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Untersuchung psychosozialer Parameter bei Kindern und Jugendlichen mit Typ-1 Diabetes und Insulinpumpentherapie

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Abkürzungsverzeichnis

agip	Arbeitsgruppe Insulinpumpentherapie im Kindes- und Jugendalter
AGPD	Arbeitsgemeinschaft für Pädiatrische Diabetologie
CGM	continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DDG	Deutsche Diabetesgesellschaft
DGKJ	Deutsche Gesellschaft für Kinder- und Jugendmedizin
DGSPJ	Deutsche Gesellschaft für Sozialpädiatrie und Jugendmedizin
DKA	Diabetische Ketoazidose
DKINDL	KINDL-R Diabetesmodul
DPV	Diabetes-Patienten-Verlaufsdokumentation
DIAS	Diabetes and social disparities
ESPE	European Society for Paediatric Endocrinology
FAS	full analysis set
HbA1c	Hämoglobin A1c
HRQOL	Health related quality of life, gesundheitsbezogene Lebensqualität
ICT	Intensive conventional insulin therapy
IG	Interventionsgruppe
ITT	Intention- to- Treat Analyse
KIGGS	Kinder- und Jugendgesundheitssurvey
MAPE	Mitteldeutschen Arbeitsgemeinschaft für Pädiatrische Endokrinologie
MDI	Multiple daily insulin injektions, Mehrspritzentherapie
pumpkin	Pumpe für Kinder
RCT	Randomised controlled study
SAP	sensor-augmented pump therapy, sensorunterstützte Pumpentherapie
SES	Socioeconomic status, sozioökonomischer Status
T1 DM	Typ 1 Diabetes mellitus
WG	Wartekontrollgruppe

1. Einleitung

Der Typ-1 Diabetes mellitus (T1 DM) ist die häufigste Stoffwechselerkrankung im Kindes- und Jugendalter und mit einer geschätzten Prävalenz von 0,15 % und einer jährlich um 3 -4 % steigenden Neuerkrankungsrate von hoher klinischer und gesundheitspolitischer Relevanz. Der T1 DM ist eine Autoimmunerkrankung, die ätiopathogenetisch durch eine Zerstörung der Beta-Zellen hervorgerufen wird und durch einen absoluten Insulinmangel gekennzeichnet ist. Die lebenslange Insulinsubstitution als Ersatz des fehlenden körpereigenen Insulins ist obligat und erfordert eine komplexe Behandlung, um die physiologische Insulinsekretion zu imitieren und dadurch eine möglichst normnahe Blutzuckereinstellung zu erreichen. Die Erkrankung manifestiert (im Gegensatz zum Typ-II Diabetes) in aller Regel im Kindes- und Jugendalter und persistiert wegen fehlender kausaler Behandlungsmöglichkeiten ins Erwachsenenalter. Lebenszeit und Lebensqualität variieren erheblich und sind in hohem Maße von der Qualität der Behandlung in Kindheit und Jugend abhängig. Als medizinische Behandlungsziele stehen die Vermeidung akuter Stoffwechselentgleisungen, insbesondere schwerer Hypoglykämien und Ketoazidosen, sowie die Prävention diabetesbedingter mikro- und makrovaskulärer Folgeerkrankungen im Vordergrund. Psychosoziale Entwicklung und Lebensqualität der Betroffenen sollen dabei so wenig wie möglich beeinträchtigt werden.

Um diese Ziele, die sich durchaus in einem Spannungsfeld befinden können, zu erreichen, sind komplexe und individuell angepasste Therapiekonzepte erforderlich, da die Insulingaben regelmäßig an die mehrmals täglich zu messenden Glukosewerte, die Nahrungsmittelzufuhr und den Aktivitätsgrad des Kindes angepasst und darüber hinaus in die familiären Routinen integriert werden müssen. Dies erfordert von Eltern sowie Patientinnen und Patienten ein hohes Maß an Wissen und Selbstmanagementkompetenz. Insbesondere die dauerhafte Reflektion des Alltagsgeschehens und der Verlust an Spontaneität sind - neben psychischen Belastungen wie Sorgen um krisenhafte Entgleisungen, Folgeerkrankungen, die psychische Befindlichkeit und soziale Inklusion des Kindes – erhebliche Herausforderungen für die Betroffenen und darüber hinaus für die Eltern und die gesamte Familie. Psychosoziale Faktoren zählen im Langzeitverlauf zu den wichtigsten Determinanten der Diabeteseinstellung.

Die zentrale Therapiekomponente beim T1 DM ist die Insulinsubstitution. Hier sind in den letzten 2 - 3 Dekaden einige technologieinduzierte Paradigmenwechsel zu verzeichnen. Wurde bis Mitte der 90er Jahre noch die Mehrheit der Kinder und Jugendlichen mit einfacheren Behandlungsschemata (1 - 3 tägliche Insulininjektionen) behandelt, setzte sich rasch die intensivierte Therapie mit 4 - 6 Insulingaben (ICT) durch. Seit etwa dem

Jahr 2000 werden immer mehr Kinder und Jugendliche mit einer Insulinpumpentherapie (continuous subcutaneous insulin infusion, CSII) behandelt, zurzeit sind dies etwa 50 % aller pädiatrischen Patientinnen und Patienten mit T1 DM. Die sprunghafte Zunahme der CSII erfolgte, obwohl medizinische Vorteile über lange Zeit nicht nachgewiesen werden konnten. Der hauptsächliche Vorteil wurde dementsprechend in psychosozialen Nutzen jenseits der Stoffwechselkontrolle vermutet. Zurzeit findet durch die zunehmende Anwendung von Sensoren, die kontinuierlich den Gewebezucker messen (continuous glucose monitoring, CGM), und, wenn sie mit einer Insulinpumpe kombiniert werden, einen Schritt zu einem „Closed- Loop"- System darstellen, wiederum ein technisch induzierter Paradigmenwechsel in der Insulintherapie statt. Insbesondere seit CGM-Systeme im Hilfsmittelkatalog der gesetzlichen Krankenkassen enthalten sind (seit 2016) und bei entsprechender Indikation verordnet werden können, ist ihre Verbreitung sprunghaft gestiegen.

Unter den psychosozialen Outcomes einer chronischen Erkrankung hat das Konzept der gesundheitsbezogenen Lebensqualität (health related quality of life, HRQOL) besondere Bedeutung gewonnen und wird inzwischen nicht nur in klinischen Studien, sondern auch z.B. in Guidelines und medizinischen Zulassungsverfahren berücksichtigt. Diagnoseunabhängige (d.h. generische) gesundheitsbezogene Lebensqualität ist ein mehrdimensionales Konzept, wobei mindestens die Dimensionen körperliches Wohlbefinden, psychisches Wohlbefinden, soziales Wohlbefinden enthalten sind, sofern diese von der Erkrankung und/oder deren Behandlung betroffen sind. Häufig werden andere Dimensionen hinzugenommen wie Rollenerfüllung im Alltag und Wohlbefinden in der Lebenswelt. Es handelt sich immer um die subjektive Wahrnehmung und Bewertung des Wohlbefindens aus Sicht der Patienten selbst, im Fall von jungen Kindern auch der Eltern als Proxy Reporter. Krankheitsspezifische Lebensqualität beinhaltet die subjektive Erfahrung von für die jeweilige Erkrankung charakteristischen Aspekten der Erkrankung u Therapie, z.B. Sichtbarkeit der Insulinpumpe, Ängste vor Unterzuckerung etc.. Krankheitsspezifische Instrumente können gezielt nach lebensqualitätsrelevanten Aspekten des T1 DM und seiner Behandlung fragen und daher die Erkrankung mit all ihren Aspekten auf der Dimension der Lebensqualität besser abbilden.

Auch der Zugang zur Therapieoptionen wie CSII oder CGM wird von psychosozialen Aspekten beeinflusst. Ein bemerkenswertes Ergebnis epidemiologischer Studien ist, dass der sozioökonomische Status (socioeconomic status, SES) auch in Ländern mit hohem Lebensstandard und freiem Zugang zu Gesundheitsleistungen einen erheblichen Einfluss auf die Gesundheit einer Person hat. Für den T1 DM im Kindes- und Jugendalter werden in internationalen Studien Zusammenhänge von niedrigem SES mit

schlechterer Stoffwechselkontrolle und vermehrten Komplikationen sowie Folgeerkrankungen bis hin zu erhöhter Mortalität (im Erwachsenenalter) berichtet. Für Deutschland konnten Registerstudien an über 29.000 jungen Patienten mit T1 DM zeigen, dass in sozioökonomisch deprivierten Regionen Patienten unter 20 Jahren eine schlechtere Stoffwechsellage aufwiesen und fortgeschrittene Diabetestherapien wie die CGM seltener eingesetzt wurden. Diese Studien verwendeten einen aggregierten sozioökonomischen Indikator, der auf Basis des Wohngebietes die regionale Deprivation ermittelt. Der individuelle SES der Patienten wurde jedoch nicht erhoben und ist für Kinder und Jugendliche mit T1 DM bisher in Deutschland unzureichend untersucht.

Die in dieser Dissertation vorgelegten Arbeiten widmen sich der gesundheitsbezogenen Lebensqualität, den psychosozialen Belastungen und den Effekten sozialer Ungleichheit in Familien von Kindern und Jugendlichen mit T1 DM unter Insulinpumpentherapie.

Studien 1 und 2 untersuchen die Auswirkungen der Insulinpumpentherapie auf die gesundheitsbezogene Lebensqualität der Kinder und Jugendlichen sowie die krankheitsbedingte Belastung der Eltern. Zu diesem Zweck wurde zunächst eine Pilotstudie durchgeführt (Studie 1), um relevanter psychosoziale Outcomes zu identifizieren und geeignete Instrumente zu identifizieren bzw. zu adaptieren. Die Ergebnisse wurden anschließend durch eine randomisierte kontrollierte Studie (Studie 2) überprüft.

Studie 3 untersuchte die Assoziation zwischen dem individuellen SES der Familie und verschiedenen Diabetes- und Versorgungsoutcomes, u.a. Nutzung einer CSII, bei Kindern und Jugendlichen mit T1 DM in Deutschland Die Assoziationen zwischen SES und Diabetesoutcomes wurden mittels multivariabler Regressionsmodelle unter Nutzung von Daten aus dem DPV-Register (Diabetes- Patienten- Verlaufsdokumentation) analysiert.

Studie 4 beschreibt die subjektive Erfahrung von Kindern und Jugendlichen mit T1 DM und deren Eltern mit einer fortgeschrittenen Form der Insulinpumpentherapie, welche die CSII mit einer CGM kombiniert. Dazu wurde ein qualitativer Forschungsansatz gewählt, da für diese neue Therapieoption keine validen standardisierten Messinstrumente vorlagen.

2. Zusammenfassung von Publikation 1: Investigation of quality of life and family burden issues during insulin pump therapy in children with Type 1 diabetes mellitus—a large- scale multicentre pilot study

Fragestellung

Ausgangspunkt der in dieser Publikation beschriebenen Studie war die Beobachtung des sprunghaften Anstiegs der Insulinpumpennutzung, obwohl medizinische Vorteile über lange Zeit nicht nachgewiesen werden konnten. Der hauptsächliche Vorteil wurde dementsprechend – bei allerdings unzureichender Datenlage – in psychosozialen Outcomes wie gesundheitsbezogener Lebensqualität und familiärer Belastungen vermutet. Die Untersuchung dieser Outcomes setzte allerdings die Verfügbarkeit von psychometrisch geprüften und validen Befragungsinstrumente voraus. Diabetesspezifische Instrumente zur Überprüfung von psychosozialen Outcomes waren aber in der Regel im Rahmen der Injektionstherapie entwickelt worden; über die Angemessenheit und Gültigkeit für die CSII lagen nur geringfügige Erfahrungen vor. Außerdem waren kaum Instrumente aus dem deutschen Sprachraum verfügbar.

Im Auftrag der Arbeitsgruppe Insulinpumpentherapie im Kindes- und Jugendalter (agip) der Arbeitsgemeinschaft Pädiatrische Diabetologie (AGPD) wurde daher die vorliegende Pilotstudie mit folgenden Zielen durchgeführt:
(1) Identifikation möglicher für die Umstellung auf CSII relevanter psychosozialer Outcomes (2) Bereitstellung von geeigneten Instrumenten zu deren Erfassung.

Untersucht wurde die Therapieumstellung von der Standardtherapie (Multiple daily insulin injections, MDI) auf CSII in der Assoziation mit folgenden psychosozialen Endpunkten: generische und diabetesspezifische HRQOL, elterlicher Stress, familiäre Belastung, Hypoglykämieangst und Familienkonflikte. Zusätzliche Endpunkte, die vor allem der Patientensicherheit dienten, waren Level des Hämoglobion A1c (HbA1c) und Auftreten akuter Komplikationen (schwere Hypoglykämien, diabetische Ketoazidosen (DKA)).
Die eingesetzten Instrumente wurden auf Reliabilität und Sensitivität gegenüber behandlungsbedingten Veränderungen durch die Umstellung auf CSII untersucht.

Die Studie wurde nach positivem Votum der Ethikkommissionen der Universität zu Lübeck und der beteiligten Kliniken zwischen Dezember 2005 und August 2007 im Auftrag der Arbeitsgruppe Insulinpumpentherapie im Kindes- und Jugendalter (agip) der Arbeitsgemeinschaft für Pädiatrische Diabetologie (AGPD) durchgeführt. Koordination und Datenauswertung erfolgten durch das Studienzentrum (Universität zu Lübeck). Die Studie wurde durch Roche Diagnostics GmbH gefördert.

Methoden

Bei der vorliegenden Studie handelt es sich um eine multizentrische Kohortenstudie, die als Längsschnittuntersuchung mit zwei Messzeitpunkten ohne Kontrollgruppe konzipiert war. Eingeschlossen wurden Kinder und Jugendlichen von 4-16 Jahren mit T1 DM, die in den beteiligten Kliniken in der Erhebungsphase der Studie von einer anderen Therapieform auf Insulinpumpentherapie umgestellt wurden, sowie jeweils ein Elternteil. Bei jüngeren Kindern (4-7) Jahre erfolgte nur eine Elternbefragung. Medizinische Daten wurden mit einem Arztfragebogens erhoben.

Die Umstellung auf CSII erfolgte anhand der von der AGPD erstellten Guidelines nach einem standardisierten Curriculum. Die psychosozialen Zielparameter und Daten zur Stoffwechseleinstellung wurden zu Studienbeginn (vor Therapieumstellung der Kinder/ Jugendlichen) und sechs Monate nach Therapieumstellung erhoben, soziodemographische und ergänzende klinische Variablen einmalig bei Studienbeginn. Tabelle 1 beschreibt die eingesetzten Fragebögen und wer sie beantwortet hat.

Tabelle 1: Zielbereiche, Instrumente und Responder

Outcomes	**Instrument**	**Responder**
HRQOL	KIDSCREEN -10-Index	Kinder 8-11 J, Jugendliche 12-16 J
	KINDL-R Diabetesmodul (DKINDL)	Kinder 8-11 J, Jugendliche 12-16 J
	KINDL-R Core-Set + Diabetesmodul	Eltern (proxy) 4-7 J
Familiäre Belastung insgesamt	Belastungsskala	Eltern 4-16 J
	Pediatric Inventory for Parents (PIP)	Eltern 4-16 J
Hypoglykämieängste	Hypoglycemia Fear Survey (HFS)	Eltern 4-16 J
Mahlzeiten	Behavioural Pediatric Feeding Assessment Scale (BPFAS)	Eltern 4-7 J
Familienkonflikte	Diabetes Family Conflict Scale (DFCS)	Jugendliche 12-16 Eltern 8-16 J

Die Übersetzung der Fragebögen aus dem anglo- amerikanischen Sprachraum folgte einem international anerkannten mehrstufigen Protokoll. Die Reliabilitätsprüfung der Instrumente im Studienkollektiv erfolgte durch Prüfung der internen Konsistenz der Skalen der verwendeten Instrumente (Cronbach's alpha). Die HbA1c- Werte wurden lokal erhoben und mathematisch auf den DCCT- Referenzwert standardisiert. Zur Prüfung der Assoziationen der Therapieumstellung mit den Endpunkten der Studie wurden Gruppenvergleiche für die Messzeitpunkte durchgeführt. Die Testung erfolgt mit T-Tests und nicht parametrische Verfahren für abhängige Stichproben (Wilcoxon-Test).

Ergebnisse

Instrumentenentwicklung

Die aus dem angloamerikanischen Sprachraum stammenden Instrumente wurden übersetzt und im Wortlaut an den Gebrauch bei CSII adaptiert. Das KINDL- Diabetesmodul (DKINDL) wurde ebenfalls im Wortlaut adaptiert und durch insulinpumpenspezifische Items erweitert.

Die folgenden übersetzten/ adaptierten Instrumente zeigten eine interne Konsistenz nahe an oder über Cronbach's α= 0,7 und wurden für den Einsatz bei weiteren Studien empfohlen: DKINDL, PIP, HFS-P, DFCS, BPFAS. Lediglich in der Gruppe der Kinder 4-7 Jahre zeigten zum einen das DKINDL im elterlichen Proxy- Report, zum anderen eine Subskala des PIP α-Werte deutlich unter 0,7.

Outcomes

Kinder und Jugendliche aller Altersgruppen zeigen eine höhere diabetesspezifische Lebensqualität nach Umstellung auf CSI mit mittelhohen bis hohen Effektstärken ($p < 0,001$, $d = 0,6- 1,3$), während bzgl. der generischen HRQOL keine Veränderungen nachgewiesen wurden. Eltern berichteten über signifikant geringere Belastungen nach Umstellung auf CSII sowohl in dem eingesetzten chronisch-generischen Instrument (PIP Frequency $p < 0.001$, PIP Difficulty $p < 0.01$) wie auch diabetesspezifisch über geringere Hypoglykämieängste (HFSP Worries $p < 0,01$) und diabetesbezogene Belastungen insgesamt (Belastungsskala $p < 0,05$). Eltern jüngerer Kinder (4-7 J.) berichteten über eine geringere Belastung durch Mahlzeiten (BPFAS $p < 0,001$). Die Effektstärken waren insgesamt umso höher, je jünger die Kinder waren; in der Altersgruppe der Jugendlichen waren eher mittlere Effektstärken zu verzeichnen.

Stärken und Schwächen der Studie

Vorteile der Studie sind in der für eine Pilotstudie recht großen Fallzahl und der Stratifizierung nach Altersgruppen zu sehen sowie in der Reliabilitätsprüfung der Instrumente im Studiensample. Da es sich lediglich um eine Prä- Post- Studie ohne Kontrollgruppe handelt, konnte nicht entschieden werden, ob die Veränderungen im Studienzeitraum ursächlich auf die Therapieumstellung zurückzuführen waren. So könnte beispielsweise vermutet werden, dass sich Entwicklungsfortschritte der Kinder im Studienzeitraum sowie allgemeine Schulungseffekte positiv auswirkten, da im Rahmen einer Umstellung auf CSII krankheits- und behandlungsbezogenes Wissen aufgefrischt wurde. Eine randomisierte kontrollierte Anschlussstudie wurde empfohlen, um gesicherte Aussagen über die Wirksamkeit der CSII treffen zu können.

3. Zusammenfassung von Publikation 2: Psychosocial benefits of insulin pump therapy in children with diabetes type 1 and their families: The pumpkin multicenter randomized controlled trial

Fragestellung

Diese Publikation beschreibt die Ergebnisse der pumpkin- Studie (pumpe für Kinder). In pumpkin wurden die Auswirkungen der Insulinpumpentherapie (CSII) auf psychosoziale Endpunkte im Vergleich zur Standardtherapie (MDI) bei Kindern und Jugendlichen mit T1 DM in einem randomisierten kontrollierten Studiendesign untersucht. Da sowohl Kinder und Jugendliche wie deren Eltern befragt werden sollten und eine altersstratifizierte Analyse bevorzugt wurde, wurden drei primäre Outcomes festgelegt: die diabetesbezogene Lebensqualität der Kinder, die der Jugendlichen und die Belastung der Eltern durch die Erkrankung ihres Kindes (bzgl der elterlichen Belastung erlaubten die geringeren Effektstärken in der Pilotstudie keine Aufteilung nach der Altersgruppen der Kinder). Als sekundäre Outcomes wurden Auswirkungen der CSII auf die generische Lebensqualität der Kinder und Jugendlichen, die Angst vor Hypoglykämien bei den Eltern, den elterlicher Stresslevel, Familienkonflikte, die Stoffwechseleinstellung (HbA1c) und die Therapiezufriedenheit dargestellt.

Aufgrund der Ergebnisse der Pilotstudie wurde unter der Insulinpumpentherapie eine Verbesserung der diabetesspezifische gesundheitsbezogene Lebensqualität (DHRQOL) sowohl der Kinder wie der Jugendlichen und eine geringere diabetesbezogene Belastung der Eltern hypothetisiert.

Die Studie wurde nach Genehmigungen durch die Ethikkommissionen der Universität zu Lübeck und der beteiligten Kliniken von Januar 2011 bis Februar 2016 im Auftrag der agip der AGPD durchgeführt und von der Deutschen Forschungsgemeinschaft (DGF) und Roche Diagnostics GmbH gefördert. Die Studienleitung lag bei der Universität zu Lübeck; Monitoring, statistische Auswertung und Qualitätssicherung erfolgten durch das Zentrum für Klinische Studien der Universität.

Methoden

Bei pumpkin handelte es sich um eine multizentrische, zweiarmige offene Interventionsstudie im Wartekontrollgruppendesign mit zwei Messzeitpunkten im Abstand von 6 Monaten. Die Zuweisung zu Interventions- (IG) und Wartekontrollgruppe (WG) erfolgte randomisiert. Die Intervention bestand in der Umstellung von der Standardtherapie MDI auf CSII. Die Befragungen erfolgen unmittelbar vor (Baseline- Erhebung IG) und 6 Monate nach Umstellung auf CSII (Follow- Up- Erhebung IG) bzw. 6 Monate vor

(Baseline- Erhebung WG) und unmittelbar vor Umstellung auf CSII (Follow- Up-Erhebung WG) mit den in der Pilotstudie evaluierten Instrumenten sowie zusätzlichen Fragebögen zur diabetespezifischen Therapiezufriedenheit und generischen HRQOL der Eltern. Die statistische Analyse wurde auf der Basis des full analysis set (FAS) nach dem Intention- to- Treat (ITT) Prinzip durchgeführt. Da mehr als ein primärer Outcome vorlagen, wurde das Signifikanzniveau zunächst auf einem globalen Signifikanzniveau von 0,05 getestet und auf jeweils 0,025 für jeden der drei primären Outcomes festgelegt. Durch sequentielle Auswertung im Rahmen einer „Fall-Back"-Strategie, beginnend bei der Auswertung über die Gesamtgruppe, konnte sich -bei signifikantem Ergebnis von einer der getesteten Hypothesen- das Signifikanzniveau auf 0,05 erhöhen. Die Analysen erfolgten mittels exaktem 2-seitigem U- Test zum Zeitpunkt der Nachtestung sowie durch eine Kovarianzanalyse mit Adjustierung für Baseline- Unterschiede, Alters- und Zentrumseffekte. Das Signifikanzniveau in der Darstellung der sekundären Outcomes wurde wegen Mehrfachtestung auf 0,01 (zweiseitig) festgelegt.

