T1DM. The question was raised whether long term Hb_{A1c} values influence QoL and the specific subscales in patients with T1DM or might even serve as predictor for QoL. Identifying a somatic parameter associated with QoL could lead to a better understanding and increase of QoL.

Paper 2: Accuracy of Flash Glucose Monitoring in a Patient with Dravet Syndrome on a Ketogenic Diet

KD is a non-pharmaceutic treatment and often implemented in the management of drug refractory epilepsies such as DS. As a side effect of the specific nutrition during the KD, hypoglycemia can arise. The goal of this study was to control glucose concentrations with a flash glucose monitoring system from onset of KD over six months to reduce hypoglycemia and therefore enhance QoL of children with DS.

Paper 3: Visual Impairment and Functional Classification in Children with Cerebral Palsy

In this study, the main goal consisted of the evaluation of the prevalence of visual impairment among children with CP and to investigate a possible association between type and severity of visual impairment and CP-subtypes, functional classification and etiology. Treatment of visual impairment as comorbidity of CP could be very helpful for the development of children by facilitating daily life actions and increasing QoL.

7 Contributions to the Papers

Paper 1: Long-term Hb_{A1c}, Physical Fitness, Nerve Conduction Velocities and Quality of Life in Children with Type 1 Diabetes mellitus – a Pilot Study

Together with my supervisor PD Dr. Markus Rauchenzauner, initiating this study, the collection of data was conducted with help of Prof. Dr. Martin Frühwirth and Dr. Michaela Fantur. The data input as well as the statistical evaluation fell into my field of responsibility as well as the visualization. The writing (original draft preparation) of the paper was done by me and PD Dr. Markus Rauchenzauner. Prof. Dr. Markus Kofler performed the review and editing.

Paper 2: Accuracy of Flash Glucose Monitoring in a Patient with Dravet Syndrome on a Ketogenic Diet

In cooperation with my colleague Dr. Aline Kortas and my supervisor Markus Rauchenzauner, initiating the study, data collection was carried out with help of Dr. Gabriele Unterholzner. My area of responsibility included the data input, the statistical evaluation and the visualization. Finally, Dr. Aline Kortas and I equally contributed to writing the paper with support of PD Dr. Markus Rauchenzauner as editor.

Paper 3: Visual Impairment and Functional Classification in Children with Cerebral Palsy

Together with my supervisor PD Dr. Markus Rauchenzauner, I analyzed the data of the register and I was responsible for the statistical evaluation and generating figures. Dr. Michaela Honold was responsible for the data curation, was helping with validation and interpretation of the data as well as contributing with ideas for writing the first draft. Dr. Ivo Baldissera contributed with the data curation, validation, methodology and investigation especially of the data regarding the visual examination. PD Dr. Rainer Biedermann collected the clinical data together with Birgit Tschiderer, Dr. Ursula Albrecht and Claudia Arnold, who were also responsible for data curation and interpretation. PD Dr. Markus Rauchenzauner and I equally contributed to writing the paper. Prof. Dr. Kevin Rostasy had the study idea, supervised and managed the project and together with Markus Rauchenzauner he reviewed and edited the paper.

8 Paper 1: Long-term Hb_{A1c}, Physical Fitness, Nerve Conduction Velocities, and Quality of Life in Children with Type 1 Diabetes Mellitus – A Pilot Study

Schiller K, Kofler M, Frühwirth M, Kiechl-Kohlendorfer U, Rauchenzauner M. Long-term Hb_{A1c}, Physical Fitness, Nerve Conduction Velocities, and Quality of Life in Children with Type 1 Diabetes mellitus – A Pilot Study. Healthcare (Basel). 2020;8(4).

DOI: 10.3390/healthcare8040384

9 Paper 2: Accuracy of Flash Glucose Monitoring in a Patient with Dravet Syndrome on a Ketogenic Diet

Kortas A*, **Schiller K***, Unterholzner G, Rauchenzauner M. Accuracy of Flash Glucose Monitoring in a Patient with Dravet Syndrome on a Ketogenic Diet. Neuropediatrics. 2020;51(1):45-8.

DOI: 10.1055/s-0039-1697621

*equally contributed to this paper

10 Paper 3: Visual Impairment and Functional Classification in Children with Cerebral Palsy

Rauchenzauner M*, **Schiller K***, Honold M, Baldissera I, Biedermann R, Tschiderer B, Albrecht U, Arnold C, Rostasy K. Visual Impairment and Functional Classification in Children with Cerebral Palsy. Neuropediatrics.2021.

DOI: 10.1055/s-0040-1722679

*equally contributed to this paper

11 Conclusion

The three studies contributed to QoL in children with chronic diseases: i) children with T1DM, ii) children with DS under KD, and iii) children with CP. The most important findings are the enhancement of QoL by i) detecting a predictor of QoL in patients with T1DM, ii) controlling side effects of KD as therapy for DS, and iii) categorize visual impairment and functional classifications in patients with CP for improved comprehension of comorbidities and facilitate daily life.

In paper 1, a positive correlation between the development of Hb_{A1c} from onset of T1DM over a year and QoL at time of study inclusion was found. Showing higher Hb_{A1c} values in the first 12 months after the diagnosis, children evaluated their QoL significantly lower later on. These outcomes might lead to the assumption that early Hb_{A1c} values could serve as potential predictor of QoL. The modification of metabolic control from onset of T1DM is apparently related to the rating of QoL of the patients in the course of the disease. Another essential result was the rating of lower self-esteem from children with T1DM. Self-esteem was found to be correlated with psychiatric diseases for example depression or substance use (55, 56) implicating a need for a close follow-up for children with T1DM. Additionally and as already discussed in 6.3, the evaluation of QoL was significantly different between children and their parents. Patients showing higher Hb_{A1c} experienced lower overall QoL and importantly also lower scores on the subscale of self-esteem while parents rated lower QoL of their child regarding the subscales of friends and school. Therefore, the different QoL evaluations of children and their parents should be considered in T1DM management and in search of problem areas of the patients.

In paper 2, hypoglycemia as a side effect of KD were monitored by implementing a flash glucose monitoring system in the treatment of DS. This is of interest because hypoglycemia can be related to seizures and by using a flash glucose monitoring system, severe hypoglycemia might be avoided and the extent of hypoglycemic episodes could be decreased (31). The findings showed a significant decline of the hypoglycemia rate after the first three months of KD and a low number of seizures related to hypoglycemic events was registered. Therefore, implementing KD in the treatment of children with DS appears to be a safe option on condition that glucose concentrations are observed particularly in the first months of KD. QoL was enhanced significantly by controlling hypoglycemia as a side effect of KD and in our case, a positive impact on behavior, cognition and motor development was reported.

In the paper 3, visual impairment was identified as one important comorbidity in children with CP as almost two-thirds of CP patients had a wide range of visual problems. Especially patients diagnosed with spastic CP and with severe forms of CP (due to brain malformations or extreme prematurity) are likely to develop severe visual impairment and should undergo detailed ophthalmologic assessment as soon as the diagnosis CP is made. Additionally, it seems important to consider the possibility of visual impairment having an impact on the activities and participation of patients with CP. QoL, especially the part of psychological well-being, is influenced by daily experiences and reducing CP comorbidities had a positive effect on psychological QoL in children (57). Therefore, treatment of visual impairment as comorbidity of CP could be very helpful to enhance QoL and for the development of children by facilitating daily life actions.

To sum up, enhancement of QoL is a central goal in the treatment of children with chronic diseases. Different approaches showed possibilities to influence QoL in the facet of physical health, psychological state, everyday functioning and social embedment to provide children a better QoL despite their chronic disease.

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