Ergebnisse

2011 Patientinnen und Patienten wurden in die Studie eingeschlossen, und 186 Eltern sowie 170 Kinder und Jugendliche konnten in die ITT Analyse einbezogen werden.

Kinder von 8- 11 Jahren aus der IG zeigten verglichen mit der WG eine höhere DHRQOL zum Zeitpunkt der Follow- Up- Befragung ($p = 0{,}004$, Signifikanzlevel 0,025). Jugendliche von 12- 16 Jahren zeigten keine Unterschiede zwischen IG und WG ($p = 0{,}353$, Signifikanzlevel 0,05 nach Fallback- Strategie- Anwendung). Eltern aus der IG berichteten verglichen mit der WG eine geringere diabetesbezogene Belastung zum Zeitpunkt der Follow- Up Befragung ($p = 0{,}029$, Signifikanzlevel 0,05 nach Fallback-Strategie- Anwendung).

Diese Unterschiede zugunsten der CSII bei der DHRQOL der Kinder sowie der diabetesbezogenen Belastung der Eltern fielen erheblich deutlicher aus, wenn eine für initiale Unterschiede zwischen den Gruppen adjustierte Analyse durchgeführt wurde. Wie die in Tabelle 2 dargestellten Mittelwerte zeigen, wurde eine Adjustierung notwendig, da sowohl die Kinder wie die Jugendlichen der IG zum Zeitpunkt der Baseline- Erhebung verglichen mit der WG eine höhere DHRQOL berichteten. Die IG wies zudem im Vergleich zur WG einen niedrigeren HbA1c-Wert (7,3 % ± 0,9 % versus 7,8 % ± 1,3 %) und somit eine initial bessere Stoffwechseleinstellung auf. Bzgl. der sekundären Outcomes berichteten Eltern der IG im Vergleich zur WG über eine größere Abnahme von elterlichem Stress und Angst vor Hypoglykämien sowie über eine höhere Therapiezufriedenheit. Bzgl. Veränderungen der generischen HRQOL, der Familien-konflikte, der DHRQOL und der Therapiezufriedenheit von Jugendlichen sowie der Stoffwechseleinstellung wurden keine signifikanten Unterschiede zwischen den Gruppen berichtet.

Tabelle 2: Diabetesspezifische Lebensqualität bei T1 DM und elterliche Belastung

	CSII			MDI			CSII vs MDI	
	n	**mean**	**sd**	**n**	**mean**	**sd**	**med dif (95 % CI**	**p**
DHRQOL DKindl 8-11y								
baseline	36	68.1	14.9	29	61.8	15.2		
follow-up	35	74.5	12.0	31	64.3	14.9	9.5 (3.6–16.7)	0.001
DKindl 12.16y								
baseline	46	70.6	11.9	57	67.8	16.9		
follow-up	46	74.2	13.0	53	70.9	16.0	2.7 (-3.2–9.5)	0.606
Elterliche Belastung Belastungsskala								
baseline	92	3.4	1.0	94	3.2	1.1		
follow-up	90	2.7	1.1	89	3.0	1.1	0 (-1–0)	0.005

sd: standard deviation; med dif: Mediandifferenz, CI: 95 % Konfidenzintervall; p: Asymptotischer Test nach Adjustierung für Baseline-Unterschiede, Alter und Zentrum

Stärken und Schwächen der Studie

Pumpkin konnte belastbare Ergebnisse zur Verbesserung der DHRQOL von Kindern mit T1DM und der elterlichen Belastung unter CSII präsentieren. Das randomisierte kontrollierte Design, die relativ hohe Fallzahl, die altersstratifizierte Analyse und die Nutzung validierter Instrumente sind als Stärken der pumpkin Studie anzusehen. Die lange Rekrutierungszeit und die geringe Fallzahl in der Altersgruppe der Kinder von 6-7 Jahren sowie die nicht vollständig gelungene Randomisierung sind als Limitationen zu nennen. Das Wartegruppendesign sicherte zwar, dass nur klinisch vergleichbare Patientinnen und Patienten (mit einer Indikation zur Umstellung auf CSII) in die Studie eingeschlossen wurden; gleichzeitig trugen positive Effekte in dieser Gruppe möglicherweise zu einer geringeren Differenz zwischen IG und WG bei.

Die Unterschiede zwischen IG und WG waren in pumpkin kleiner als in der Pilotstudie. Dies ist ein für RCT's bekannter Effekt und vermutlich großenteils auf einen Rekrutierungsbias zurückzuführen, da Patienten, die nicht bereit waren sich randomisieren zu lassen oder für die eine ärztliche Indikation zur möglichst raschen Umstellung auf CSII (ohne Wartezeit) vorlag, nicht eingeschlossen werden konnten. Da zu erwarten ist, dass insb. diese Patientengruppen von einer CSII profitieren, kann man davon ausgehen, dass die Wirkung der CSII im klinischen Alltag eher unterschätzt wurde.

Ein Erratum betr. zwei fehlende Minuszeichen bei Darstellung der sekundären Outcomes ist publiziert in Pediatr Diabetes 21(1): 144- 145; 2020. doi: 10.1111/pedi.12919.

4. Zusammenfassung von Publikation 3: The association between socio-economic status and diabetes care and outcome in children with diabetes type 1 in Germany: The DIAS study (diabetes and social disparities)

Fragestellung

Die DIAS (Diabetes and Social Disparities)- -Studie wurde durchgeführt, um die Zusammenhänge verschiedenen Krankheits- und Versorgungsoutcomes von Kindern und Jugendlichen mit T1 DM mit dem sozioökonomischen Status (SES) ihrer Familie zu untersuchen.

Die Studiendurchführung erfolgte im Auftrag der agip der AGPD und in Kooperation mit dem Institut für Epidemiologie und Medizinische Biometrie (ZIBMT) der Universität Ulm, welches mit der Diabetes- Patienten- Verlaufsdokumentation (DPV) ein EDV- basiertes Dokumentationsprogramm aufgebaut hat, das über 90 % der pädiatrischen Patienten erfasst. Neben medizinischen werden hier routinemäßig auch soziodemographische Daten erfasst; der SES wird bisher nicht systematisch erhoben**.** Die Studie wurde nicht finanziell gefördert.

Methoden

Im Rahmen der DIAS-Studie erhoben 13 deutsche Diabeteszentren den SES der Patienten bei deren regulären ambulanten Besuchen von Juni 2013 bis Juni 2014.

Der SES wurde anhand von Angaben der Eltern zu ihrer Schul- und beruflichen Bildung, ihrer aktuellen beruflichen Stellung und dem Haushaltsnettoeinkommen ermittelt. Die Bestimmung des Bildungsstands und des Haushaltseinkommens entsprach den Fragen des ‚Kinder- und Jugendgesundheitssurveys' (KiGGS); die berufliche Stellung wurde anhand der routinemäßig in DPV verwendeten Fragen erfasst.

Der Eintrag in eine studienspezifische DPV- Zusatzmaske ermöglichte die Kombination mit den routinemäßig in DPV erhobenen Daten zu Alter und Geschlecht der Patienten, Migrationsstatus und Diabetesdauer sowie zu folgenden Outcomes: Stoffwechselkontrolle (HbA1c), Diabetestherapie (CSII oder MDI), schwere Hypoglykämien und DKA, tägliche Selbstmessung der Blutglukose, Body-Mass-Index (BMI), Dauer stationärer Aufenthalte, und Teilnahme an Diabetes-Schulungen.

Zur Beurteilung der Assoziationen des SES mit den Studienoutcomes wurden, deren jeweiligen Verteilungscharakteristika entsprechend, für Alter, Geschlecht und Diabetesdauer adjustierte Regressionsmodelle berechnet, jeweils mit und ohne Einbeziehung des Migrationshintergrundes in die Analyse.

Ergebnisse

Eingeschlossen wurden Kinder und Jugendliche bis zum vollendeten 17. Lebensjahr und ihre Eltern. Von den 2453 Patienten, die im Studienzeitraum die Diabetesambulanzen der teilnehmenden Kliniken besuchten, nahmen 2113 (86 %) an der Studie teil, davon waren 1989 Patienten unter 18 Jahre alt.

Die folgende Tabelle beschreibt einige wichtige Studienoutcomes stratifiziert nach SES adjustiert für Alter, Geschlecht und Diabetesdauer. Die p-Werte stellen die statistisch signifikanten Unterschiede zwischen niedrigem und mittlerem sowie niedrigem und hohem SES dar. Unterschiede zwischen mittlerem und hohem SES werden im Text beschrieben.

Tabelle 3: SES, Assoziationen mit Diabetes- und Behandlungsoutcomes

Stichprobe N = 1829	**Assoziationen mit SES**		
Outcomes[1)]	mean or %	95% CI	p
HbA1c: %/ mmol/ mol [2)]			
hoher SES	7,6/ 59,8	7,5 – 7,7/ 58,8 – 60,9	<0,0001
mittlerer SES	7,8/ 61,3	7,7 – 7,8/ 60,5 – 62,2	<0,001
niedriger SES	8,0/ 64,3	7,9– 8,2/ 63,0 – 65,6	
Anteil Pumpentherapie % [3)]			
hoher SES	54,9	50,4 – 59,3	<0,01
mittlerer SES	54,5	50,9 – 58,1	<0,01
niedriger SESS	43,6	38,2 – 49,2	
Blutglukose- Selbstmessungen pro Tag[2)]			
hoher SES	6,1	6,0 – 6,3	<0,01
mittlerer SES	6,0	5,9 – 6,2	<0,01
niedriger SES	5,7	5,5 – 5,9	
Stationäre Aufenthalte, Tage pro Patientenjahr [5)]			
hoher SES	3,4	3,3 – 3,6	<0,0001
mittlerer SESS	4,5	4,3 – 4,6	<0,0001
niedriger SES	5,8	5,5 – 6,0	

[1)] Adjustiert nach Geschlecht, Altersgruppen:< 6 J, 6-11 J, 12-18 J; Diabetesdauer: <2 J, ≥2 J
[2)] lineares Regressionsmodell, [3)] logistisches Regressionsmodell,[4)] negativ-binomiales Regressionsmodell,[5)] Poisson Regressionsmodell

Kinder und Jugendliche mit niedrigem familiären SES nutzten demnach signifikant seltener eine Insulinpumpe als solche mit mittlerem und hohem SES. Sie zeigten ebenfalls einen signifikant höheren HbA1c als solche mit mittlerem und hohem SES, die Unterschiede zwischen mittlerem und hohem SES waren ebenfalls signifikant ($p < 0.05$). Patientinnen und Patienten mit niedrigem SES berichteten eine signifikant geringere Anzahl täglicher Blutglukose- Selbstmessungen als solche mit mittlerem oder hohem

SES. Die Dauer der stationären Aufenthalte zeigte einen ausgeprägten sozialen Gradienten mit signifikanten Unterschieden zwischen jeweils niedrigem, mittlerem und hohem SES ($p < 0,0001$). Auch der BMI- SDS war bei Patienten mit niedrigem SES signifikant höher als bei Patienten mit mittlerem oder hohem SES. Bzgl, schwerer Hypoglykämien und DKA sowie des Anteil an Schulungsmaßnahmen gab es keine bedeutsamen Unterschiede zwischen den Gruppen. Die Einbeziehung des Migrationshintergrundes änderte die Ergebnisse nur unwesentlich.

Insgesamt zeigten die Analysen, dass ein niedriger SES im Vergleich zu mittlerem/ höherem SES mit seltenerem Zugang zur fortgeschrittenen Therapieoptionen (Insulinpumpentherapie), einer schlechteren Stoffwechseleinstellung, ungünstigerem Selbstmanagementverhalten sowie einer höheren Inanspruchnahme stationärer Gesundheitsleistungen assoziiert war.

Stärken und Schwächen der Studie

The DIAS Studie konnte zeigen, dass ein niedriger SES auch bei Kindern mit T1DM mit einer Vielzahl ungünstiger Diabetesoutcomes assoziiert war, u.a. mit schlechterem Zugang zu fortgeschrittenen Technologien wie der CSII. Die Ergebnisse bestätigen damit die Bedeutung des SES als Risikofaktor, die aus populationsbezogenen Studien und auch aus internationalen Studien für T1 DM im Kindes- und Jugendalter bekannt ist, auch für diese in Deutschland gut interdisziplinär versorgte und gut geschulte Patientengruppe. Die Ergebnisse der Studie lassen vermuten, dass ungünstige Diabetesoutcomes von Kindern mit T1 DM in Deutschland, die bisher einer Migrationsbiographie zugeschrieben wurden, großenteils auf einen niedrigen SES zurückzuführen sind.

Die Stichprobengröße und die Messung des SES über jeweils niedrige, mittlere und hohe Ausprägung sind als Stärken der Studie anzusehen. Trotz der relativ hohen Zahl der eingeschlossenen Patientinnen und Patienten beruhen die Ergebnisse allerdings auf einer willkürlichen Stichprobe (convenience sample), was die Generalisierbarkeit auf alle Betroffenen in dieser Altersgruppe einschränkt. Familien mit niedrigem SES waren im Vergleich zur KIGGS- Basisstudie etwas unterrepräsentiert und der Westen Deutschlands hinsichtlich der regionalen Verteilung der teilnehmenden Kliniken deutlich überrepräsentiert. Bzgl. des Anteils an Patientinnen und Patienten mit Migrationshintergrund waren keine systematischen Verzerrungen zu verzeichnen.

5. Zusammenfassung von Publikation 4: Experiences in Sensor-Augmented Pump Therapy in Families with two Children with Type 1 diabetes: A Qualitative Study

Fragestellung

Die in dieser Publikation beschriebene Studie untersuchte mit einem qualitativen Forschungsansatz den Einfluss einer sensorgestützten Pumpentherapie (sensor-augmented pump therapy, SAP) auf die Lebensqualität und den Alltag von Familien mit zwei an T1 DM erkrankten Kindern.

CGM- Systeme messen kontinuierlich den Glukosegehalt in der Gewebeflüssigkeit des Unterhautfettgewebes. Im Gegensatz zur klassischen intermittierenden Blutzuckermessung kann so die Stoffwechsellage kontinuierlich überprüft werden.. Die CGM- Systeme senden bei festzulegenden Über- und Unterzuckerungsgrenzwerten Alarme aus und bieten in Kombination mit einer Insulinpumpe die Möglichkeit der automatischen Abschaltung der Insulininfusion bei Erreichen eines bestimmten Unterzuckerungsgrenzwertes. Die SAP kann so dazu beitragen, schwere Unterzuckerungen zu verhindern. Außerdem wird die Anzahl der Blutzuckermessungen erheblich vermindert. Weiter erforderlich bleiben die händische Eingabe der Kohlenhydrataufnahme zu den Mahlzeiten sowie eine regelmäßige Blutzuckermessung zur Kalibration des Sensors. Die regelmäßige Nutzung der SAP scheint im Kindes.- und Jugendalter wegen der Komplexität der Therapie schwierig zu erreichen zu sein. Ein Ziel der Studie war es, die subjektiven Erfahrungen von Familien bei der Transition zu SAP zu beschreiben und so mögliche förderliche Bedingungen und Barrieren für die Nutzung dieser Technologie zu identifizieren.

Die Studie wurde von der Ethikkommission der Universität zu Lübeck genehmigt und von 2013 bis 2014 durch die Klinik für Kinder- und Jugendmedizin, Universität zu Lübeck, durchgeführt. Eine finanzielle Förderung erfolgte durch die Damp- Stiftung

Methoden

5 Familien mit 10 Kindern zwischen 4 und 20 Jahren in Schleswig-Holstein erfüllten die Einschlusskriterien und waren bereit zur Nutzung von SAP für mindestens 6 Monate mit telemedizinischer Begleitung. Die Intervention bestand in einer strukturierten Einführungsschulung zum Gebrauch des SAP- Systems (MiniMed- VeoTM pump und Minimed Medtronic Enlite® Sensors) und regelmäßiger 14- tägiger telemedizinischer Beratung durch die ärztliche Studienleitung (pädiatrische Diabetologin).
Nach 6 Monaten SAP wurden leitfadengestützte halbstandardisierte Interviews mit unterschiedlich komplexen Versionen für Eltern, Jugendlichen und Kindern > 8 Jahren

durchgeführt (Dauer 30 bis 90 Minuten). Die Interviews wurden digital aufgenommen, anonymisiert und vollständig transkribiert. Die Auswertung erfolgte mit der Methode der qualitativen Inhaltsanalyse unter Nutzung des MAXQDA 10 Software Programms. Das Kategoriensystem basierte auf den Interviewleitfäden und wurde im Auswertungsprozess präzisiert. Die Auswertung erfolgte zunächst unabhängig durch die beiden Studienpsychologinnen FB und EMG und die Ergebnisse wurden in einem anschließenden Diskussionsprozess harmonisiert.

Ergebnisse

9 Eltern, 4 Jugendliche (13-20 J.) und 4 Kinder (8 – 10 J.) wurden befragt. Dabei wurden vier Hauptthemen identifiziert: (1) Der Adaptationsprozess an SAP,
(2) Diabetesmanagement, (3) Psychosoziale Outcomes, (4) Persönliche Bewertung.

(1) Adaptationsprozess

Die neue Technik zu verstehen und richtig anzuwenden (Setzten des Sensors, Software, Kalibration, Umgang mit den Alarmen) stellte eine große Herausforderung für die Familien dar. Alle Eltern beschrieben sich in diesen ersten Wochen als unsicher und belastet.

Im weiteren Verlauf. entwickelten insbesondere die älteren Kinder rasch ein Verständnis für die technischen Vorgänge. In zwei Fällen waren größere Akzeptanzprobleme zu beobachten, die in einem Fall zum Abbruch der Sensornutzung führten. Der Adaptationsprozess verlief in den Familien unterschiedlich schnell. Letztlich entwickelten alle eine Routine im Umgang mit der neuen Technologie, wobei das ursprünglich gelernte Management der SAP an die jeweiligen familiären Alltagsroutinen angepasst wurde.

(2) Diabetesmanagement

Die Mehrzahl der Familien berichtete von Erleichterungen im Alltag für die Kinder. Insbesondere wurde es als angenehm empfunden, nicht mehr so oft den Blutzucker messen und generell weniger Equipment bei sich führen zu müssen.

Alle Eltern und die Jugendlichen schätzten das Gefühl der Sicherheit, das sie durch die Hypoabschaltung der Pumpe empfanden, insb. in Bezug auf nächtliche Hypoglykämien. Die Familien nannten die kontinuierliche Datenerfassung als eine Chance der SAP-Technologie: Durch die ständige Rückmeldung der Stoffwechselvorgänge erlebten sich die Eltern und Jugendliche als informierter, motivierter und mutiger. So berichteten Eltern, dass sie selbstständiger und aktiver in die Diabetestherapie ihrer Kinder eingriffen als zuvor. Die teils erheblichen Verbesserungen des HbA1c wurden von den Eltern als wichtigster Erfolg der SAP bewertet.

Das Diabetesmanagement mit der SAP-Technologie wies auch einige Nachteile auf. Die Mehrzahl der Familien beschrieben die SAP als zeitlich aufwändig, auch das Kalibrieren empfanden die Eltern als schwierig in den Tagesablauf zu integrieren. Das Setzen des Sensors war für mehrere Kinder schmerzhaft und unangenehm, einige Kinder hatten erhebliche Hautprobleme. Alle Familien waren in bestimmten Situationen mit der Alarmfunktion des Sensors unzufrieden. Für die jüngeren Kinder waren dauerhaft auftretende Alarme der am häufigsten genannte Nachteil des Sensors.

(3) Psychosoziale Outcomes
Die Eltern berichteten mehrheitlich, dass die Kinder und Jugendlichen durch den Sensor mehr Sicherheit erfuhren, sich ihr Aktivitätsradius im Alltag deutlich erweiterte und sie mehr Selbstvertrauen entwickelten. Ein Kleinkind machte aufgrund seiner Angst vor den Alarmen allerdings vorübergehende Entwicklungsrückschritte. In einigen Familien traten verstärkt Konflikten auf, da durch die kontinuierliche Datendokumentation Therapiefehler sichtbar wurden, die vorher nicht so offensichtlich waren. Die Kinder und Jugendlichen selbst schienen wenig Probleme mit diesem Aspekt der „Durchsichtigkeit“ zu haben, vielleicht auch, weil sich die Eltern der Sensibilität dieses Problems durchaus bewusst waren.

(4) Persönliche Bewertungen
Die SAP wurde trotz des erheblichen zeitlichen und organisatorischen Aufwandes von den meisten Familien als positiv gewertet und weiterempfohlen. Eine gewisse Technikaffinität wurde als hilfreich, die Motivation aller Familienmitglieder als notwendige Bedingung benannt.

Insgesamt zeigte die Studie, dass die SAP Stoffwechselverbesserungen und Verbesserung der DHRQOL für Kinder und Jugendlichen mit T1 DM mit sich bringen kann. Die Eltern berichteten reduzierte Hypoglykämieängste, aber keine Abnahme alltäglicher diabetesbezogener Belastung. Intensive professionelle Unterstützung bei der Therapieumstellung, z.B. durch telemedizinische Begleitung, ist erforderlich.

Stärken und Schwächen der Studie

Mit ihrem qualitativen Forschungsansatz fokussierte die Studie auf die subjektiven Erfahrungen von Eltern, Kindern und Jugendlichen bei der Umstellung auf SAP in deren eigener Sprache. Die kleine Stichprobe bei großem Altersspektrum und die Beschränkungen auf ein CGM-System sowie auf Familien mit zwei an T1 DM erkrankten Kindern können als die Verallgemeinerbarkeit der Studie einschränkende Schwächen angesehen werden.

6. Diskussion

Die beschriebenen wissenschaftlichen Arbeiten untersuchten auf verschiedenen Ebenen psychosoziale Parameter bei Kindern und Jugendlichen mit T1 DM unter Insulinpumpentherapie.

Die Hauptergebnisse der pumpkin Studie waren der Nachweis einer besseren diabetesspezifischen Lebensqualität der Kinder und einer geringeren familiäre Belastung der Eltern (primäre psychosoziale Outcomes) unter Insulinpumpentherapie im Vergleich zur Standardtherapie (Mehrspritzentherapie). Die pumpkin Studie zeichnet sich insb. durch ihre methodischen Fundiertheit aus. Während bisherige Studien aufgrund methodischer Mängel und/ oder kleiner Stichproben als wenig zuverlässig galten, konnte pumpkin als weltweit eine der größten randomisierte kontrollierten Studien belastbare Ergebnisse zur Überlegenheit der Insulinpumpentherapie bzgl. psychosozialer Parameter nachweisen. Neben einer Verbesserung der primären outcomes wurden Verbesserungen bzgl. elterlichem Stress, Hypoglykämieängsten und Therapiezufriedenheit berichtet.

Die Ergebnisse können dazu beitragen, bei der Indikationsstellung zur und im Monitoring der Pumpentherapie mehr auf Lebensqualität und Belastung der Familien zu fokussieren. Die Verbesserung der Lebensqualität ist ein anerkanntes Therapieziel und wird in neueren Guidelines der DDG als mögliche Indikation zur Pumpentherapie genannt. Wegen häufig beklagter fehlender Evidenz war dies aber bisher gegenüber medizinischen Indikationen von nachrangiger Bedeutung. Die pumpkin-Studie kann dazu beitragen, dass das Konzept der Lebensqualität leichter Berücksichtigung finden kann.

Die gesundheitsbezogene Lebensqualität wird bei Kindern mit chronischen Erkrankungen häufig quasi „erkauft“ durch eine hohe Belastung der Eltern. Es ist bemerkenswert, dass sich in pumpkin sowohl die diabetesspezifische Lebensqualität der Kinder wie auch die elterliche Belastung unter Insulinpumpentherapieverbesserte und somit die gesamte Familie von der Umstellung profitierte.

Im Gegensatz zu den Kindern unter 12 Jahren waren für die Jugendlichen keine signifikante Verbesserungen der diabetesspezifischen Lebensqualität und auch der Therapiezufriedenheit unter Insulinpumpentherapie nachzuweisen. Ein Grund dafür könnte eine veränderte familiäre Aufgabenverteilung beim Diabetesmanagement sein: im Jugendalter geht die Therapieverantwortung in der Regel zunehmend von den Eltern auf die Jugendlichen über, und die Eltern ziehen sich häufig zu früh aus dem Diabetesmanagement zurück. Dies wurde in pumpkin leider nicht erfragt und somit eine mögliche Überforderung der Jugendlichen nicht erfasst. Auch ist zu bedenken, dass Jugendliche

mit T1DM erhebliche Entwicklungsaufgaben zu bewältigen haben, vor denen der Diabetes und möglicherweise auch eine Umstellung auf Insulinpumpentherapie subjektiv eher in den Hintergrund treten können.

Eine weitere Studie stellte unter Nutzung qualitativer Methoden verschiedene psychosoziale Vorteile und Belastungen im Erleben von Kindern und Eltern bei der Einführung einer sensorgestützter Insulinpumpentherapie dar. Neben der verbesserten Stoffwechsellage wurden insbesondere ein größeres Sicherheitsgefühl und und Verbesserungen der Lebensqualität der Kinder und Jugendlichen in Schule und Freizeit als Vorteile benannt. Großer Zeitbedarf, Probleme bei der Kalibrierung und unangemessene Alarme wurden nachteilig bewertet. Die Studie konnte zeigen, dass Eltern bereit sind, aufwändige und komplexe Therapien zum Nutzen ihrer Kinder zu managen; solange eine bestimmte Grenze der Belastung nicht überschritten wird. Die Eltern reflektieren auf subjektiver Ebene das Spannungsfeld, das sich in der Diabetestherapie regelmäßig aus dem Abwägen des Ziels einer möglichst normnahen Stoffwechseleinstellung mit anderen Gesundheitszielen ergibt, wie Entfaltung der Persönlichkeit, Entwicklung von Autonomie, Umgang mit Gleichaltrigen. Diese sollten als gleichberechtigte Behandlungsziele im Rahmen von shared decision making ausgehandelt werden, um langfristige eine optimale Adherence, gute Lebensqualität und günstige psychosoziale Entwicklung zu erreichen.

Durch die kontinuierliche Datenerfassung konnten Eltern und Jugendliche ihr diabetologisches Wissen verbessern und wurden in ihrer Selbstwirksamkeit gestärkt. Allerdings traten in einigen Familien vermehrt Konflikte auf, da durch die lückenlose Datendokumentation Abweichungen von Therapieregeln sichtbar wurden. Obwohl die „Durchsichtigkeit“ von den Kindern und Jugendlichen selbst nicht als Problem angesehen wurde, sollten sich Eltern wie auch die behandelnden Diabetesteams dieser Problematik bewusst sein und mit besonderer Sensibilität auf den Verlust von Privatsphäre reagieren. Einige der berichteten technischen Nachteile sind inzwischen verbessert worden, z.B. die Alarmfunktionen. Die Komplexität der Therapie stellt aber zumindest in näherer Zukunft weiter erhebliche Anforderungen an Kompetenz und Motivation der Familienmitglieder.

Unter methodischen Gesichtspunkten ist der Beitrag der drei bisher vorgestellten Arbeiten zur Entwicklung diabetesspezifischer Lebensqualitätsinstrumente hervorzuheben. Diabetesspezifische Instrumente erfassen im Detail lebensqualitätsrelevante Aspekte des T1 DM und gelten daher i.d.R. als sensitiver gegenüber Therapieveränderungen. Ein Nachteil dieser Verfahren ist, dass sie häufig sehr eng auf bestimmte

Therapieformen zugeschnitten sind, z.B. fehlten in den für die vorgestellten Studien verfügbaren Fragebögen für die Pumpentherapie relevante Aspekte wie die Abhängigkeit von technischen Prozessen. Die Adaptation des KINDL-Diabetesmoduls an die Pumpentherapie war deshalb ein zentrales Studienergebnis. Der zurzeit stattfindende Technologiewandel durch die sprunghafte Zunahme der Sensornutzung erfordert wiederum eine Anpassung diabetesspezifischer Fragebögen. Die Validität eines Instruments hängt dabei in hohem Maße davon ab, ob alle relevanten Aspekte Eingang in die Items des Instrumentes finden. Dabei ist entscheidend, dass nicht nur auf Fachliteratur und Expertenmeinungen zurückgegriffen wird, sondern die subjektiven selbstgeäußerten Erfahrungen der betroffenen Kinder und Jugendlichen und Angehörigen bei der Fragebogenentwicklung einbezogen werden. Die Studie zur sensorgestützten Pumpentherapie konnte mit ihrem qualitativen Forschungsansatz hier Aspekte der diabetesspezifischen Lebensqualität herausarbeiten, die für diese Therapieform bedeutsam sind, und in der Sprache der Betroffenen dokumentieren, wie z.B. das erhöhte Sicherheitsgefühl sowie mögliche Konflikte durch die Offenlegung der Stoffwechselverläufe in allen Einzelheiten. Diese Aspekte können künftig bei der Weiterentwicklung von Instrumenten im Bereich der Lebensqualitätsforschung von Nutzen sein.

Die DIAS-Studie zeigte unter Nutzung von Registerdaten, dass Familien mit niedrigem sozioökonomischen Status im Vergleich zu solchen mit mittlerem/ hohem sozioökonomischen Status seltener Zugang zu fortgeschrittenen Therapien wie der Insulinpumpentherapie hatten. Dies kann zum einen auf personelle Faktoren zurückzuführen sein. Patienten mit höherem Sozialstatus sind häufiger in Therapieentscheidungen involviert und fordern möglicherweise eher den Zugang zu innovativen Therapieoptionen. Aber auch Zugangshemmnisse im System der Gesundheitsversorgung können zu dieser geringeren Nutzung beitragen. So ist die Arzt-Patient-Kommunikation eher an einem Kommunikationsstil ausgerichtet, der einem mittleren oder höheren sozioökonomischen Status entspricht. Möglicherweise wird daher von Seiten des behandelnden Diabeteteams vorschnell angenommen, dass die Patienten mit einem niedrigen sozioökonomischen Status den Anforderungen der komplexere Insulinpumpentherapie nicht gewachsen sind. Letzterer Gesichtspunkt erscheint im Hinblick auf zukünftige Entwicklungen wie der zunehmenden Verbreitung der sensorgestützten Pumpentherapie besonders bedeutsam. Diese Systeme erfordern ein hohes Maß an Selbstmanagementkompetenz der Kinder und Eltern. Auch hier sind dementsprechend Zugangshemmnisse für Familien mit niedrigem sozioökonomischen Status zu befürchten.

7. Zusammenfassung

Technische Geräte wie Insulinpumpen oder Glukosesensoren sind zunehmend bedeutsame Bestandteile der Diabetestherapie für Kinder und Jugendliche mit T1 DM und bieten große Chancen zur Verbesserung der Stoffwechsellage. Die Anwendung des technischen Fortschritts, der zum Teil mit zunehmend komplexen Therapieanforderungen einhergeht, wird von psychosozialen Faktoren mitbestimmt. Die vorliegenden Studien konnten zeigen, dass die Technologien ihr Potential nur entfalten können, wenn sie hinreichend benutzerfreundlich und alltagstauglich sind und so eine gute Adherence ermöglichen. Familien messen die Therapien sowohl an ihrer Wirksamkeit wie auch daran, ob sie psychosoziale Vorteile bieten und das Leben mit T1 DM erleichtern. Im Rahmen einer randomisierten kontrollierten Studie konnten eine bessere diabetesspezifische gesundheitsbezogene Lebensqualität von Kindern mit T1 DM und eine geringere elterliche Belastung als psychosoziale Vorteile der Insulinpumpentherapie nachgewiesen werden. Die Studien konnten, u.a. durch den Einsatz qualitativer Forschungsmethoden, einen Beitrag zur diabetesspezifischen Instrumentenentwicklung im Bereich der Lebensqualitätsforschung leisten. Unter Verwendung von Registerdaten wurde dargestellt, dass der sozioökonomische Status einer Familie als psychosozialer Einflussfaktor mit dem Zugang zur Insulinpumpentherapie und einer Vielzahl weiterer diabetesbezogener Outcomes assoziiert ist.

Psychosoziale Parameter sollten als bedeutsame Outcomes, eigenständige Einflussgrößen und wesentliche Confounder in Behandlungskonzepten und der Dokumentation von Gesundheitsdaten mehr Berücksichtigung finden.

Anlagen

Ethikvoten zu den vorgestellten Studien

Publikation 1: AktZ. 05 –144 vom 14. 09. 2005, Universität zu Lübeck

Publikation 2: AktZ. 09 – 096 vom 24. 02. 2011, Universität zu Lübeck

Die Studie wurde registriert als NCT01338922 in clinicaltrials.gov

Publikation 3: AktZ 202/ 09 vom 14.08. 2009, Universität Ulm

Publikation 4: AktZ. 13 -143 vom 13. 08. 2013, Universität zu Lübeck

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Original Article: Education and psychological aspects

Investigation of quality of life and family burden issues during insulin pump therapy in children with Type 1 diabetes mellitus—a large-scale multicentre pilot study[1]

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Abstract

Aims To investigate psychosocial aspects of continuous subcutaneous insulin infusion (CSII) therapy in children with Type 1 diabetes and to identify relevant and sensitive measures.

Methods We performed a multi-centre prospective pre-/post-study with children (53 girls, 64 boys, age 10.5 ± 3.7 years, mean ± SD) with Type 1 diabetes and their main carer from 18 German diabetic centres. Twenty-five children aged 8–11 years and 63 adolescents aged 12–16 years and their parents, plus 29 parents of children aged 4–7 years completed standardized questionnaires on generic and diabetes-specific quality of life (QOL), generic parenting stress, mealtime behaviour, fear of hypoglycaemia and family conflict immediately before and 6 months after transition to CSII.

Results After transition to CSII, diabetes-specific QOL of children increased significantly ($P < 0.001$) in all age groups, with moderate to large effect sizes (children aged 4–7 years: Cohen's effect size $d = 1.3$; 8–11 years: $d = 0.9$, adolescents 12–16 years: $d = 0.6$). Parents reported reduced frequency ($P < 0.01$, $d = 0.4$–0.7) and difficulty ($P < 0.01$, $d = 0.3$–0.6) of overall parenting stress and decreased worries about hypoglycaemia ($P < 0.01$, $d = 0.4$–0.6). Parents of younger children (4–7 years) reported reduced problems with nutrition management (frequency: $P < 0.001$, $d = 1.1$; difficulty: $P < 0.05$, $d = 0.7$).

Conclusions CSII may have substantial psychosocial benefits. Controlled studies are needed.

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Keywords children, CSII, diabetes, quality of life

Abbreviations BPFAS, Behavioural Paediatrics Feeding Assessment Scale; CI, confidence intervals; CSII, continuous subcutaneous insulin infusion; DFCS, Diabetes Family Conflict Scale; HbA_{1c}, glycated haemoglobin; HFS, Hypoglycaemia Fear Survey; HRQOL, health-related quality of life; IPR, Inappropriate Parental Responses; PIP, Paediatric Inventory for Parents; QOL, quality of life; Type 1 DM, Type 1 diabetes mellitus

Introduction

Over the past decade, continuous subcutaneous insulin infusion (CSII) has gained increasing popularity among paediatric patients with Type 1 diabetes mellitus (Type 1 DM) in Germany. The focus of research has mainly been on metabolic outcomes such as glycated haemoglobin (HbA_{1c}) and episodes of severe hypoglycaemia and ketoacidosis; inconsistent results have been reported [1,2]. It is presumed that CSII provides more psychosocial benefits [3].

The aim of this pilot study was to investigate different psychosocial features which might be relevant for patients and parents using CSII therapy and to identify appropriate sensitive measures before undertaking an expensive large-scale randomized controlled trial.

CSII provides greater flexibility in lifestyle, which may affect different aspects of family burden and children's quality of life

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(QOL) [4,5]. In the main, QOL effects of CSII have been investigated with conflicting results [6]. Other aspects may pertain to fear of hypoglycaemia, parenting stress, nutrition management, parent–child teamwork in sharing diabetes responsibility and diabetes-related family conflict. These may change over time as a result of age-specific development. Consequently, we stratified the study sample and analysed all outcomes separately for the age groups: younger children (4–7 years); school-aged children (8–11 years); adolescents (12–16 years).

Patients and methods

We performed a multi-centre prospective observational pre-/post-study on a cohort of patients from 18 German specialist diabetes centres. The patients were consecutively assigned to CSII therapy between December 2005 and August 2006. All children and adolescents with Type 1 DM aged 4 to 16 years, and their main carer, were eligible for the study. Exclusion criteria were diabetes duration of less than 6 months, learning disabilities and insufficient German literacy to answer questionnaires. The ethics committees of the participating centres approved the study. Parents gave written consent for themselves and their child. The children gave assent to their participation.

A sample of $n = 100$ was calculated to be adequate to detect a moderate intervention effect with a power of 0.80 for two-tailed testing on a 0.05 probability level. As we expected a loss to follow-up of 20%, we planned to include 120 families in the study.

The patients were transfered from multiple daily insulin injection therapy (MDI) to CSII by an interdisciplinary diabetes team following the guidelines of the German Working Group for CSII Therapy in Children and Adolescents. To ensure comparability, the cooperating institutions participated in a training curriculum developed by the study centre. For change of therapy, the children were admitted to hospital for 3–7 days.

Instruments

Patient-reported outcomes were assessed by standardized questionnaires. Translations were conducted according to international guidelines [7]. Few questionnaires were available in a validated German version (KIDSCREEN10-Index, KINDLR)

Health-related quality of life (HRQOL)

Generic as well as diabetes-specific QOL was assessed. Patients 8 years and older completed the KIDSCREEN-10 Index and the diabetes-specific module (KINDL-DM) of the KINDL-R. Parents of younger children aged 4–7 years proxy-reported on their child's QOL, using the KINDL-R and KINDL-DM.

The KIDSCREEN-10 Index was developed from the European KIDSCREEN-27 generic HRQOL questionnaire, which was derived from focus group work with children across Europe [8]. Ten items are scored on a five-point Likert scale, scores are summarized and transformed to give a one-dimensional global HRQOL index (range 0–100); higher scores indicate better HRQOL. Good internal consistency (Cronbach's $\alpha = 0.82$) and good test–retest reliability [intraclass correlation coefficient (ICC) = 0.72] as well as discriminant validity have been reported [9]. The KINDL-R modular QOL questionnaire provides age-appropriate versions; among these a parent-proxy version for the 4–7-year age group (KIDDY-KINDL). The KIDDY-KINDL comprises 24 items on six scales (Cronbach's $\alpha \geq 0.70$) and a KINDL Total Score (Cronbach's $\alpha > 0.80$). Convergent and discriminant validity have been reported [10]. The original KINDL-DM (17 diabetes-specific items; Cronbach's $\alpha = 0.80$) [11] was adapted for CSII, as the original version only covered aspects related to multiple daily insulin injection therapy. The CSII-adapted version of the KINDL-DM comprises 21 items, which are summarized for a diabetes-specific KINDL-DM Total Score. Higher scores indicate better QOL in all instruments.

Family burden

To assess generic family burden, we used the Paediatric Inventory for Parents (PIP). The 42-items instrument comprises four scales which are combined for a Total Frequency Score (PIP-F) and a Total Difficulty Score (PIP-D) with higher scores indicating more parenting stress. Good internal consistency (Cronbach's α 0.80–0.96) and construct validity are reported [4,12].

Parents also reported on the family members' Overall Diabetes Burden using a one-dimensional five-point intensity scale which was developed for this study.

Parents completed the Hypoglycaemia Fear Survey, parent version (HFS-P). The HFS-P comprises 25 items on two scales: Behaviour (Cronbach's $\alpha = 0.72$) and Worry (Cronbach's $\alpha = 0.88$) [13]. Parents of the younger age group (4–7 years) also reported on feeding problems, using the 10-items parents' scale (Inappropriate Parental Responses; IPR) of the Behavioural Paediatrics Feeding Assessment Scale (BPFAS). Scale scores are combined for Total Frequency and Total Problem Scores; higher scores indicate more inappropriate parental responses. Cronbach's α for the IPR was reported to be 0.74 [14,15].

Diabetes-specific family conflict

Adolescents and their parents completed the adapted version of the Diabetes Family Conflict Scale (DFCS). Nineteen items are summarized for a DFCS Total Score, higher scores indicating a higher level of family conflict. Previous reports showed good reliability in both child and parent responses [16,17].

To measure the child's level of self-care responsibility in managing diabetes, we developed a short questionnaire for parents of children 8 years and above. The instrument comprises seven items which cover different diabetes management tasks. Scores are combined to a Self-Care Total Score, with higher

scores indicating a higher level of self-care responsibility of the child.

Statizstical analysis

Blood samples were collected locally with standardized equipment. The mean HbA_{1c} value was calculated for each patient from the last three measurements taken during the previous 6 months. HbA_{1c} values were mathematically standardized to the Diabetes Control and Complications Trial (DCCT) equivalent in agreement with published guidelines [18]. All questionnaires which had been translated and/or adapted to CSII were tested as to descriptive characteristics and internal consistency reliability in the study sample.

Descriptive statistics are presented as frequencies or means ± standard deviation (SD). Outcomes at follow-up are presented as mean differences of baseline scores and 95% confidence intervals (CI). Effects of the intervention on the main outcome parameters were analysed using paired Student's *t*-test or Wilcoxon test, depending on the distributional characteristics of outcome parameters. Group differences at baseline were tested via Student's *t*-test and Mann–Whitney test. In order to allow for the simultaneous testing of many psychosocial outcomes (QOL, diabetes burden, parenting stress, fear of hypoglycaemia, family conflict), the significance level was defined as $P < 0.005$ after Bonferroni correction ($P < 0.05$ corrected by number of paired tests within each age group). To assess effect sizes, we used Cohen's effect size d, with $d \geq 0.2$ being classified as small effect, $d \geq 0.5$ as medium effect and $d \geq 0.8$ as large effect [19].

Results

At baseline, 38 schoolchildren aged 8–11 years, 76 adolescents aged 12–16 years, 108 parents of school-aged children and adolescents and 29 parents of younger children aged 4–7 years participated. Seventeen of the 18 cooperating centres reported a total of eight non-responders: patients who made the transition to CSII, but did not participate in the study. Reasons were given as: insufficient German literacy; one patient not regularly treated in the centre and therefore not available for the study; one patient accidentally not asked to participate. Five patients gave no reason or stated that they were not interested.

At follow-up 6 months after transition to CSII, 25 school-aged children, 63 adolescents, 85 parents of school-aged children and adolescents and 29 parents of younger children participated (study sample). The loss to follow-up in the school-aged children and adolescents group was 23% and in the parents group 18%. Three children withdrew from pump therapy during the observational period because of the inconvenience of wearing the pump. There were no differences in demographic (child age, gender) and clinical characteristics (mean HbA_{1c}, duration of diabetes, number of injections per day) between those who completed both assessments and those lost to follow-up.

Table 1 presents the demographic and medical characteristics of the final study sample (patients and parents who completed both assessments) at baseline.

Episodes of hypoglycaemia in the past 6 months were defined according to International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus Guidelines [20]. These events are associated with severe neurological dysfunction (e.g. seizures, loss of consciousness, disorientation, inability to arouse from sleep) that require intervention with glucagon or intravenous dextrose (grade 3) or moderate forms of hypoglycaemia associated with neurological dysfunction that are not recognized by the patient but where oral treatment is successful (grade 2).

The internal consistency reliability of all instruments which were translated into German (PIP, HFS-P, BPFAS, DFCS), adapted for use in CSII (KINDL-DM) or specifically developed for this study (Questionnaire on Child's Self-Care Responsibility) was tested in the study sample after transition to CSII. Cronbach's α approached or exceeded the minimum standard for group comparison of 0.70 in all scales in the children and

Table 1 Baseline demographic and clinical characteristics of the final study sample

Child age (mean ± SD) (n = 117)	10.5 ± 3.7 years
Child gender (n, %) (n = 117)	53 (45) female
Main caretaker (n, %) (n = 114)	96 (84) mothers
HbA_{1c} (mean ± SD) (n = 107)	7.7 ± 1.3%
Duration of diabetes (mean ± SD) (n = 112)	3.8 ± 2.9 years
Initial treatment (number of injections per day, n, %) (n = 106)	
3	4 (3.8)
4	45 (42.5)
5	26 (24.5)
6	18 (17.0)
7	13 (12.2)
Insulin (n) (n = 108, multiple responses were permitted)	
Bolus insulin	
Regular insulin	65
Short-acting analogue	44
Basal insulin	
NPH insulin	61
Long-acting analog	20
Semilente insulin	26
Hypoglycaemia in the past 6 months	
ISPAD II	3
ISPAD III	1
Main indications for CSII (n = 112, multiple responses were permitted)	
Dawn phenomenon	71
Labile metabolic control	70
Problems at mealtimes	57
Recurring hypoglycaemia	33
Fear of injections	13

CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycated haemoglobin; ISPAD, International Society for Pediatric and Adolescent Diabetes; NPH, neutral protamine Hagedorn; SD, standard deviation.

adolescent age group and in most scales in the younger children age group, with the exception of the KINDL-DM ($\alpha = 0.59$) and the MC Frequency subscale of the PIP ($\alpha = 0.44$).

Generic and diabetes-specific QOL

Table 2 presents the generic as well as diabetes-specific QOL scores before (baseline) and the difference to the baseline score at 6 months after transition to CSII (follow-up).

Generic QOL at follow-up was not different from baseline QOL in any age group. Parent-reported diabetes-specific QOL of the younger children as well as self-reported diabetes-specific QOL of school-aged children and adolescents (KINDL-DM Total Score) increased considerably, with medium effect size in adolescents and large effect size in school-aged children and younger children.

Family burden

Tables 3–5 present generic as well as diabetes-specific aspects of family burden before and at 6 months after transition to CSII.

Six months after transition to CSII, parents of younger children reported significant less frequent parenting stress as well as less difficulty with parenting stress in the Total Scores of the PIP (TS-F, TS-D) and in all PIP subscales; however, the decrease in some of the subscales did not meet the previously defined significance level of $P < 0.005$. They also reported a significant decrease in hypoglycaemia-related worries (HFS-P Worry scale), but no decrease in the HFS-P Behaviour scale, and less frequency of feeding behaviour problems (BPFAS-F). Effect sizes in all scales were moderate to large.

Parents of younger children also reported significantly less Overall Diabetes Burden with regard to themselves (mean t0 = 3.62 ± 1.06, mean t1 = 3.12 ± 1.11) and to the child with diabetes (mean t0 = 3.00 ± 1.12, mean t1 = 2.36 ± 0.76). The differences were statistically significant ($Z = -3.23$, -4.15, $P < 0.01$, Wilcoxon test, two-tailed testing), with moderate to large effect sizes ($d = 0.5$–0.8).

Parents of school-aged children and adolescents reported significant less frequent parenting stress and less difficulty with parenting stress in the PIP Total Scores (TS-F, TS-D) and in some subscales. Effect sizes were moderate.

Parents of school-aged children also reported a significant decrease in fear of hypoglycaemia, both on the Behaviour and the Worry subscale of the HFS-P, with moderate effect sizes. Parents of adolescents reported significantly less HFS-P-related worries after transition to CSII, although the decrease on the HFS-P behaviour subscale did not meet the predefined criterion.

Parents of school-aged children and adolescents reported significant less Overall Diabetes Burden with regard to themselves (8–11 years: mean t0 = 3.54 ± 0.92, mean t1 = 2.64 ± 0.87, $Z = -3.57$, $P < 0.001$); 12–16 years: mean t0 = 2.70 ± 1.01, mean t1 = 2.40 ± 0.82, $Z = -2.36$, $P < 0.05$) and to the child with diabetes (8–11 years: mean t0 = 3.50 ± 0.95, mean t1 = 2.54 ± 1.03, $Z = -3.24$, $P < 0.01$; 12–16 years: mean t0 = 3.07 ± 1.02, mean t1 = 2.64 ± 1.01, $Z = -3.05$, $P < 0.01$). Effect sizes were large in the school-aged children group and moderate in the adolescents group.

Family conflict

We found no significant change in the level of family conflict (DFCS Total Score) over the 6-month study period (DFCS Total Score t0: 27.42 ± 6.83), mean difference t1: −0.85, 95% CI: −2.56 to 0.86). We also found no significant change in the level of self-care responsibility (Self-Care Total Score) of their child in managing his or her diabetes (Self-Care Total score t0: 29.90 ± 3.88), mean difference t1: −0.67, 95% CI: −0.31 to 1.65).

Analysing families with a considerable amount of family conflict at baseline (DFCS Total Score ≥ 29) separately,

Table 2 Difference in QOL before (baseline) and 6 months after (follow-up) transition to CSII

QOL	Mean baseline	SD	Mean difference t1–t0*†	95% CI	T	*P*‡	Effect size *d*
Young children aged 4–7 years, *n* = 24 (proxy-report)							
KINDL-R Total Score (1–100)	75.1	9.75	3.82	−0.27–7.92	1.93	0.066	—
KINDL Diabetes Module (1–100)	62.3	11.74	17.61	10.36–24.85	5.02	0.0001	1.3
School-aged children aged 8–11 years, *n* = 22							
KIDSCREEN-Index (1–100)	78.8	12.67	2.14	−2.51–6.79	0.96	0.348	—
KINDL Diabetes Module (1–100)	64.2	15.09	13.16	7.35–18.98	4.71	0.0001	0.9
Adolescents aged 12–16 years, *n* = 61							
KIDSCREEN-Index (1–100)	79.4	12.08	0.07	−3.13–3.28	−0.05	0.964	—
KINDL Diabetes Module (1–100)	69.6	11.74	6.68	3.68–9.68	4.45	0.0001	0.6

*Positive scores indicate increased QOL at follow-up.
†Negative scores indicate decreased diabetes burden at follow-up.
‡Paired Student's *t*-test, two-tailed testing.
CI, confidence interval; CSII, continuous subcutaneous insulin infusion; QOL, quality of life; SD, standard deviation.

Table 3 Difference in family burden before (t0) and 6 months after (t1) transition to CSII in parents of children aged 4–7 years (n = 25)

Family burden	Mean t0	SD	Mean difference t1–t0*	95% CI	T	P†	Effect size d
Paediatric Inventory for Parents (PIP)							
Communication (CM)							
Frequency (9–45)	22.0	5.75	−2.20	−4.11 to −0.29	−2.38	0.026	−0.6
Difficulty (9–45)	19.0	5.97	−1.29	−3.55 to 0.96	−1.19	0.248	—
Emotional Distress (ED)							
Frequency (15–75)	40.7	7.56	−6.04	−9.36 to −2.72	−3.76	0.001	−0.8
Difficulty (15–75)	41.1	8.56	−6.52	−10.06 to −2.98	−3.82	0.001	−0.8
Medical Care (MC)							
Frequency (8–40)	21.5	5.51	−3.88	−5.87 to −1.89	−4.02	0.0001	−0.7
Difficulty (8–40)	16.0	4.33	−2.88	−4.71 to −1.04	−3.24	0.004	−0.7
Role Function (RF)							
Frequency (10–50)	24.4	5.84	−3.04	−5.52 to −0.56	−2.54	0.018	−0.5
Difficulty (10–50)	23.4	5.87	−2.71	−4.86 to −0.56	−2.61	0.016	−0.5
Total Score (TS)							
Frequency (42–210)	108.2	19.86	−4.72	−22.20 to −7.24	−4.06	0.0001	−0.7
Difficulty (42–210)	99.2	21.07	−1.83	−19.76 to −3.90	−3.09	0.005	−0.6
Hypoglycaemia Fear Survey (HFS-P)							
Behaviour (10–50)	29.1	5.32	1.42	−1.46 to 4.30	1.02	0.319	—
Worry (15–75)	42.2	9.31	−7.69	−11.49 to −3.90	−4.18	0.0001	−0.8
Behavioural Paediatric Feeding Assessment Scale (BPFAS)							
Inappropriate Parental Response							
Frequency (10–50)	20.7	5.08	−5.61	−7.64 to −3.58	−5.74	0.001	−1.1
Problem (0–10)	2.1	2.06	−1.48	−2.62 to 0.34	−2.70	0.014	−0.7

*Negative scores indicate decreased diabetes burden at follow-up.
†Paired Student's t-test, two-tailed testing.
CI, confidence interval; CSII, continuous subcutaneous insulin infusion; SD, standard deviation.

adolescents (n = 17) reported some decrease in family conflict after transition to CSII (DFCS Total Score t0: 36.12 ± 5.86), mean difference t1: −5.29, 95% CI: −9.58 to −1.01), which, however, did not meet the significance criterion of $P < 0.005$ (T = 2.62, $P = 0.02$). Parents (n = 23) with an initially substantial level of family conflicts showed no decrease in the DFCS (DFCS Total Score t0: 31.39 ± 2.93), mean difference t1: −1.87, 95% CI: −4.48 to 0.74).

Glycaemic control

The mean HbA_{1c} of the younger children aged 4–7 years was 7.4 ± 1.38%, range 3.7–10.1) before and 7.3 ± 1.08%, range 4.7–9.4) 6 months after transition to CSII. The mean HbA_{1c} of the school-aged children aged 8–11 years was 7.6 ± 0.78%, range 5.8–9.2) before and 7.4 ± 0.85%, range 5.7–9.4) after transition to CSII. Both age groups showed no significant decrease of HbA_{1c} in the study period. The mean HbA_{1c} of the adolescents aged 12–16 years was 8.0 ± 1.56%, range 5.5–12.0) before and 7.6 ± 1.33%, range 5.4–11.7) 6 months after transition to CSII. The difference was statistically significant ($Z = 2.43$, $P < 0.05$, Wilcoxon test, two-tailed testing).

There was no significant decrease in severe hypoglycaemia in the study period (six ISPAD II, one ISPAD III before and five ISPAD II/one ISPAD III after transition to CSII).

Discussion

Most of the published studies on CSII focus on medical outcomes such as HbA_{1c}, hypoglycaemia and acute complications, as recommended in international guidelines. As healthcare providers, we need to understand the impact of diabetes and its treatment on the lives of our patients and their families. From the patient's perspective, the greatest benefits may lie in outcomes beyond measures of glycaemic control, such as QOL. These putative psychosocial benefits of CSII are understudied; one reason may be that they refer to psychological constructs which are not as easily measurable as well-defined biomedical parameters [3]. In our study, diabetes-related QOL and diabetes burden, generic parenting stress, feeding behaviour and fear of hypoglycaemia were recognized as relevant key parameters of psychosocial benefit in CSII therapy; we also identified standardized questionnaires to measure these key parameters.

The translated and adapted measures showed good internal consistency. It was only in the younger age group that some alpha

Table 4 Difference in family burden before (t0) and 6 months after (t1) transition to CSII in parents of children and adolescents aged 8–11 years (n = 29)

Family burden	Mean t0	SD	Mean difference t1–t0*	95% CI	T	P†	Effect size d
Paediatric Inventory for Parents (PIP)							
Communication (CM)							
Frequency (9–45)	20.2	4.34	−1.34	−2.78 to −0.09	−1.92	0.065	−0.3
Difficulty (9–45)	16.8	4.66	−1.24	−2.84 to 0.36	−1.59	0.124	—
Emotional Distress (ED)							
Frequency (15–75)	39.3	9.24	−3.34	−5.90 to −0.79	−2.68	0.012	−0.4
Difficulty (15–75)	40.1	12.69	−4.17	−7.35 to −0.99	−2.69	0.012	−0.4
Medical Care (MC)							
Frequency (8–40)	19.0	5.78	−2.31	− 4.16 to −0.46	−2.56	0.016	−0.4
Difficulty (8–40)	14.6	5.47	−2.28	−3.93 to −0.62	−2.82	0.009	−0.5
Role Function (RF)							
Frequency (10–50)	23.4	6.31	−1.96	−3.74 to −0.18	−2.26	0.032	−0.4
Difficulty (10–50)	23.2	7.70	−2.96	−5.09 to −0.83	−2.87	0.008	−0.5
Total Score (TS)							
Frequency (42–210)	101.7	23.21	− 9.14	−14.62 to −3.65	−3.41	0.002	−0.4
Difficulty (42–210)	93.9	28.91	−10.03	−16.41 to −3.66	−3.23	0.003	−0.4
Hypoglycaemia Fear Survey (HFS-P)							
Behaviour (10–50)	31.3	7.44	−4.11	−6.15 to −2.07	−4.13	0.0001	−0.6
Worry (15–75)	42.5	12.91	−6.52	−10.03 to −3.00	−3.80	0.001	−0.5

*Negative scores indicate decreased diabetes burden at follow-up.
†Paired Student's t-test, two-tailed testing.
CI, confidence interval; CSII, continuous subcutaneous insulin infusion; SD, standard deviation.

Table 5 Difference in family burden before (t0) and 6 months after (t1) transition to CSII in parents of children and adolescents aged 12–16 years (n = 55)

Family burden	Mean t0	SD	Mean difference t1–t0*	95% CI	T	P†	Effect size d
Paediatric Inventory for Parents (PIP)							
Communication (CM)							
Frequency (9–45)	18.1	4.08	−1.44	−2.82 to −0.56	−2.09	0.042.	−0.4
Difficulty (9–45)	14.86	4.63	−0.80	−2.05 to 0.45	−1.28	0.206	—
Emotional Distress (ED)							
Frequency (15–75)	33.8	8.27	−2.47	−4.45 to −0.50	−2.51	0.015	−0.3
Difficulty (15–75)	33.0	10.32	−2.51	−4.50 to −0.52	−2.54	0.014	−0.3
Medical Care (MD)							
Frequency (8–40)	15.5	4.54	−2.50	−3.90 to −1.10	−3.59	0.001	−0.6
Difficulty (8–40)	12.5	3.68	−1.50	−2.54 to −0.46	−2.89	0.006	−0.4
Role Function (RF)							
Frequency (10–50)	19.8	5.26	−1.74	−3.17 to −0.31	−2.44	0.018	−0.4
Difficulty (10–50)	18.5	5.50	−2.00	−3.42 to −0.58	−2.84	0.007	−0.4
Total Score (TS)							
Frequency (42–210)	87.2	18.83	−8.21	−13.25 to −3.18	−3.27	0.002	−0.4
Difficulty (42–210)	78.8	22.21	−6.73	−11.18 to −2.29	−3.04	0.004	−0.3
Hypoglycaemia Fear Survey (HFS–P)							
Behaviour (10–50)	26.2	5.95	−1.81	−3.32 to −0.30	−2.41	0.019	−0.3
Worry (15–75)	37.4	10.11	−3.84	−6.16 to −1.51	−3.30	0.002	−0.4

*Negative scores indicate decreased diabetes burden at follow-up.
†Paired Student's t-test, two-tailed testing.
CI, confidence interval; CSII, continuous subcutaneous insulin infusion; SD, standard deviation.

values did not meet the criterion for group comparisons. This may be as a result of the small sample size within this age group. The instruments also proved to be sensitive to treatment change, which is an important qualification for use in clinical trials.

Studies regarding the psychosocial impact of CSII in paediatric populations showed conflicting results: CSII was associated with improvements in children's QOL and less parenting stress in some studies [4,21,22] and no difference in others [5,23]. Inconsistent results may depend on different methods of measurement and on the age differences in the study samples.

In this study, diabetes-related QOL improved in all age groups after transition to CSII, while generic QOL did not differ. Our findings confirm the general presumption that condition-specific quality of life measures are more sensitive to changes of condition or treatment than generic ones and also demonstrate the sensitivity to change of the CSII-adapted KINDL-DM. Unlike generic instruments, diabetes-specific instruments focus on the day-to-day management of diabetes and its impact on QOL. CSII provides greater flexibility with insulin administration and meal planning. This greater flexibility of lifestyle [3] may be the underlying factor which facilitates making adjustments to diabetes management and thus reduces diabetes burden and improves the patients' QOL.

Childhood diabetes may be a profound stressor for all family members. The parents of all paediatric age groups reported a reduction in both the frequency and impact of generic parenting stress after transition to CSII treatment. Parents also reported reduced diabetes burden in the patient and themselves and, to a lesser degree, in other family members.

Some aspects of family burden and quality of life in children with Type 1 DM change over time. In young children, the burden of day-to-day diabetes management rests entirely on adult carers; variability of food intake and activity level place considerable stress on the parents, specifically regarding nutrition management. Nutrition management is one of the more demanding disease-specific tasks concerning mealtimes, being affected by changing appetite and food preferences, particularly in young children [24]. In this study, parents reported fewer concerns about their ability to manage mealtime behaviour in families of young children after transition to CSII. These findings may have important implications, not only because nutrition management is a cornerstone of Type 1 diabetes treatment but also because it is understudied in clinical research [25].

Hypoglycaemia is frequently the limiting factor in achieving best glycaemic control and the possible effects of severe hypoglycaemia on cognitive development receive much attention and debate. Parents' fear of hypoglycaemia may have implications for diabetes management and glycaemic control. It may impact parenting style and the child's physical and psychological health [26,27]. In this study, after transition to CSII the fear of hypoglycaemia was significantly reduced without compromising glycaemic control. Insulin delivered by CSII leaves no depot in subcutaneous tissue and CSII therapy therefore may allow parents to feel confident about the effect of the insulin.

Parents of younger children experienced more worries of hypoglycaemia than parents of older children. Effect sizes were generally larger in the younger age group, which may indicate that parents of younger children have more benefit from CSII therapy related to general and disease-specific parenting stress.

Assessment of parent–child interaction is a relevant aspect when investigating psychosocial outcome in diabetes-intervention studies. Problems of sharing diabetes responsibility and diabetes-related family conflict may contribute to family burden and children's QOL, specifically in adolescents [28,29]. CSII means greater flexibility of insulin administration and meal planning and may give parents less reason to criticize the child about diabetes management tasks and thus reduce family conflict. However, our findings on family conflict showed only a slight decrease of conflict from the adolescents' point of view, which did not meet the predefined significance criterion. Apparently, families with a high initial level of conflict need more support than just changing the technical device for delivering insulin to change their family interactions. Factors related to family conflict such as adolescents' perception of parental worry, understanding and intrusive and blaming behaviours [30] need to be addressed in further studies of CSII. We found no changes in parent-reported self-care responsibility of the child. Following transition to CSII, parents apparently remain involved in diabetes management, which is in accordance with recent findings [31].

Some limitations of the study have to be considered. Nearly all participating centres reported the number of non-responders to the study; however, mostly without any demographic and medical information. Therefore, a comparison between families who participated in the study and those who made the transition to CSII but did not participate was not possible. However, the study sample is fairly representative, as the number of patients who did not participate was quite small (7%). The main limitations of the study are the lack of a control group, which is because of its character as a pilot study, and the small sample size within the age groups, which limits the statistical power of the tests. However, in spite of the small sample size within the stratified sample, most results were statistically significant, which may indicate that psychosocial benefits of CSII for children with Type 1 diabetes and their families may be substantial. However, only a controlled study design would allow interpreting these results because of the transition to insulin pump therapy.

Conclusion

This pilot study identified relevant psychosocial key parameters of CSII and showed that instruments are available which are reliable and sensitive to treatment change. CSII may mean improved quality of life and reduced diabetes burden for children with Type 1 DM and their families. Evidence of these benefits needs to be provided by randomized controlled studies.

Competing interests

This study was funded by a grant from Roche Diagnostics GmbH, Germany. There are no other competing interests to declare.

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WILEY ISPAD

ORIGINAL ARTICLE

Psychosocial benefits of insulin pump therapy in children with diabetes type 1 and their families: The pumpkin multicenter randomized controlled trial

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Objective: Continuous subcutaneous insulin infusion (CSII) is on the rise among pediatric patients with type 1 diabetes mellitus. Metabolic effects alone cannot explain this rising popularity. From the patient's perspective, the main benefits of CSII may be found in subjective psychosocial health outcomes (patient-reported outcomes [PRO]).

Subjects and Methods: In a multicenter open randomized controlled trial, children and adolescents aged 6 to16 years currently treated with multiple daily injections (MDI) were randomized 1:1, stratified by center, to either starting with CSII immediately after the baseline interview or to continuing MDI while waiting 6 months for transmission to CSII. The primary outcomes were patient-reported diabetes-specific health-related quality of life (DHRQOL) and diabetes burden of the main caregiver. Secondary outcomes were caregiver stress, fear of hypoglycemia, satisfaction with treatment, and HbA1c.

Results: Two-hundred and eleven patients were randomized between February 2011 and October 2014, and 186 caregivers and 170 patients were analyzed using the intention-to-treat principle for primary outcomes. Children 8 to 11 years in the CSII group reported improved DHRQOL at follow-up compared to MDI (median difference [MD] 9.5, 95% confidence interval [CI] 3.6-16.7, P = 0.004). There were no treatment differences in the adolescent age-group 12 to 16 years (MD 2.7; 95% CI −3.2-9.5; P = 0.353). The main caregivers of the CSII group reported a significant decline of overall diabetes burden at follow-up compared to the MDI group (MD 0; 95% CI −1-0; P = 0.029). Secondary PROs also were in favor of CSII.

Conclusions: CSII has substantial psychosocial benefits. PROs demonstrate these benefits. Registered as NCT01338922 at clinicaltrials.gov

KEYWORDS

children/adolescents, continuous subcutaneous insulin infusion (CSII), diabetes type 1, health-related quality of life, randomized controlled trial

An abstract of less than 300 words was presented at the IPSAD 2017, Innsbruck, Austria.

Abbreviations: CSII, continuous subcutaneous insulin infusion; DCCT, diabetes control and complications trial; DDG, : german diabetes society (Deutsche Diabetes Gesellschaft); DFCS, diabetes family conflict scale; DHRQOL, diabetes-specific HRQOL; DSMB, data safety and monitoring board; DTSQs, diabetes treatment satisfaction questionnaire, status version; DTSQs-P, parent version of the DTSQ-s; DTSQs-T, teen version of the DTSQ-s; DTSQ-P TS+, summary score of the parent version of the DTSQ-s; DTSQ-T TS+, summary score of the teen version of the DTSQ-s; FAS, full analysis set; HFS-P, hypoglycemia fear survey, parent version; HRQOL, health-related quality of life (HRQOL); IMBS, Institute of Medical Biometry and Statistics, University of Luebeck; ISPAD, International Society for Pediatric and Adolescent Diabetes; KINDL-DM, diabetes-specific module of the KINDL-R; KINDL-R, modular HRQOL questionnaire for children-–revised version; MDI, multiple daily injections; PIP, pediatric inventory for parents; PIP-D, total difficulty score of the pediatric inventory for parents PIP; PIP-F, total frequency score of the pediatric inventory for parentsPIP; PRO, patient- -reported outcomes; RCT, randomized-controlled trial; RITA, randomization in treatment arms; SAS software, statistical analysis system software; SES, socioeconomic status; WHO-5, World Health Organization-five

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1 | INTRODUCTION

The ultimate goal in treating children and adolescents with type 1 diabetes mellitus (T1DM) is to achieve optimal glycemic control, avoiding acute, and long-term complications, without compromising age-appropriate development and health-related quality of life (HRQOL).[1]

Continuous subcutaneous insulin infusion (CSII) allows for a more physiologic insulin replacement and is on the rise among pediatric patients.[2] CSII may be superior to multiple daily injections (MDI) for metabolic control and for acute complications.[3,4] However, metabolic effects alone cannot explain the rising popularity of CSII.[3,5]

To understand the true impact of a treatment regimen, researchers should look beyond metabolic efficacy and examine the families' experiences of their day-to-day living with diabetes.[6] As these are inherently subjective, they should be reported by the young patients or caregivers themselves. Patient-reported outcomes (PRO), specifically HRQOL, are increasingly incorporated in clinical diabetes research.[7]

CSII provides more flexibility in lifestyle, which may positively affect the HRQOL and disease burden. It is not yet established whether the increased flexibility translates into improved standardized measures of PRO.[8] Measures of PRO can be either generic or diabetes-specific. Generic measures cover a broad range of subjective health aspects relevant for populations with and without health problems. Diabetes-specific measures are designed to cover meaningful aspects of the disease and its treatment, and hence, offer a greater depth of insight to the experiences of patients. They are also more sensitive to treatment differences.[9,10]

Systematic reviews of pump therapy in children and adolescents[3,5,11,12] report mixed results on the HRQOL-benefits of CSII in the pediatric age-group. All in all, there are improvements in diabetes-specific rather than generic aspects of HRQOL favoring CSII over MDI, however, only with weak evidence.[5,13] There is a lack of methodologically sound studies, particularly of adequately powered randomized controlled trials (RCT).

A multicenter prospective observational pilot study preceding the pumpkin trial found increased diabetes-specific HRQOL (DHRQOL) and decreased diabetes burden after transfer to CSII and identified psychometrically sound instruments.[14]

The objective of this study was to investigate the effects of CSII on PRO in children and adolescents with T1DM and their families in an open RCT. We investigated the impact of CSII on the DHRQOL of the patients and on the overall diabetes burden of the main caregivers (primary outcomes). We hypothesized that children and adolescents treated with CSII showed better DHRQOL compared to those treated with MDI, and their caregivers less overall diabetes burden. We also investigated the impact of CSII on generic HRQOL, caregiver stress, fear of hypoglycemia, family conflict, treatment satisfaction, and HbA1c (secondary outcomes). We hypothesized better generic HRQOL, less caregiver stress, less fear of hypoglycemia, less family conflicts, a higher level of patient satisfaction, and a slightly lower level of HbA1c in the CSII group compared to the MDI group.

2 | METHODS

2.1 | Subjects and study design

We performed an open multicenter parallel randomized controlled intervention trial with waiting-list control group in children with T1DM and their main caregiver, usually a parent. Eighteen German specialized pediatric diabetes centers approved by the German Diabetes Society (Deutsche Diabetes Gesellschaft, DDG) enrolled the patients and conducted the interventions. All children and adolescents aged 6 to 16 years with T1DM currently being treated with MDI with an indication for transfer to CSII were eligible for the present study. Exclusion criteria were diabetes duration of less than 6 months, remission (less than 0.5 U insulin/kg body weight), and insufficient German literacy to complete questionnaires. The ethics committees of the participating centers approved the study. The investigations have been conducted in accordance with the principles of the Declaration of Helsinki (2008). Patients were grouped as young children (6-7 years), school-children (8-11 years), and adolescents (12-16 years). Informed consent was given by adolescents and both parents; children assented. The trial was registered in clinicaltrials.gov as NCT01338922.

Patients eligible for transfer to CSII were randomized to either immediate transition to CSII or MDI and additional individual optimization of the diabetes regimen—to control for educational effects—and transfer to CSII after second interviews 6 months later. Indication for CSII followed the clinical criteria of the German Clinical Practice Guidelines, namely, recurrent severe hypoglycemia, wide fluctuations in blood glucose levels, suboptimal diabetes control, pronounced

dawn–/ dusk phenomenon, needle phobia, and also improvement of the young patient's motivation, the wish for more flexibility in mealtimes and daily routine, and patients' preference (not specified). Patients were transferred to CSII by a multidisciplinary diabetes team.[15]

2.2 | Instruments

The main caregiver provided sociodemographic data. The family's socioeconomic status (SES) was measured with the Winkler-Index, comprising the three components: education/vocational qualification, occupational status, and net household income. The SES index was categorized as low, moderate, or high.[16]

PRO were measured using standardized questionnaires. Children and adolescents 8 to 16 years self-reported on their HRQOL, adolescents 12 years and above additionally reported on family conflicts, and satisfaction with their diabetes therapy. The main caregivers proxy-reported on the HRQOL of children younger than 8 years; those of adolescents reported on family conflicts. All other caregiver-reported outcomes were measured across all age-groups.

2.3 | Primary outcomes

Children's and adolescents' DHRQOL was measured using the diabetes-specific module of the KINDL-R modular HRQOL questionnaire.[17] The CSII-adapted version of the diabetes-specific module comprises 21 Likert-scaled items for patients 8 years and older which are summarized to give a diabetes-specific KINDL-DM total score. Higher scores indicate better DHRQOL.

The main caregivers reported on their overall diabetes burden using a one-dimensional 5-point intensity scale. Higher scores indicate a greater diabetes burden.

2.4 | Secondary outcomes

Children's and adolescents' generic HRQOL were measured with the generic core measure of the KINDL-R.[17] The instrument provides age-appropriate self-report versions (24 items) for school-aged children and adolescents, and a parent-proxy-report version for younger children. The Likert-scaled items are summarized in the generic KINDL R total core. Higher scores indicate better generic HRQOL.

Adolescents and their main caregivers completed the adapted version of the diabetes family conflict scale (DFCS). Nineteen items are rated on a 3-point Likert-scaled and summarized to give a DFCS total score, higher scores indicating a higher level of family conflict.[18,19]

Adolescents and their main caregivers completed the Diabetes Treatment Satisfaction Questionnaire, status version (DTSQs Parent, 14 items, and DTSQs Teen, 12 items), the German version being validated in the pumpkin study. Items on satisfaction with treatment and metabolic control are summarized in the DTSQ-P TS + C (caregivers) and the DTSQ-T TS + C (adolescents) summary scores. The original instrument has shown good psychometric properties, validity and sensitivity to change.[20,21] Higher scores indicate greater satisfaction with treatment.

The main caregivers' subjective mental well-being was assessed using the World Health Organization-Five Well-Being Index (WHO-5).[22] 5-point Likert-scaled items are combined to give a summary score. Higher scores indicate greater well-being.

Parenting stress was measured with the pediatric inventory for parents (PIP). The main caregiver rated each of the 42 items using a 5-point Likert scale as to both the items frequency and the level of difficulty associated with it. Items are combined to give a total frequency score (PIP-F), and a total difficulty score (PIP-D).[23] Higher scores indicate more parenting stress.

The main caregiver completed the Hypoglycemia Fear Survey, parent version (HFS-P).[24] The HFS-P comprises 25 items on two scales: Behavior (10 items) and Worry (15 items). The scales are separately reported as recommended,[25] higher scores indicating higher levels of fear of hypoglycemia.

All original versions of the questionnaires have been validated (for more detailed information see Ref. 14). With the exception of the DTSQ, all questionnaires have been used in the pilot study preceding the pumpkin trial and displayed satisfactory reliability, and sensitivity to treatment change.[14]

The multiple of the mean method (MOM) was used to mathematically standardize HbA1c-values to the diabetes control and complications trial (DCCT) reference range: 20.7 to 42.6 mmol/mol (4.05%-6.05%).[26]

2.5 | Statistical analysis

Analyses used the full analysis set (FAS) following the intention-to-treat principle. A patient was included in the FAS if randomized to CSII or MDII, regardless of which intervention the patient actually received and regardless of other protocol deviations. Patients were excluded from this dataset only for the following reasons: violation of inclusion or exclusion criteria, withdrawal of consent after randomization, or complete lack of data. Missing data were assumed to be missing completely at random, so that no imputation was needed. The three primary endpoints (school-child DHRQOL, adolescent DHRQOL, and main caregiver overall diabetes burden at 6 months) were tested using a fallback procedure at global significance level 0.05.[27] The two hypotheses on all cases and on age group 8 to 11 years were each assigned an adjusted level of 0.025. The fallback would be to either hypothesis in the first step. If both were significant, the full level would fall to the hypothesis on the effect on adolescents. A supporting figure gives a detailed description of the fallback procedure.

Endpoints were analyzed using the exact two-sided *U* test for treatment comparisons and signed-rank tests for changes from baseline within groups and Hodges-Lehmann 95% confidence interval (primary analysis). Rank-based analyses of covariance with baseline adjustments for the respective dependent variable, age as a covariate (when more than one age group was involved), and site as a random effect yielded additional descriptive *P* values.

Expected complications (severe hypoglycemia and ketoacidosis) and other adverse events were listed.

All analyses were performed with SAS software (version 9.2, SAS Institute, Cary, North Carolina, USA).

2.6 | Sample size

Sample size calculation was performed by using empirical proportions of age-groups, and means and SD for the primary endpoints observed in the pilot study.[14] The significance level (two-sided) for the testing of the primary hypotheses was set to 5%, and each hypothesis was to be tested at the 2.5% level. The power was set to 80%, and the drop-out was assumed to be 20%. Sample size calculation for t-tests was corrected by 5% for *U*-tests. For the age distribution in the pilot study, $2 \times (32 + 26 + 78) = 272$ patients of all age groups had to be initially recruited. As age groups were more balanced at data safety and monitoring board review, a total sample size of about 210 patients was considered sufficient. The recruitment was immediately amended. The power of the tests to detect differences in both subgroups given DHRQOL values from the pilot study was 96% in school-children and 77% in adolescents. The significance-level (two-sided) for the description of secondary outcomes was set to 1%. Neither adaptations nor interim analyses were planned.

2.7 | Randomization

The randomization sequence was generated by validated software RITA (randomization in treatment arms) as stratified by center with a 1:1 allocation using permuted blocks with variable confidential block lengths two and four. Randomization results were provided by telefax after registration of the patient at the Institute of Medical Biometry and Statistics, University of Luebeck. This guaranteed concealment of allocation.

3 | RESULTS

3.1 | Recruitment and participants

Between February 2011 and October 2014, 367 patients were assessed for eligibility in the clinical trial. In total, 211 patients were randomized, 106 to CSII and 105 to MDI.

Two and five patients, from CSII and MDI, respectively, did not receive the intended intervention, 14 and 16 patients, respectively, were lost to follow-up. (Figure 1) The FAS of 199 patients comprised data of 179 for primary endpoints.

Table 1 presents the demographic and clinical characteristics of the study participants.

Mean age at randomization, the proportion of male patients, mean diabetes duration, and the distribution of SES was similar in both groups. Almost all patients were on ICT, with roughly half of the patients injecting insulin four to five times per day, and nearly one-third of patients injecting insulin six times per day in both groups. The most frequently reported indications for transition to CSII were unpredictable swings in blood glucose concentration, the wish for flexibility in daily routine and patient preference with a nearly equal proportion in both the CSII and the MDI group. HbA1c-values at baseline were generally satisfying, and 0.5% lower in the CSII group.

3.2 | Primary and secondary outcomes

Table 2 presents the primary outcomes—self-reported DHRQOL of the school children and adolescents, and overall diabetes burden of the main caregiver—at baseline and at 6 months of CSII or MDI.

As test 2 of DHRQOL in school children was significant ($P = 0.004$) at level 0.025, and test 1 of parental burden was significant ($P = 0.029$) at level 0.05, test 3 was conducted at level 0.05. This test of treatment effect on DHRQOL in adolescents was not significant ($P = 0.353$), ending the confirmatory procedure.

School children (8-11 years) of the CSII group reported significantly better DHRQOL at follow-up compared to the MDI group. The difference between the groups was statistically significant in the primary and the adjusted analysis. In adolescents (12-16 years), there was no difference between the treatment groups detected. The analysis of the total sample (without age stratification) revealed a significantly better DHRQOL at follow-up in favor of CSII (MD 5.95 [1.19-10.71], $P = 0.016$).

The main caregivers of the children and adolescents (6-16 years) of the CSII group reported a significantly lower overall diabetes burden at follow-up compared to those of the MDI group. The difference was statistically significant in both the primary and the adjusted analysis.

Table 3 presents secondary patient- and caregiver-reported outcomes, and HbA1c- values.

There were no significant changes in patient-reported generic HRQOL, and family conflicts. Adolescent-reported treatment satisfaction (DTSQ-T TS+) improved in both treatment groups. The difference in favor of CSII ($P < 0.05$) failed to reach the predefined significance level of 1% for secondary outcomes in both the primary and the adjusted analysis.

Improvement in subjective well-being of the main caregivers did not differ significantly between the treatment groups. The main caregivers of the CSII group reported significantly reduced parental stress (PIP-F, PIP-D), reduced fear of hypoglycemia (HFS Behavior, HFS Worry), and improved treatment satisfaction (DTSQ-P, TS+C) at follow-up compared to the MDI group. The differences between the treatment groups were significant in both the primary and the adjusted analysis with the exception of parenting stress, which failed to reach the significance level of 1% in the unadjusted analysis ($P < 0.05$). There were no differences between the treatment groups regarding family conflict (DFCS).

Children and adolescents displayed no significant change of HbA1c in the study period independently of treatment regime. There was no significant decrease in severe hypoglycemia ISPAD II (6/3 and 2/2 at baseline and follow-up in CSII/ MDI group), ISPAD III (3/4 and 2/3), and ketoacidosis (3/3 and 5/3).

4 | DISCUSSION

In the pumpkin study, the self-reported DHRQOL in school-children aged 8 to 11 years improved 6 months after transition to CSII compared to those who stayed on MDI. In adolescents aged 12 to 16 years, there was no significant difference between the treatment

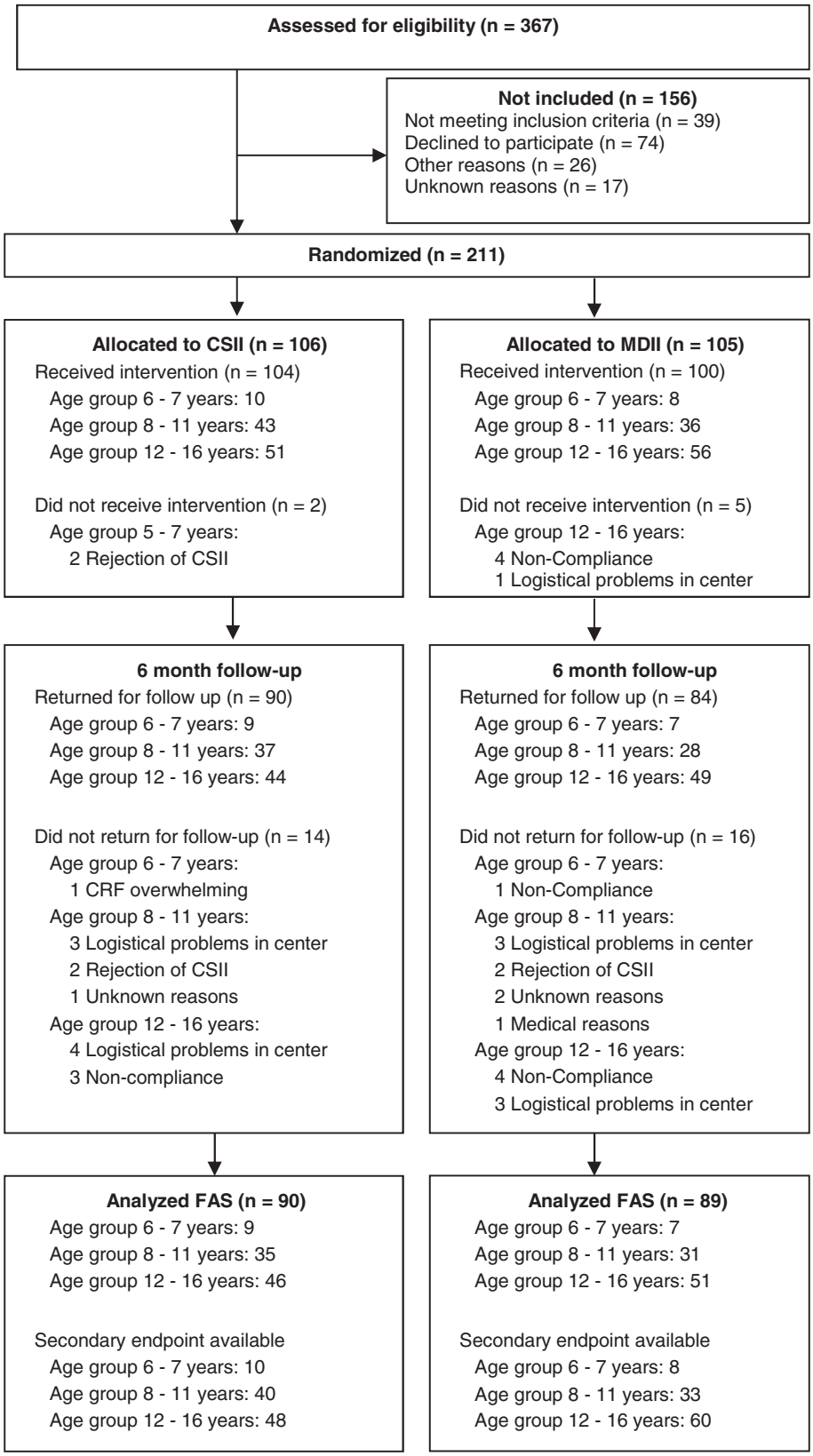

FIGURE 1 Participant flow

groups. Overall burden on the main caregiver decreased significantly in the CSII group compared to the MDI group.

The age-stratified approach to measuring children's and adolescents' DHRQOL of the pumpkin trial makes it difficult to compare the results with other studies. The analysis of the overall pumpkin sample (without age-stratification) showed significantly improved DHRQOL in the CSII group compared to the MDI group in children and adolescents aged 8 to 16 years. This result is in accordance with those of some recently published large cross-sectional or registry-based studies based on a wide age-range.[28,29] Two studies employing an age-

TABLE 1 Baseline characteristics of the study participants

	n	CSII	n	MDI
Age (years)	98	11.3 ± 2.7	101	11.9 ± 2.8
Male sex—no. (row %)	98	56 (49.6)	101	57 (50.4)
HbA1c (mmol/Mol) (%)	95	56.3 ± 9.8 (7.3 ± 0.9)	100	61.7 ± 14.2 (7.8 ± 1.3)
Diabetes duration (years)	91	3.3 ± 2.9	92	3.6 ± 3.0
Injections per day—no. (row %)	96	–	100	–
3	–	2 (100.0)	–	0
4-5	–	49 (48.9)	–	51 (51.1)
6	–	34 (48.6)	–	36 (51.4)
7-8	–	11 (42.1)	–	13 (57.9)
Indication for transition to CSII[a]				
Improvement of HbA1c	–	24 (42.1	–	33 (57.9)
Dawn/dusk-phenomenon	–	46 (47.4)	–	51 (52.6)
Unpredictable swings in blood glucose concentrations	–	61 (54.0)	–	52 (46.0)
Recurrent hypoglycemia	–	35 (54.7)	–	29 (45.3)
Flexibility in mealtime/irregular daily routine	–	61 (48.4)	–	65 (51.6)
Patient preference	–	52 (45.6)	–	62 (54.4)
Socioeconomic status - no. (row %)	85	–	83	–
High	–	35 (56.5)	–	27 (43.5)
Medium	–	37 (48.7)	–	39 (51.3)
Low	–	13 (43.3)	–	17 (56.7)

Plus-minus values are means ± SD.
[a] More than one response allowed.

TABLE 2 Primary outcomes at baseline and 6 months follow-up

		CSII			MDI			CSII vs MDI		
		n	Mean	SD [a]	n	Mean	SD [a]	Med diff[b] (95% CI)	*P*[c]	*P*[d]
Patient self-report										
Diabetes specific quality of life KINDL-DM (range 0-100)	Children 8-11 y									
	Baseline	36	68.1	14.9	29	61.8	15.2	–	–	–
	Follow-up	35	74.5	12.0	31	64.3	14.9	9.5 (3.6 to 16.7)	0.004	0.001
	Adolescents 12-16 y									
	Baseline	46	70.6	11.9	57	67.8	16.9	–	–	–
	Follow-up	46	74.2	13.0	53	70.9	16.0	2.7 (–3.2 to 9.5)	0.353	0.606
Main caregiver report	Total sample									
Overall diabetes burden (range 1-5)	Baseline	92	3.4	1.0	94	3.2	1.1	–	–	–
	Follow-up	90	2.7	1.1	89	3.0	1.1	0 (–1 to 0)	0.029	0.005

Abbreviations: CI, confidence interval; CSII, continuous subcutaneous insulin infusion; KINDL-DM, diabetes-specific module of the KINDL-R; KINDL-R, modular HRQOL questionnaire for children-revised version; MDI, multiple daily injections.
[a] Standard deviations.
[b] Difference of the median.
[c] Exact two-sided U-test.
[d] Asymptotic test after adjustment for baseline and age and with center as a random factor.

stratified approach[10,30] showed—in contrast with our results—better DHRQOL associated with CSII compared to MDI in adolescents. These studies examined pump users as a group. CSII users may represent a cluster with specific characteristics associated with better HRQOL independent of pump use. To analyze whether the individual patient benefits, studies on patient data before and after transition to the insulin pump compared to a—preferably randomized—control group are indicated.

RCTs on the impact of CSII on DHRQOL in pediatric diabetes are rare and were published 10 years ago or more. Contrary to our findings, two RCTs including a wide age-range,[31,32] as well as an RCT in children <14 years[33] found no difference in DHRQOL between CSII and MDI. An RCT in adolescents aged 14 to 18 years reported better DHRQOL in those who used CSII.[34] The differences to our results might be owing to different age-ranges, the use of different instruments, and also the small sample size of the older RCTs (n = 16-38).

Adolescent-reported diabetes treatment satisfaction improved in both treatment groups, with the difference in favor of CSII not meeting the predefined significance level for secondary outcomes. The improvement in the waiting group may be owing to the optimization of MDI treatment at the beginning of the study, and also may reflect

TABLE 3 Secondary outcomes at baseline and 6 months follow-up

		CSII			MDI			CSII vs MDI		
	Age group	n	Mean	SD[a]	n	Mean	SD[a]	Med diff[b] (95% CI)	P^c	P^d
Patient self-report										
Health-related quality of life KINDL-TS (range 0-100)	Children 8-11 y									
	Baseline	36	73.3	9.9	29	73.4	7.6	–	–	–
	Follow-up	35	72.3	10.3	31	71.7	8.7	0.2 (–4.2 to 5.2)	0.881	0.590
	Adolescents 12-16 y									
	Baseline	46	72.7	8.0	56	69.7	9.3	–	–	–
	Follow-up	46	70.6	12.0	52	71.2	8.2	0 (–3.1 to 4.2)	0.863	0.440
Family conflict DFCS (range 19-57)	Adolescents 12-16 y									
	Baseline	46	25.8	4.1	56	27.3	6.2	–	–	–
	Follow-up	46	25.7	4.9	52	26.6	6.6	0 (–1.9 to 1)	0.893	0.859
Treatment satisfaction DTSQ-TS + CTeen (range 0-54	Adolescents 12–16 y									
	Baseline	46	39.4	9.1	57	36.9	8.7	–	–	–
	Follow-up	46	44.4	7.7	53	40.5	9.7	4 (1 to 6)	0.015	0.042
Main caregiver report										
Total sample										
HRQOL, WHO-5 (range 0–100)	Baseline	92	51.9	24.5	91	50.3	22.2	–	–	–
	Follow-up	87	59.4	19.2	89	53.4	20.3	4 (0 to 12)	0.056	0.103
Parenting stress, PIP TS-F (range 42-210)	Baseline	91	96.9	22.7	92	95.7	23.2			
	Follow-up	87	83.3	21.1	87	91.6	24.7	–8 (–16 to –1)	0.020	0.001
PIP TS-D (range 42-210)	Baseline	88	90.1	25.8	88	89.7	24.1	–	–	–
	Follow-up	82	77.4	22.8	85	85.5	26.7	–7 (–15 to 0)	0.047	0.004
Fear of hypoglycemia, HFS behavior (range 10-50)	Baseline	91	30.0	5.3	93	30.2	6.1	–	–	–
	Follow-up	88	26.0	5.7	89	28.5	6.1	–2 (–4 to 1)	0.006	0.001
HFS worry (range 15-75)	Baseline	92	40.8	10.5	94	41.3	11.0	–	–	–
	Follow-up	90	35.2	10.6	89	40.4	12.2	–5 (–8 to 1)	0.004	<0.001
Family conflict, DFCS mea (range 19–57)	Adolescents 12–16 y									
	Baseline	46	28.3	7.2	57	30.0	6.6	–	–	–
	Follow-up	46	26.8	6.7	50	29.6	7.8	–3 (–5 to 0)	0.046	0.063
Treatment satisfaction, DTSQ- TS + C P (range 0-66)	Total sample									
	Baseline	92	44.0	10.5	93	41.6	10.6	–	–	–
	Follow-up	90	52.9	8.8	88	46.3	9.6	7 (4 to 9)	<0.001	<0.001
HbA1c, mmol/mol (%)	Young children 6–7 y									
	Baseline	9	53.0 (7.0)	8.7 (0.8)	8	55.2 (7.2)	8.7 (0.8)	–	–	–
	Follow-up	10	53.0 (7.0)	5.5 (0.5)	8	54.1 (7.1)	7.7 (0.7)	–0.2 (–0.9 to 0.4)	0.530	0.602
	Children 8–11 y									
	Baseline	40	55.2 (7.2)	8.7 (0.8)	33	58.5 (7.5)	12.0 (1.1)	–	–	–
	Follow-up	40	54.1 (7.1)	10.9 (1.0)	33	59.6 (7.6)	12.0 (1.1)	–0.4 (–0.8 to 0.1)	0.085	0.204
	Adolescents 12–16 y									
	Baseline	46	57.4 (7.4)	12.0 (1.1)	59	61.7 (7.8)	16.4(1.5)	–	–	–
	Follow-up	46	56.3 (7.3)	10.9 (1.0)	55	61.7 (7.8)	14.2 (1.3)	–0.5 (–0.9 to –0.1)	0.025	0.077

Abbreviations: CI, confidence interval; CSII, continuous subcutaneous insulin infusion; DFCS, diabetes family conflict scale; HFS, hypoglycemia fear survey; HRQOL, health-related quality of life; KINDL-DM, diabetes-specific module of the KINDL-R; KINDL-R, modular HRQOL questionnaire for children-revised version; MDI, multiple daily injections; PIP, pediatric inventory for parents; WHO-5, World Health Organization-five.

[a] Standard deviations.

[b] Difference of the median.

[c] Exact two-sided U-test.

[d] Asymptotic test after adjustment for baseline and with center as a random factor.

the fact that patients may experience some benefits, for example, in terms of hope or positive expectations, even before they receive the intended treatment change. This may have reduced the effect between the treatment groups. All in all, neither DHRQOL, nor treatment satisfaction improved as much as we expected in adolescents.

Adolescents with T1DM form a challenging patient group. They are confronted with biological and psychosocial changes which may threaten their metabolic control, mental health, and HRQOL. They have to take progressively more self-responsibility for their treatment, and both taking premature responsibility and the over-involvement of

the parents may impact negatively on the adolescents' metabolic control and HRQOL.[35] Self-management activities and the need to wear insulin administration devices may induce a feeling of being different from peers.[36,37] Also, adolescents may understand for the first time the implications of having a lifelong disease. These issues inherent to the adolescents' developmental stage may result in a lower increase in DHRQOL than with school-aged children. In order to improve adolescents' DHRQOL, additional efforts beyond the transition to CSII are needed.

Childhood diabetes is a profound stressor for all family members. As other studies, we found a decline of caregiver stress,[12,23] and fear about hypoglycemia[38,39] associated with CSII. These results of our trial, representing different aspects of how the care for a child with diabetes may impact life and well-being of the caregivers, clearly favored CSII over MDI. The main caregivers in the CSII group were highly satisfied with their child's diabetes regimen, significantly more so than those whose child stayed on MDI. High satisfaction with CSII is also reported by other studies,[40] among these RCTs.[21,33]

The initial HbA1c values of the study sample as a whole were satisfactory. Changes in HbA1c were small, and there was no difference between the treatment groups. This large-scale RCT showed no significant differences between treatment groups in acute complications. Acute complications are infrequent events, and they may not have occurred during the comparatively short study period.

Despite the thorough randomization, the initial self-reported DHRQOL and some secondary outcomes differed between the treatment groups to a clinically relevant degree. An analysis of covariance was conducted to adjust for baseline differences. Furthermore, as these initial dissimilarities favored the CSII group and nonetheless the patients reported higher improvements compared to the MDI group, these imperfections of randomization did not weaken our findings. In general, the RCT pumpkin confirmed the benefits of CSII described in the pilot study, albeit with smaller effects, and not in all age groups.

The effects in RCTs tend to be smaller than those in observational pre-post trials. Patients may have been not included, either because they themselves were not willing to wait or because they were recommended for immediate transfer to CSII for medical reasons. Precisely these patients may be expected to benefit strongly from CSII, and thus, the RCT may underestimate the benefit of CSII in routine care.[11]

4.1 | Strengths and limitations of the study

We regard our study as the largest RCT to date which assesses the impact of CSII on HRQOL and diabetes burden in the pediatric age group. The age-stratified analysis of child self-reported outcomes, the use of CSII-adapted and previously tested instruments and the participation of 18 certified diabetes centers add further strength to this trial.

However, because of the already common use of CSII in Germany, the recruitment time was much longer than expected. And in the age group <8 years, the number of patients was too small to reliably detect differences.

The waiting-list design of the pumpkin trial ensured that only clinically comparable patients—those with an indication for CSII—were included. However, we found some positive effects in the waiting group, which may have reduced the differences observed between the treatment groups.

The DHRQOL of the adolescents in the pumpkin trial did not improve, while their caregivers reported a decline of their own diabetes burden. This study did not examine whether the diabetes management tasks between child and caregivers changed after the transition to CSII, and how satisfied caregivers and adolescents were with those eventual changes. Future studies are necessary to understand the processes leading to the findings observed.

5 | CONCLUSIONS

CSII has substantial psychosocial benefits, as it increases preadolescent children's diabetes-specific quality of life and decreases caregiver burden. Patient-reported outcome measures help to understand the patients' and parents' experience.

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AUTHOR CONTRIBUTIONS

The agip, C.L.S., B.H., C.B., D.H., and E.L contributed research data. E.M.G., V.W., N.H., and R.V. wrote the manuscript. R.V., E.M.G., and A.Z. planned the analysis. N.H. and R.V. conducted the analysis. E.M.G., V.W., N.H., R.V., and A.Z. reviewed/edited the manuscript. All contributed significantly to discussion.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supplementary text: Description of the fallback procedure and its application in the pumpkin trial

Fallback procedure of the pumpkin trial

To test the three primary endpoints we used a fallback procedure. The general principle of fallback procedures has been described by Bretz et al. (2009 Stat Med doi: 10.1002/sim.3495). In the pumpkin trial, there are three primary endpoints:

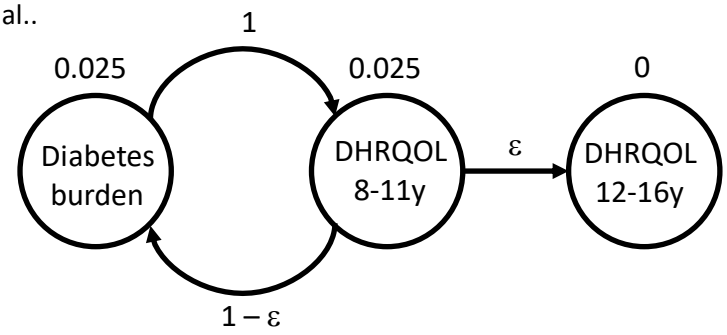
- Diabetes burden in caregivers,
- DHRQOL in the age group 8-11 years and
- DHRQOLin the age group 12-16 years.

The aim of the trial is to demonstrate superiority of CSII over MDI. The pilot study (Müller-Godeffroy et al. 2009 Diabet Med doi: 10.1111/j.1464-5491.2009.02707.x) showed a strong effect in children (ages 8-11 years) but a weak effect in adolescents (ages 12-16 years) for DHRQOL. We therefore decided to utilize the 0.05 test level as follows:

- $\alpha_1 = 0.025$ for diabetes burden
- $\alpha_2 = 0.025$ for DHRQOL age group 8-11
- Fallback for α_1 to α_2 and for α_2 to α_1
- $\alpha_3 = 0.05$ for DHRQOL age group 12-16 *only if both* the thest for diabetes burden and the test for DHRQOL in age group 8-11y are significant

Graphical display of the fallback procedure for the pumpkin trial

This means that the test for diabetes burden in caregivers and DHRQOL in the lower age group are equally important. A graphical display of the procedure is given below. It follows the description of Bretz et al..



Possible p-value combinations in the pumpkin trial

1. Diabetes burden has $p < 0.025$, DHRQOL 8-11y has $p < 0.025$. Both test are significant. DHRQOL 12-16y can be tested at 0.05 because the other two tests are significant.
2. Diabetes burden has $p < 0.025$, DHRQOL 8-11y has $0.025 \leq p < 0.05$. Diabetes burden is significant. DHRQOL is significant because the significance level of 0.025 from the diabetes test is shifted to DHRQOL 8-11y. Since $p < 0.05$ for DHRQOL 8-11y, this test is significant in the second step. DHRQOL 12-16y can be tested at 0.05 because the other two tests are significant.
3. Diabetes burden has $0.025 \leq p < 0.05$, DHRQOL 8-11y has $p < 0.025$. DHRQOL 8-11y is significant. Diabetes burden is significant because the significance level of 0.025 from the

diabetes test is shifted to DHRQOL 8-11y. Since $p < 0.05$ for diabetes burden, this test is significant in the second step. DHRQOL 12-16y can be tested at 0.05 because the other two tests are significant.

4. Diabetes burden has $p \geq 0.025$ and DHRQOL 8-11y has $p \geq 0.025$. No test is significant in this case. This holds true irrespective of the p-value for DHRQOL 12-16y.
5. Diabetes burden has $p < 0.025$ but DHRQOL 8-11y has $p \geq 0.05$. In this case only diabetes burden is significant. DHRQOL 12-16y is not significant irrespective of the p-value.
6. Diabetes burden has $p \geq 0.05$ but DHRQOL 8-11y has $p < 0.205$. In this case only DHRQOL 8-11y is significant. DHRQOL 12-16y is not significant irrespective of the p-value.

The fallback procedure in practice for the pumpkin trial

The p-values in the trial are

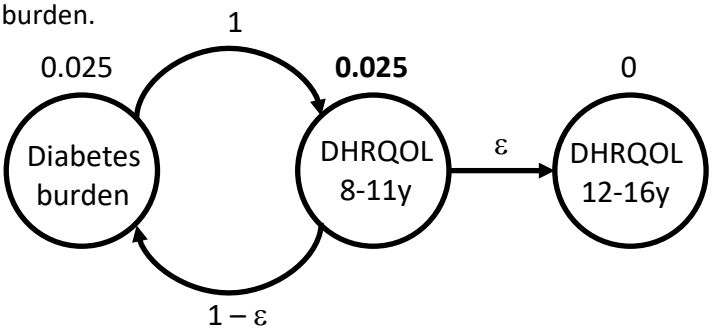
- $p_1 = 0.029$ for diabetes burden
- $p_2 = 0.003$ for DHRQOL age group 8-11y
- $p_3 = 0.353$ for DHRQOL age group 12-16y

Case 3 of the test procedure is realized in this trial so that

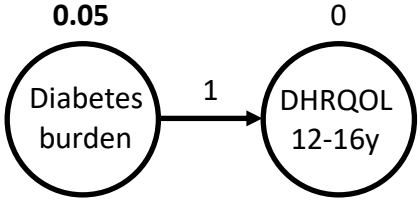
1. DHRQOL age group 8-11 is significant at the 0.025 test-level because $p = 0.003$. The significance level from this test falls back to the test for diabetes burden.
2. Diabetes burden is significant at the 0.05 test level because $p = 0.029$. The test for DHRQOL age group 12-16y may be performed.
3. DHRQOL age group 12-16y is not significant at the 0.05 test level because $p = 0.353$.

Graphical displays of the fallback procedure for the pumpkin trial in practice

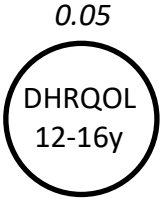
In step 1, the p-value of DHRQOL 8-11y is smaller than 0.025. The significance level of 0.025 falls back to diabetes burden.



In step 2, diabetes burden has a p-value smaller than 0.05. The significance level of 0.05 falls back to DHRQOL 12-16y.



In step 3, DHRQOL 12-16y is tested, but this test does not reveal significance.



Supplementary table S: Use of instruments by responders

Area of interest	Responder / Domain	Child self-report		Parent-report
		8-11 y	12-16 y	
Sociodemografic data				Parent questionnaire at baseline
Health related quality of lifen(HRQOL)	Diabetes-specific HRQOL	KINDL-Diabetes module	KINDL-Diabetes module	< 8 y: KINDL-Diabetes module, parent-proxy version
	Generic HRQOL	KINDL-R short form	KINDL-R short form	WHO 5: < 8 y: KINDL-R parent-proxy version
Diabetes burden	Overall Diabetes [1] burden			Overall diabetes burden scale
Specific areas of diabetes burden	Caregiver stress			Pediatric Inventory for Parents (PIP)
	Fear of hypoglycemia			Hypoglycemia Fear Survey for Parents(HFS-P)
	Familily conflict		Diabetes Family Conflict Scale (DFCS)	≥12 y: Diabetes Family Conflict Scale (DFCS)
Treatment satisfaction	Satisfaction with diabetes treatment		Diabetes Treatment Satisfaction Questionnaire for Teens, status version (DTSQs Teen	Diabetes Treatment Satisfaction Questionnaire for Parents, status version (DTSQs Parent)

DOI: 10.1111/pedi.12919

CORRECTION

ISPAD International Society for Pediatric and Adolescent Diabetes WILEY

Psychosocial benefits of insulin pump therapy in children with diabetes type 1 and their families: The pumpkin multicenter randomized controlled trial

In Mueller-Godeffroy E, Vonthein R, Ludwig-Seibold C, et al. (2018), the authors would like to notify the readers of two incorrect values in Table 3. The variable Fear of hypoglycemia, "HFS behavior", column CSII vs MDI/ Med. Diff (95% CI) should read as "-2 (-4 to -1)" instead of "-2 (-4 to 1)", and for "HFS worry" the correct MDI (CI) is "-5 (-8 to -1)" instead of "-5 (-8 to 1)". Please see below corrected version of the table.

TABLE 3 Secondary outcomes at baseline and 6 months follow-up

		CSII			MDI			CSII vs MDI		
	Age group	n	Mean	SD[a]	n	Mean	SD[a]	Med diff[b] (95% CI)	P^c	P^d
Patient self-report										
Health-related quality of life KINDL-TS (range 0-100)	Children 8-11 y									
	Baseline	36	73.3	9.9	29	73.4	7.6	–	–	–
	Follow-up	35	72.3	10.3	31	71.7	8.7	0.2 (–4.2 to 5.2)	0.881	0.590
	Adolescents 12-16 y									
	Baseline	46	72.7	8.0	56	69.7	9.3	–	–	–
	Follow-up	46	70.6	12.0	52	71.2	8.2	0 (–3.1 to 4.2)	0.863	0.440
Family conflict DFCS (range 19-57)	Adolescents 12-16 y									
	Baseline	46	25.8	4.1	56	27.3	6.2	–	–	–
	Follow-up	46	25.7	4.9	52	26.6	6.6	0 (–1.9 to 1)	0.893	0.859
Treatment satisfaction DTSQ-TS + CTeen (range 0-54	Adolescents 12–16 y									
	Baseline	46	39.4	9.1	57	36.9	8.7	–	–	–
	Follow-up	46	44.4	7.7	53	40.5	9.7	4 (1 to 6)	0.015	0.042
Main caregiver report										
Total sample										
HRQOL, WHO-5 (range 0–100)	Baseline	92	51.9	24.5	91	50.3	22.2	–	–	–
	Follow-up	87	59.4	19.2	89	53.4	20.3	4 (0 to 12)	0.056	0.103
Parenting stress, PIP TS-F (range 42-210)	Baseline	91	96.9	22.7	92	95.7	23.2			
	Follow-up	87	83.3	21.1	87	91.6	24.7	–8 (–16 to –1)	0.020	0.001
PIP TS-D (range 42-210)	Baseline	88	90.1	25.8	88	89.7	24.1	–	–	–
	Follow-up	82	77.4	22.8	85	85.5	26.7	–7 (–15 to 0)	0.047	0.004
Fear of hypoglycemia, HFS behavior (range 10-50)	Baseline	91	30.0	5.3	93	30.2	6.1	–	–	–
	Follow-up	88	26.0	5.7	89	28.5	6.1	–2 (–4 to –1)	0.006	0.001
HFS worry (range 15-75)	Baseline	92	40.8	10.5	94	41.3	11.0	–	–	–
	Follow-up	90	35.2	10.6	89	40.4	12.2	–5 (–8 to –1)	0.004	<0.001
Family conflict, DFCS mea (range 19–57)	Adolescents 12–16 y									
	Baseline	46	28.3	7.2	57	30.0	6.6	–	–	–
	Follow-up	46	26.8	6.7	50	29.6	7.8	–3 (–5 to 0)	0.046	0.063

(Continues)

TABLE 3 (Continued)

		CSII			MDI			CSII vs MDI		
	Age group	n	Mean	SD[a]	n	Mean	SD[a]	Med diff[b] (95% CI)	P^c	P^d
Treatment satisfaction, DTSQ- TS + C P (range 0-66)	Total sample									
	Baseline	92	44.0	10.5	93	41.6	10.6	—	—	—
	Follow-up	90	52.9	8.8	88	46.3	9.6	7 (4 to 9)	<0.001	<0.001
HbA1c, mmol/mol (%)	Young children 6–7 y									
	Baseline	9	53.0 (7.0)	8.7 (0.8)	8	55.2 (7.2)	8.7 (0.8)	—	—	—
	Follow-up	10	53.0 (7.0)	5.5 (0.5)	8	54.1 (7.1)	7.7 (0.7)	–0.2 (–0.9 to 0.4)	0.530	0.602
	Children 8–11 y									
	Baseline	40	55.2 (7.2)	8.7 (0.8)	33	58.5 (7.5)	12.0 (1.1)	—	—	—
	Follow-up	40	54.1 (7.1)	10.9 (1.0)	33	59.6 (7.6)	12.0 (1.1)	–0.4 (–0.8 to 0.1)	0.085	0.204
	Adolescents 12–16 y									
	Baseline	46	57.4 (7.4)	12.0 (1.1)	59	61.7 (7.8)	16.4(1.5)	—	—	—
	Follow-up	46	56.3 (7.3)	10.9 (1.0)	55	61.7 (7.8)	14.2 (1.3)	–0.5 (–0.9 to –0.1)	0.025	0.077

Abbreviations: CI, confidence interval; CSII, continuous subcutaneous insulin infusion; DFCS, diabetes family conflict scale; HFS, hypoglycemia fear survey; HRQOL, health-related quality of life; KINDL-DM, diabetes-specific module of the KINDL-R; KINDL-R, modular HRQOL questionnaire for children-revised version; MDI, multiple daily injections; PIP, pediatric inventory for parents; WHO-5, World Health Organization-five.

[a]Standard deviations.

[b]Difference of the median.

[c]Exact two-sided U-test.

[d]Asymptotic test after adjustment for baseline and with center as a random factor.

[Correction added on 19 Nov 2019, after first online publication: In Table 3, column CSII versus MDI/ Med. Diff (95% CI), the variable for Fear of hypoglycemia, HFS behavior and HFS worry have been corrected in this version.]

The publisher apologizes for this error.

The online version has been corrected.

REFERENCE

Mueller-Godeffroy E, Vonthein R, Ludwig-Seibold C, et al. Psychosocial benefits of insulin pump therapy in children with diabetes type 1 and their families: The pumpkin multicenter randomized controlled trial. *Pediatr Diabetes*. 2018;19:1471-1480. https://doi.org/10.1111/pedi.12777.

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ORIGINAL ARTICLE

ISPAD International Society for Pediatric and Adolescent Diabetes WILEY

The association between socio-economic status and diabetes care and outcome in children with diabetes type 1 in Germany: The DIAS study (diabetes and social disparities)

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Abstract

Objective: To evaluate the association between socioeconomic status (SES) and diabetes outcomes in German children and adolescents.

Methods: A total of 1829 subjects <18 years old with type 1 diabetes mellitus from 13 German diabetes centers were included from June 2013 until June 2014. Data were collected within the multicenter DPV (Diabetes Prospective Follow-up) registry. SES was measured with a composite index. Multivariable regression models were applied to analyze the association of SES and outcomes adjusted for age, sex, diabetes duration, and migration status.

Results: Low SES was significantly associated with worse diabetes outcomes: higher hemoglobin A1C (HbA1c) (64.3 mmol/mol), lower proportion of insulin pump therapy (43.6%), fewer daily self-monitored blood glucose (SMBG) measurements (5.7), more inpatient days per patient-year (5.8) compared to patients with medium/high SES (HbA1c: 61.3 mmol/mol, $P < 0.001$/59.8 mmol/mol, $P < 0.0001$; proportion of pump therapy: 54.5%, $P < 0.01$/ 54.9%, $P < 0.01$; SMBG: 6.0, $P < 0.01$/ 6.1, $P < 0.01$; inpatient days: 4.5, $P < 0.0001$/3.4, $P < 0.0001$). The inclusion of migration status in the models resulted in only minor changes in the outcomes.

Conclusion: Despite free health care, low SES is associated with unfavorable diabetes outcomes in Germany. The poorer diabetes outcomes of children with diabetes have been attributed to their migration status and may be partly explained by low SES. Both factors must become part of targeted diabetes care in children and adolescents with type 1 diabetes.

KEYWORDS

access to care, migration background, outcome, risk factors, socio-economic-status

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1 | INTRODUCTION

There has been an increasing awareness in recent decades that social and ethnic disparities have a significant impact on health outcomes in children and adolescents with type 1 diabetes mellitus (T1D).[1] The World Health Organization (WHO) emphasizes the importance of non-biological factors in their concept of social determinants of health, described as "the circumstances in which people are born, grow up, live, work and age."[2]

The impact of ethnic disparities,[1,3,4] family status,[1,5] and socioeconomic status (SES) have been examined most frequently, separately or in combination. The SES of a family is usually measured by determining education, income, occupation, or a composite of these dimensions.[6] Individualized measures are preferable.[7] Family SES may be linked to diabetes outcomes, such as metabolic control,[8–10] mortality,[11] or major complications,[12] both directly as well as through mediating variables, such as health literacy,[13] adherence,[14] diabetes self-management,[15] or access to advanced diabetes care.[16] Children and adolescents with T1D and their families are required to practice effective self-management and follow a healthy lifestyle to prevent acute and chronic health complications. Because of the challenges of diabetes therapy, access to high-quality diabetes care and patient education is crucial to achieving good health outcomes, and optimal diabetes care must be based upon the resources of the patients and their families.

Most studies on SES in pediatric diabetes research have been carried out in countries where a financial contribution to health care is required. However, even in high-income countries with universally free access to health care, socioeconomic disadvantages may impact the health outcomes of children with T1D.[8–10,16,17]

The German health care system provides free access for pediatric patients and no additional costs. Nevertheless, studies using data from the German diabetes registry have demonstrated that social disparities in pediatric diabetes care still exist for vulnerable patient groups, for example, those with a migration background.[18,19] However, these studies did not include individualized measures of SES. Generally, data on the association between SES and diabetes outcomes in the German pediatric age group are sparse. Therefore, the Workgroup on Insulin Pump Treatment (Arbeitsgruppe Insulinpumpentherapie im Kindes- und Jugendalter, AGIP) within the AGPD (German Workgroup on Pediatric Diabetes) initiated a study on SES and T1D in children and adolescents. The aim of the "DIAS" (Diabetes and Social Disparities) study has been (a) to examine the associations between SES and diabetes outcomes (metabolic control, severe complications, self-monitored blood glucose measurement (SMBG), BMI, insulin regimen, and access to and utilization of diabetes care) and (b) to perform the first step in disentangling SES and migration background as predictors of diabetes care and outcomes.

2 | METHODS

2.1 | Data Collection

Data were collected within the DPV software system (Diabetes-Patienten-Verlaufsdokumentation). In this system, 372 specialized German/Austrian pediatric diabetes centers deliver data on patient characteristics and the process and outcome of diabetes care using a standardized electronic health record.[20] Analysis of the anonymized data within the DPV initiative has been approved by the Ethics Committee of the University of Ulm, Germany. To contribute to the "DIAS"

study, 13 German specialized diabetes centers additionally collected data on the SES of patients aged 17 years and younger during their regular visits to the center from June 2013 to June 2014. Data were documented in a study-specific electronic DPV case report form, allowing SES to be combined with the data routinely included in the DPV, such as age, sex, migration background, diabetes duration, median glycated hemoglobin (HbA1c), events of severe hypoglycemia and diabetic ketoacidosis (DKA), daily number of self-monitored blood glucose measurements (SMBG), body mass index score (BMI-SDS), insulin regimen, hospital admissions, inpatient days, and attendance at a diabetes education program. The centers were instructed that it was essential for the success of the study to include all eligible patients, as patients with low SES often prefer not to participate in questionnaire-driven studies. Questionnaires were translated in both directions by native speakers and were available in English, French, Spanish, Turkish, Arab, and Russian.

2.2 | Patients

Of the 2453 patients who had at least one visit in the participating centers, 2113 (86%) participated in the "DIAS" study, comprising 1989 participants aged <18 years.

2.3 | Measures

Parents reported sociodemographic data using a questionnaire. SES was measured with an adapted version of the Winkler Index, a composite index consisting of education/vocational qualification, occupational status, and net household income.[21] The components education/vocational qualification and income were measured following the German Health Interview and Examination Survey for Children and Adolescents (KiGGS); the component occupational status was measured using routine DPV questions. A summative score was calculated if two of the three indicators were available; missing values were replaced by the mean of the two other variables. Scores (range 3-21 points) were computed for each parent separately, and the higher score was used to define the SES of the patient as low (3-8 points), moderate (9-14 points), or high (15-21 points).[21] Migration background was defined as at least one parent not born in Germany. HbA1c was mathematically standardized to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05% to 6.05% (20-42 mmol/mol) by applying the multiple-of-the-mean transformation method.[22] Hypoglycemic events were defined as severe if the patient required another person's assistance to administer carbohydrates or glucagon and were categorized as either with or without hypoglycemic coma (loss of consciousness or seizures). DKA was defined as a blood pH value <7.3 or a clinical diagnosis of DKA leading to inpatient care.

BMI values were transformed to SD scores (BMI-SDS) based on German reference values.[23] The insulin regimen was categorized as either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII).

Diabetes education was defined as participating in either a structured education program or educational content as documented by the diabetes center in the DPV system.

2.4 | Statistical analysis

Descriptive data were presented as unadjusted means and SDs for continuous variables and as percentages for categorical variables. Child age was grouped as <6 years (n = 187), 6<12 years (n = 680), and 12-18 years (n = 962); diabetes duration was grouped as <2 years (n = 599) and 2 years and more (n = 1230). Regression models were used to analyze the associations of SES and the respective outcome variables adjusted for age, sex, and diabetes duration. Linear models were used for HbA1c, SMBG, and BMI-SDS; logistic models were used for CSII and diabetes education; negative-binomial models were used for hypoglycemia and DKA; and Poisson models were used for hospital admissions and inpatient days. In a second step, we also adjusted for migration background in all models. Outcomes are presented as adjusted means or proportions and 95% confidence intervals (CI) stratified by SES. Rates of severe hypoglycemia, DKA, hospital admissions, and inpatient days were expressed per patient-year with 95% CI. Two-tailed *P*-values of <0.05 were considered statistically significant.

3 | RESULTS

A total of 1829 participants were included in the analysis after 160 were excluded because of two or more missing values in the SES score.

Table 1 displays the patient characteristics. A total of 1268 (69.3%) of the parents were born in Germany. The group with a migration background (30.7%, n = 561) was heterogeneous, with the following groups being most numerous: 21% (n = 115) of Turkish origin; 15% (n = 83) of Polish origin; 9% (n = 48) of African origin; 8% and 5% (n = 43 and 32) of Russian and Kazakhstani origin, respectively; 8% (n = 43) of southern European origin (ie, Italy, Greece, Spain, and Portugal); and 6.3% of former Yugoslavian origin (n = 38). Nearly half of the patients were categorized into the medium SES group, nearly one-third of patients were categorized into the higher SES group, and approximately 20% were categorized into the lower SES group.

Table 2 displays the study outcomes stratified for SES and adjusted for age, sex, diabetes duration, and additional migration background. Table 2 presents outcome differences for low SES compared to medium or high SES. The *P*-values of testing for outcome differences between patients with medium compared to high SES are additionally presented in the text if significant differences were observed.

3.1 | Metabolic control and complications

Adjusted HbA1c values were significantly higher in children and adolescents with low SES than in those with medium or high SES. To a

TABLE 1 Sociodemographic and clinical characteristics of the study sample

Variable	N	Mean (SD) or percent
Age (years)	1829	11.7 (3.9)
Male (%)	1829	51.2
Diabetes duration (years)	1829	4.4 (3.7)
HbA1c:(%/mmol/mol)	1825	7.8 (1.2)/ 61.5 (13.2)
Pump therapy (%)	1829	51.2
BMI-SDS	1825	0.36 (0.9)
SMBG (per day)	1824	6.0 (2.2)
Severe Hypoglycemia (per patient year)	1829	0.15
Severe Hypoglycemia with coma (per patient year)	1829	0.04
DKA (per patient year)	1829	0.02
Hospitalization rate (per patient year)	1829	0.6
Inpatient days (per patient year)	1829	4.7
Attendance at diabetes education (%)	1829	45.9
Living with one parent (%)	1812	16.1
Migration background (%)	1829	30.7
SES (%)	1829	
High	563	30.8
Medium	887	48.5
Low	379	20.7

BMI-SDS: Body Mass Index SD scores based on German reference values; DKA, Diabetes ketoacidosis; SES, socioeconomic status; SMBG: Self-monitoring blood glucose.

lesser degree, adjusted HbA1c values were significantly higher in those with medium SES than in those with high SES ($P < 0.05$ with and without adjustment for migration background). Regarding acute diabetes complications, there were no statistically significant differences between patients with low SES compared to those with either medium or high SES. However, with regard to severe hypoglycemia, there was a (nearly) significant difference between participants with high SES and those with medium SES ($P < 0.05$, and $P = 0.05$ if migration status was included), with a higher rate of hypoglycemic events in patients with high SES. However, regarding severe hypoglycemia with coma, there were no significant differences between the groups.

3.2 | Diabetes self-management and weight status

The adjusted number of daily SMBG measurements was significantly lower in patients with low SES than in those with medium or high SES.

Adjusted BMI-SDS values were significantly higher among children and adolescents with low SES than among those with medium or high SES.

3.3 | Diabetes care

The adjusted proportion of patients using CSII was significantly lower in children and adolescents with low SES than in those with either medium or high SES.

The number of hospital admissions per patient-year was significantly higher in patients with low SES than in those with medium or high SES and in those with medium SES than in those with high SES ($P < 0.05$ with and without adjustment for migration background). The hospital stays lasted longer for patients with lower SES ($P < 0.0001$ with and without adjustment for migration background). Participation in diabetes education did not differ among patients with low, medium or high SES.

4 | DISCUSSION

In this multicenter cross-sectional study, SES was measured with a composite index of educational/vocational status, household income, and parents' occupation on an individualized level. We had a good response rate of 86%, sufficiently representing the SES distribution of the participating centers.

Compared to the population-based German KiGGS survey,[21] our data show a smaller number of participants with low SES (20.7; 27.5) and a higher number of participants with medium SES (48.5, 45.4) and high SES (30.8; 27.1). These differences may be because of methodological differences in the measurement of parental occupation. Upon application of the German Index of Multiple Deprivation (GIMD) from official statistics, we found that the centers taking part in the "DIAS" study are located in regions with GIMD quintiles between 21% and 80%.[24] As both the most affluent and the most deprived regions are not fully represented in our sample, we conclude that there is no systematic bias weakening our findings.

Regarding migration background, we had a proportion of families similar to that in the microcensus data of 2014[25] (31%; 30%), as well as a similar distribution of the ethnic groups.

Our data show a negative gradual association between SES and metabolic control, with children and adolescents from families with high SES having the best and those from families with low SES the poorest HbA1c. The differences in the adjusted HbA1c values were remarkable: 0.2% (2.2 mmol/mol) and 0.4% (4.4 mmol/mol) between low and medium/high SES, respectively. They are comparable to or larger than the mean reduction of the HbA1c levels of 0.2% (2.2 mmol/mol) in Germany and Austria in recent decades (1995-2003 to 2004-2012)[20]). They are also comparable to modifiable factors, such as the impact of the diabetes regimen; for example, meta-analyses of RCTs in the pediatric age group revealed an improvement in HbA1c of 0.2% to 0.3% (2.2-3.3 mmol/mol) for CSII compared to MDI.[26,27]

Our findings are consistent with results from a registry study in England and Wales[28] showing a negative association between low SES and metabolic control with a dose effect. Other studies report a negative linear association between metabolic control and household income,[8] negative correlations with extremes of material deprivation,[10] and associations with parental education and occupation.[16] SES, along with media consumption time and diabetes duration,[29] have been shown to be significant risk factors for higher HbA1c levels in a German study.

TABLE 2 SES, diabetes outcomes, and diabetes care, adjusted for age groups, gender, and diabetes duration (model 1), with additional adjustment for migration status (model 2)

Total sample N = 1829	Model 1 adjusted for age, gender, and diabetes duration			Model 2 additionally adjusted for migration background		
Outcomes	**Mean or %**	**95% CI**	***P***	**Mean or %**	**95% CI**	***P***
HbA1c, %/mmol[a]						
High SES	7.6/ 59.8	7.5-7.7/ 58.8-60.9	<0.0001	7.6/ 59.8	7.5-7.7/ 58.7-60.8	<0.0001
Medium SES	7.8/ 61.3	7.7-7.8/ 60.5-62.2	<0.001	7.8/ 61.3	7.7-7.8/ 60.5-62.2	<0.001
Low SES	8.0/ 64.3	7.9-8.2/ 63.0-65.6		8.0/ 64.4	7.9-8.2/ 63.1-65.8	
Proportion pump therapy[b]						
High SES	54.9	50.4-59.3	<0.01	54.5	49.9-59.0	<0.01
Medium SES	54.5	50.9-58.1	<0.01	54.4	50.8-58.0	<0.01
Low SES	43.6	38.2-49.2		44.3	38.7-50.1	
SMBG[a]						
High SES	6.1	6.0-6.3	<0.01	6.1	5.9-6.2	<0.05
Medium SES	6.0	5.9-6.2	<0.01	6.0	5.9-6.2	<0.05
Low SES	5.7	5.5-5.9		5.8	5.6-6.0	
BMI-SDS[a]						
High SES	0.30	0.23-0.37	<0.0001	0.31	0.23-0.38	<0.001
Medium SES	0.33	0.27-0.38	<0.0001	0.33	0.27-0.38	<0.001
Low SES	0.54	0.46-0.63		0.53	0.44-0.62	
Severe hypoglycemia per patient-year[c]						
High SES	0.19	0.14-0.26	0.13	0.19	0.14-0.25	0.24
Medium SES	0.13	0.10-0.16	0.86	0.13	0.10–0.16	0.72
Low SES	0.13	0.09-0.19		0.14	0.09-0.21	
Severe hypoglycemia with coma per patient-year[c]						
High SES	0.03	0.02-0.06	0.52	0.03	0.02–0.06	0.37
Medium SES	0.03	0.02-0.05	0.27	0.03	0.02-0.05	0.19
Low SES	0.04	0.02-0.08		0.05	0.03-0.09	
DKA per patient-year[c]						
High SES	0.01	0.00-0.02	0.12	0.01	0.00–0.02	0.08
Medium SES	0.02	0.01-0.03	0.92	0.02	0.01–0.03	0.86
Low SES	0.02	0.01-0.04		0.02	0.01–0.04	
Hospital admission per patient-year[d]						
High SES	0.5	0.5-0.6	<0.0001	0.5	0.4-0.6	<0.0001
Medium SES	0.6	0.5-0.7	<0.0001	0.6	0.5–0.6	<0.0001
Low SES	0.8	0.7-0.9		0.8	0.7–0.9	
Inpatient days per patient-year[d]						
High SES	3.4	3. 3-3.6	<0.0001	3.4	3.2-3.6	<0.0001
Medium SES	4.5	4.3-4.6	<0.0001	4.5	4.3–4.6	<0.0001
Low SES	5.8	5.5-6.0		5.9	5.7-6.2	
Attendance at diabetes education[b]						
High SES	44.6	40.5-48.9	0.57	44.0	39.8-48.3	0.29
Medium SES	46.2	42.9-49.6	0.91	46.1	42.8-49.5	0.60
Low SES	46.6	41.5-51.8		47.8	42.5-53.2	

[a]Linear regression model.
[b]Logistic regression model.
[c]Negative binomial regression model.
[d]Poisson regression model.

However, our study is the first to examine the association between SES and metabolic control as well as complications, lifestyle and diabetes care by measuring all three components of SES on an individualized level. Remarkably, hypoglycemia and DKA were not related to low SES. In Germany, the rate of severe hypoglycemia and hypoglycemic coma has decreased significantly in the past decade.[30] Severe hypoglycemia is no longer related to HbA1c levels.[20,31] Our findings may reflect improvements in diabetes education, enhancing the ability of patients, and parents to recognize high-risk situations, although an equally satisfying metabolic control across SES groups has not yet been achieved. It is interesting that the incidence of severe hypoglycemia was slightly higher in the group with high SES. It is possible that diabetes care should focus on these patients as a risk group that accepts a higher risk of hypoglycemia to achieve good HbA1c values. This finding could also reflect a communication problem between patients and the diabetes team. Patients with high SES may be more accurate and self-confident discussing hypoglycemic events with health professionals.

Low SES was associated with fewer SMBG compared to either medium or high SES. SMBG is an essential tool for the improvement of glycemic control and adherence to treatment.[32,33] More frequent SMBG may also be a general sign of good health behaviors.[32] Less frequent SMBG thus may indicate difficulties in taking care of oneself in families with lower SES and display a need for targeted interventions.

A higher BMI-SDS was associated with low SES, reflecting a less favorable lifestyle in those families.[34] The BMI-SDS of children and adolescents with T1D is higher compared to that of healthy children, with young age and female sex in adolescence being identified as special risk factors.[35] Our findings indicate that low SES is an additional risk factor for overweight, to be addressed early in diabetes care.

The frequency of insulin pump use was lower in patients with low SES compared to those with medium or high SES, indicating that even in a country with free access to health care, high-risk patient groups may experience problems with access to advanced care. Our data indicate that SES contributes significantly to the treatment options for the families. People with higher SES may be more actively involved in therapy decisions and may take greater initiative in asking for innovative and technically advanced diabetes therapies.[36] However, limited access to care should be viewed as both a patient and a system phenomenon,[37] with the relationship between the families and the diabetes team being a key factor. Physicians may presume that families with low SES are not capable of meeting the challenges of the more demanding pump therapy. In addition, teams may not be able to offer the individualized education required.

We found that patients with lower SES were admitted more frequently to the hospital and tended to stay longer, even though the rate of acute complications (severe hypoglycemia, DKA) was not higher than in patients with medium or higher SES. Although there was no difference among participants with different levels of SES in diabetes education attendance, more hospital admissions and longer hospital stays among patients with lower SES may reflect the fact that these patients receive individual coaching by the diabetes teams in addition to regular diabetes education.[38] Furthermore, they may be admitted earlier to prevent acute complications. A need for additional individual coaching may indicate that the structured education programs available do not enable patients and families with social disadvantages to practice diabetes management sufficiently.

Adjusting for migration background did not weaken the association of SES and metabolic control. In fact, the poorer diabetes outcomes of children with diabetes, which have been attributed to their migration status[18,19] can be partly explained by low SES. This finding is consistent with the fact that families with migration backgrounds have a higher poverty risk and, on average, lower vocational qualifications, as in Germany.[39]

Remarkably, only with regard to SMBG and BMI-SDS was the significance level higher if the migration background was not included in the model, which indicates that the inclusion of migration status in the model lowers the impact of SES. This finding accounts for the slightly higher rate of severe hypoglycemia, which was no longer significant if the migration background was included in the model. However, neither DKA nor hypoglycemia with coma or access to care were associated with migration background. Our data indicate that both low SES and migration background may be separate risk factors, with SES being a stronger determinant in Germany. Presumably, low SES may be considered a different "culture" by diabetes teams. Families with low SES and their children often experience a broad spectrum of social (shift work, financial burden, poor housing, and neighborhood quality) and psychological (parental anxiety, stressful life events) challenges.[40] Children and adolescents with low SES have chronically higher levels of cortisol, suggesting that chronic stress may mediate the association of low SES and adverse health outcomes in children and adolescents.[41] This mechanism may pose a higher risk to youth with T1D in managing their diabetes, as cortisol is one of the counterregulatory hormones of insulin.

The large sample size, which included German patients and those with a migration background; the use of a composite index to measure SES; and the report of an association between SES and a broad range of diabetes outcomes across low, medium, and high SES are strengths of the "DIAS" study.

However, despite the large sample size, this was a convenience sample, which may limit the generalization of the findings to all children and adolescents with T1D in Germany. Regrettably, the sample was too small to differentiate among the different ethnic groups to better understand the effects of different ethnicities. For practical reasons, we measured parents' education and household income according to the KiGGS survey, but we measured parents' occupational status with a different categorization used in the DPV program, thus, limiting comparisons with the population-based survey results.

Our findings indicate that SES is an important confounder, in addition to migration background, regarding diabetes outcomes and diabetes care. The predictive value of the following determinants must be addressed in controlled studies: SES, specific ethical groups, and others, such as family status and health literacy. SES needs to be included in standardized diabetes documentation systems to examine

social disparities in outcomes research and quality assessment. Qualitative studies are indicated to facilitate a deeper understanding of the processes leading to the findings observed.

5 | CONCLUSION

Low SES is an important risk factor for diabetes outcomes in children with T1D, forcing us to incorporate this aspect into our diabetes care. The impact of SES and other social and ethnic disparities must be further examined to identify patients at risk and to develop targeted interventions that meet the specific needs of vulnerable patient groups.

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CONFLICT OF INTEREST

K.M. has received travel expenses and speaking fees, from Novartis and FomF (Forum für medizinische Fortbildung, Forum for Medical Education) (less than $10 000 each), B.H. has received travel expenses/attendance fee from IPSEN (less than 10.000€); and all other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

K.M., E.M.-G., and R.W.H conceived and developed the study design, K.M. performed the study. R.W.H. and E.B. conducted statistical analysis. E. M-G. and K.M. wrote and edited the manuscript. E.L., B.H., M.B., L.F., M.F., D.H., K.B., E.P., A.S., K.O.S. H.S., and J.W. contributed to the discussion and reviewed/edited the manuscript. K.M. and E. M.-G. are responsible for the integrity of the data and the work as a whole.

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Thieme

Experiences in Sensor-Augmented Pump Therapy in Families with two Children with Type 1 diabetes: A Qualitative Study

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ABSTRACT

Background Caring for a child with type 1 diabetes is a tremendous challenge for a family. The aim of the study was to explore the experiences of transition to sensor-augmented pump therapy (SAP) in families with 2 affected children and the internal and external conditions which potentially impede or facilitate the adjustment process.

Methods 5 families (9 parents, 8 children and adolescents) who used the SAP technology for 6 months were interviewed to describe their experiences. The interviews were analysed using thematic content analysis.

Results Qualitative analysis of the transcribed interviews revealed that the adaptation process to SAP consisted of several phases and differed among families. There were benefits as well as hassles of using SAP with regard to managing the diabetes, and psychosocial issues: school and peer relations, as well as family relations. While parents clearly regarded the improved metabolic control and hypoglycaemic safety as the most important benefits of SAP, the hassles reported as most important covered a wide range, from technical problems of the system to family conflicts. On the whole, families rated the experience of using SAP as a positive one, with most recommending SAP to other families as long as they were willing to come to terms with the technology and commit to the work and time involved.

Conclusion Sensor-augmented pump therapy can be extremely beneficial and a resource for families who care for more than one child with diabetes. During the adaptation process there is a great need of education and frequent follow-up e. g., by telemedical support.

Introduction

Continuous glucose monitoring (CGM) can provide near real-time information on blood glucose levels and trends. Combined with continuous subcutaneous insulin infusion (CSII), the sensor-augmented pump therapy (SAP) is a further step towards an automatic artificial pancreas, especially if the system provides an automatic suspension of insulin delivery in hypoglycaemic conditions [1–3].

In spite of being the most advanced technology, CGM and SAP are still rarely used in routine care of children and adolescents with type 1 diabetes mellitus (Type 1 DM) [4, 5].

SAP can improve metabolic control in the paediatric age-group. However, the benefits depend on a longer and consistent usage of CGM, which is difficult to achieve in children and adolescents [6–9]. In order to understand possible barriers to CGM use in children and adolescents, it is important to examine how young patients and their carers perceive the everyday benefits and hassles associated with CGM/SAP and the process of adaptation to the new technology.

Qualitative studies which allow an insight into patients' experience with CGM/SAP are rare. A recently published online survey reported positive user experience, with improved glycaemic control, easier diabetes management, improved sleep, more independence of the child, and a reduction in stress and anxiety. The main barriers were technical problems, "alarm fatigue", and barriers regarding the health service system [10]. Using in-depth interviews with adolescents and parents, Rashotte et al. [11] identified 4 main bar-

riers to finding a harmonious life with SAP: struggling with hopes and expectations; being ready for the challenges that SAP brings to everyday life; suffering the burdens of CGM, and creating supporting partnerships.

Parents commonly experience stress and burden even when caring for one child with Type 1 DM [12, 13]. We know from clinical experience that caring for more than one child with Type 1 DM is even more of a challenge for a family. We used the opportunity of our study to give families caring for 2 children with diabetes access to SAP, assuming that this particularly vulnerable group would benefit from the advanced technology.

The objective of the study was to investigate the views and experiences of families who care for children with Type 1 DM while adapting to SAP and to reveal conditions which can impede or facilitate the adjustment process.

Methods

Participants and intervention

Families eligible for the study were those with 2 or more children (< 21 years) with Type 1 DM in the state of Schleswig-Holstein, Germany. The ethics committee of the University of Luebeck approved the study. The parents and youths of 13 years and above gave written consent; the children above 8 years also consented to their participation.

Inclusion criteria were: > 6 months experience of CSII, and willingness of the family to change to SAP for 6 months with telemedical support by a paediatric diabetologist. Exclusion criteria were: diabetes duration < 6 months, multiple daily injections, current SAP user, insufficient German literacy, and known psychiatric disease. All paediatric diabetes teams in the state Schleswig-Holstein identified families with 2 or more children with Type 1 DM in August and September 2013 (N = 21). 5 families and their 10 children aged between 4 and 20 years fulfilled all inclusion criteria and agreed to participate. From these families, 9 parents, 4 adolescents and 4 children were interviewed (see ▶ **Table 1**).

▶ **Table 1** Sample characteristics of the interviewees (N = 17).

Children and adolescents (n = 8)	
Children: n = 4	8 y, 2 × 9y, 10 y
Youths: n = 4	13y, 16y, 19y, 20 y
Gender (%)	
Females (n = 3)	37,5 %
Males (n = 5)	62,5 %
Duration of diabetes (years), mean (SD)	5.7 (3.0)
Mean HbA1c at baseline, mean (SD), range	7.8 (0.7), 6.6 - 8.9
Parents (n = 9)	
Fathers	4
Mothers	5
Highest qualification	5 General Certificate of Secondary Education (GCSE) 2 University of applied sciences entrance qualification 2 General university entrance qualification

A SAP with low glucose suspend was initiated using a MiniMed-VeoTM pump and Minimed Medtronic Enlite®Sensors, with enhanced versions of the latter being provided after 3 months of the study period. After the initial set-up, families received structured internet-based and telephone support every 2 weeks. The evaluation of medical outcomes and telemedical counselling will be reported elsewhere (von Sengbusch et al., in preparation).

Interviews

The interviews addressed the adaptation process to SAP, experienced benefits and hassles and the evaluation of the telemedical support (reported elsewhere). The semi-structured interview guidelines for parents, adolescents and children differed in their complexity but covered the same key topics.

The feasibility of the interview questions were pre-tested by an adolescent patient and his mother. Parents and children were interviewed separately in May 2014 by 2 research psychologists EMG and FB not involved in the care of the families. All interviews lasted between 30 and 90 min and were digitally recorded and completely transcribed. The data were anonymised as part of the transcription process.

Data analysis

The interviews were evaluated using the qualitative content analysis method [14] and the MAXQDA 10 software program. A baseline category system was derived from the interview guide and continuously checked during the coding process. Each response-sequence was coded and assigned to one or more categories. Quality control and greater analysis objectivity, was achieved by the independent coding of the interviews by FB and EMG, followed by discussion, modification and revision until a coding consensus was reached.

Results

4 main themes were identified from the responses regarding daily life with SAP.

(1) Adaptation process to SAP
(2) Diabetes management
(3) Psychosocial outcomes
(4) Personal summary and future sensor usage.

(1) Adaptation process to SAP

Initial situation: caring for 2 children with Type 1 DM

Parents described everyday life with 2 children with diabetes as very exhausting. One family mentioned that the experiences with the first child made them more capable of coping with the stresses of diabetes in the second child but on the whole families described the double experience as piling burden upon burden. Above all, the permanent need for vigilance without let-up was described as particularly challenging. Parent: "Sometimes if one child is away for a little while and you say to yourself: 'At least I won't need to think of it for an hour' – but the other one is still there. So you never get any peace, no break."

First weeks of the adaptation process

To understand and handle the SAP technology was a real challenge for the families and required a strong commitment to the time and work necessary.

Parent: "It's quite different at the beginning, it's a massive multi-stress burden to use the sensor."

In the first 2 weeks after starting SAP, all parents described themselves as being "stressed out", "uncertain" or "weighed down". Their reports as to the main challenge varied: some felt that the uploading data and the installation of the sensor software in particular was too much for them; some reported difficulties with calibration and the reorganisation of their daily tasks as the main problems. One family, which had started their holiday immediately after transition to SAP, nearly stopped SAP because they felt overwhelmed by the abundance of data.

Developing a routine

Finally, all families developed a routine in using SAP: "It really just became part of our everyday life."

The time needed to adapt to SAP differed from family to family: some parents reported that their children got used to the new technology very rapidly: "in no time he had made friends with the sensor". For other families, according to the parents, it had been "a long and winding road".

The adaptation was usually not a linear process, but proceeded in phases. One family described it like this: there were phases when the child "felt good about the sensor and others where they were just stressed by it."

Nearly all families reported that there were times when they felt really frustrated with the sensor and 2 families temporarily seriously considered stopping using it.

Some parents reported that their main difficulty was to develop a regular structure and implement rules for conducting SAP, e. g., always calibrating after lunch. Others reported that their main difficulty was to adapt the rules they had learned to their own needs and make them more flexible: "To begin with, we painstakingly calibrated 3 times but as the values were always quite positive and the sensor measured very well we cut down calibrating to just twice and got along well."

Parents reported that the initial motivation of their children and the willingness to deal with SAP helped them to adapt to the new technology. One family focused on the openness of the child to new experiences as a more general personality factor which facilitated adaptation to SAP. Adolescents and children were generally interested in the functioning of new technological devices and liked to try them out, which helped with learning how to use the sensor. For most of them, the sensor was felt to be in line with other 'in' technological devices, like iPhones.

Parent about her daughter: "She was actually a bit proud she went around with it and showed everyone where she had it (the sensor)".

Some parents found the new technology easy to understand; "Anyone who can operate a smart phone can work with a pump plus sensor." However, others reported that they found it difficult. According to the statements of the families, a certain affinity to technology makes handling SAP easier, being "something of a tech-savvy".

(2) Diabetes management during SAP

Benefits due to SAP

Families highly valued the reduction in the number of blood sugar measurements and the overall reduction of equipment needed during the day.

Parent: "The best feature is that you don't have to prick your finger all the time."

All parents reported a reduction of fear of hypoglycemia and an improved feeling of security and trust due to the low-glucose suspend. There were several comments from parents like: "peace of mind", "inner calmness" or "significant relief".

The adolescents also valued this feeling of security: "The good thing is that it goes off when you are too low. This is the most practical aspect, especially at night."

All families thought that the large amount of available data due to CGM is a great advantage and improves the knowledge about the diabetes. The adolescents reported an increased understanding of their metabolism and their body's reactions in certain situations, e. g., during sports. Parents also reported that they felt more confident and more competent in the diabetes management. Parent: "So when I take a measurement I can see where I can change something. If I want to change the basal rate a bit, I feel a bit more confident about it."

The adolescents especially also appreciated the sophisticated technical features: "The trend arrows were really cool. You knew straight away "Something's happening"."

One family reported that the transition to the new form of therapy had generally increased the willingness to confront the illness positively.

Parent: "To start with we were a bit tired, diabetes fatigue had set in (…) But the sensor woke us up a little, we now look more carefully and don't just correct. We do more about it actively."

Hassles due to SAP

Some parents found it challenging to find a good time for calibration and felt the performance to be time-consuming and difficult to integrate in the family's daily routine.

Families reported that setting the sensor was painful and wearing it was uncomfortable as well as irritating the skin due to the tape holding the sensor. It was sometimes difficult to find suitable sensor sites, especially for the younger children.

All families were sometimes dissatisfied with the alarm function of the sensor: either the alarm settings were felt to be inadequate or the alarm could not be turned off, which was seen as very annoying. Also the adolescents mentioned the nightly disturbance of the alarms. This was one of the reasons for discontinuing SAP for one participant. For other parents, the alarms were too quiet at night so their children or they themselves did not wake up.

For the younger children the alarms were the most frequently mentioned disadvantage of the SAP. Child "The greatest disadvantage of the sensor is the beeping. (They) really have to work on that one."

The families also mentioned other technical problems, such as transmitting information between sensor and pump, installing a suitable computer program and difficulties with the regular data upload. According to one family it took too long from the insulin suspend until the restart of insulin delivery, so that the child was in the hyperglycaemic range.

Nocturnal measures

The burden of nocturnal blood glucose measuring was diminished only for roughly half of the families. Others even needed to get up

more frequently, either to switch off unnecessary alarms, or because the improved information about their children's metabolic processes led to increased vigilance. Some found this increased demand a burden, others as an opportunity to optimise their children's diabetes management. Parent: "You know that it is going to be useful to you in the long run. That certainly outweighs those 10 nights when you were woken up."

(3) Psychosocial outcomes during SAP

Changes in the child's personal development

Many parents reported that children and adolescents felt more secure using SAP, e. g., before school tests, at work or while driving, that their activity radius in everyday life advanced significantly and that they were more adventurous. Parent: "He has come on pretty well with the sensor. Before, he was always anxious, tense. He is clearly more relaxed"

However one toddler developed fears associated with the alarms that caused a temporary regression in his personal development. For a while, he wanted to sleep with his parents again and dared not go to the toilet alone at night.

School and peer relations

There were mixed reports about the SAP regarding school and social activities:

Measuring blood sugar in school or during activities with friends, which was felt to be embarrassing by some children, and was consequently regularly omitted by them, was no longer a problem. Looking at the sensor readings was easier, more discrete and less time-consuming.

Younger children also reported that games are interrupted less often through SAP.

On the other hand, some felt impaired by the alarms, which could not be turned off, during school or when they were with friends, and they were embarrassed when they attracted attention.

Parent: "He just found it annoying if it started beeping during lessons and he was embarrassed to cause a disturbance in the lesson." 2 families noted that their older children felt at least temporarily disturbed by the sensor because it negatively affected their appearance.

Parent: "There is this additional part that's stuck to your body which is a little bit thicker and bigger than the actual catheter. Of course you can see this under tight clothes."

2 adolescent felt disturbed at being dependent on a technical device. For one of them this was a serious enough reason to stop using the sensor.

Adolescent: "I didn't feel free any more. I had the feeling I needed some sort of device and I was totally dependent on it so then I felt I'd rather measure my blood sugar myself."

Changes in family relations: "the transparent child"

As a result of SAP the parents reported getting much more information about the daily routine and the adherence of their children to diabetes therapy than before. They spoke of having "transparent" children. 2 families with younger schoolchildren reported that this initially led to increased conflict and stress within the family, because of therapy flaws, and not sticking to diabetes management rules, which had not been obvious before, were revealed through the continuous data documentation.

Parent: "Because you could really see everything, well, you could perhaps see when chocolate went into the mouth. You saw when they did not bolus, that the infusion set had not been changed, that in school the blood sugar level had not been used for correction). Well, you could see – and this is the word that I am choosing to call it - every transgression."

The parents had the problem of how to address the errors in therapy.

Parent: "And how do I deal with it without permanently causing aggravations at home because of diabetes… On the other hand, the lapses were so serious that I could not let them go. That was really difficult."

At the same time, the documentation of the data also offered provided the basis for getting the children on board and discussing the problems objectively.

Child: "Perhaps if I secretly have some sweets in the evening my mum would see it because I bolussed for it. And then my mum catches me and so I don't do it any more."

The parents of the adolescents were also aware of the reduced privacy associated with sensor usage:

Parent: "The data would also show if they had been with a girl or something (..) But no, I don't like to pry."

The issue of transparency did not seem to be a problem for the adolescents themselves, either because their parents were no longer actively involved in diabetes management, or they trusted their parents to respect their privacy.

(4) Personal summary and future sensor usage

The families rated the improved HbA1c values as the biggest benefit of SAP, followed by increased security and more relaxed therapy management for their children. Also better quality of life and increased knowledge about diabetes were reported.

Asked about the greatest burden of SAP, every family mentioned different challenges: "Transparency" of the children leading to family conflicts, adjusting the family rhythm to the times of calibration, fears of the child regarding the sensor, alarms, and pain with sensor insertion.

In 4 families the benefits of SAP clearly outweighed the disadvantages. For 8 children and adolescents the parents wanted to continue using SAP after the study period. One family would, in retrospect, not opt again for SAP for their younger child, and one adolescent discontinued SAP after 2 months because of the nightly disturbance of the alarms.

The parents emphasised the importance of discussing the expectations of SAP in order to get a realistic view of what could be expected from the new technology

Parent: "I would really tell the users: What do you expect from it? (..) it won't be this huge relief. You will have some other big advantages from it, but the sensor does not make life easier straight away."

All parents wished to get SAP paid for by the health insurance.

Discussion and Conclusions

The adaptation to SAP provided some initial challenges, but at the end of the study period, all families had developed a routine for dealing with SAP. The first 2 weeks after initiation seem to repre-

sent a critical window in which the family needs to be closely monitored. Through the whole process, an intensive support and education for the families e. g., by telemedical support, regular contacts via e-mail or phone should be guaranteed. Successful adaptation to SAP meant that each family had to find its own way to include SAP in its daily routine. Healthcare professionals need to consider that adaptation to SAP is not a linear process and that there will be times when the families feel frustrated with the imposition of having to use the sensor.

While the children and adolescents generally were interested in the functioning of the new technical devices, not all parents had a positive attitude to the new technology. A certain "technical affinity" is probably a prerequisite for the adequate handling of SAP.

Similar to the findings of other studies, the improved metabolic control, lower number of blood glucose measurements, improved feelings of security caused by the low glucose suspend, and an increased knowledge about metabolic processes due to the continuous data acquisition were mentioned as main benefits of SAP [10, 11, 15–17]. The enhanced knowledge, along with the technical possibilities of the SAP, especially the trend arrows, resulted in a perceived increased competence that made the parents feel more confident regarding the diabetes management [15, 18]. We feel that this empowerment is an important possible aspect of longer consistent usage of CGM, and may have long-term effects on metabolic control. In accordance with other studies [4, 10, 11, 19–21] the main negative aspects were financial barriers, the large amount of time for calibration, the difficulty of integrating it into the daily routine, the frequency and length of the alarms, suboptimal accuracy, and pain and skin problems at insertion. The last may be a challenge specifically in the younger age-group [22].

While all parents valued the improved metabolic control of their children and most also felt that their children's quality of life was improved, they did not report a reduction of their own burden, particularly with respect to the time needed for nocturnal measurements. Previous studies have already pointed out how important it is to educate the parents about possible unrealistic expectations, and that SAP may not reduce the time and effort of diabetes management [19, 23]. Our results underline the important role of a comprehensive education at the beginning for a successful use of SuP. In Germany, a structured training program called SPECTRUM was developed for this reason and translations into other languages are in progress [24]. However, the parents were prepared to commit themselves to SAP to improve their children's metabolic control even if they considered the technology demanding. In general, the families in our studies reported similar benefits and hassles compared to those who care for one child with Type 1 DM, except that they have to bear an even greater burden. So, the results of our study may be valid for all families who wish to use SAP.

Although the parents in our study reported similar burdens of SAP, their identification of the most irksome burden varied widely, ranging from technical problems to aggravated family conflicts. Healthcare professionals should be aware that the main challenges may vary and tailor their support to the families' individual needs.

One important result of our study is that due to continuous data deliverance the child's diabetes management failures and activities in general become visible for the parents. The transparency of the child may put a strain on the parent-child relationship and may lead to family conflicts. This problem was most serious in families with school-aged children who shared responsibilities for the diabetes management. The loss of privacy also might be a problem for adolescents [18], but in our study parents were well aware of the problem and handled it in a sensitive way. The problem of the transparent patient should be recognized in SAP education programs and parents should learn how to meet this challenge.

Families rated the experience of using SAP on the whole as positive, with the benefits outweighing the hassles. This is in accordance with questionnaire-driven studies which generally report high parental satisfaction with CGM/SAP even if quality of life (measured with standardised questionnaires) is not improved [25, 26].

The initial motivation of all family members and their willingness to commit to the work and time involved is crucial for consistent usage of CGM and an important criterion for patient selection [1, 27].

There were some limitations to our study. Since our participants were families with 2 children with type 1 DM, we only investigated quite a small sample with a wide age-range. However this limitation gave us the opportunity to examine all eligible families of a German state (Schleswig-Holstein) and thus avoiding the risk of a bias by convenience sampling. A further limitation was the replacement of the sensor by an enhanced Enlite sensor in the middle of the study period. Yet this just emphasised the importance of improving the devices to make the use of them more comfortable. The next Medtronic Minimed 640G pump launched after the end of the study already has overcome some technical problems, i. e., it provides improved alarm settings and insulin dosing software functions. Based on individual sensor glucose values, its SmartGuard®-function can predict approaching low glucose levels and automatically stop insulin delivery.

Another limitation is the fact that we only investigated the use of one device. However, this was the only available system with automatic insulin suspension, and the study team chose to provide the participants with the most technologically advanced equipment.

From the findings of our study we conclude with some suggestions for healthcare professionals who want to guide families through the process of transition to SAP (▶ **Table 2**).

Our study showed that families who care for more than one child with type 1 diabetes can maintain SAP and may benefit in terms of glycaemic control and psycho-social issues. Consistent use of SAP can empower carers and increase their perceived competence.

▶ **Table 2** Take-home messages for healthcare professionals supporting families using SAP.

– Initial motivation of all family members is crucial for continued use of SAP.
– Expectations of SAP must be discussed and possible burdens must be mentioned prior to the transition to the new technology.
– An intensive support of the families should be guaranteed, especially in the first 2 weeks after the change to SAP; both families and HP should remain available in this period.
– Families should be warned that, due to SAP therapy, errors may be more visible ("transparent child") which can trigger family conflicts. HP should ensure a sensitive and appreciative handling of the privacy of the families and provide a motivating counselling style.
– Particular attention should be paid to families with very young or anxious children, and children with skin problems.

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Publikationen im Zusammenhang mit der Promotion

1. **Müller-Godeffroy E**, Treichel S, Wagner VM; German Working Group for Paediatric Pump Therapy: Investigation of quality of life and family burden issues during insulin pump therapy in children with Type 1 diabetes mellitus - a large-scale multicentre pilot study. Diabet Med. 26(5): 493- 501; 2009 doi: 10.1111/j.1464-5491.2009.02707.x

2. **Mueller-Godeffroy E**, Vonthein R, Ludwig-Seibold C, Heidtmann B, Boettcher C, Kramer M, Hessler N, Hilgard D, Lilienthal E, Ziegler A, Wagner VM, German Working Group for Pediatric Pump Therapy (agip): Psychosocial benefits of insulin pump therapy in children with diabetes type 1 and their families: The pumpkin multicenter randomized controlled trial. Pediatr Diabetes 19(8): 1471- 1480; 2018
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3. Mönkemöller K*, **Müller-Godeffroy E*,** Lilienthal E, Heidtmann B, Becker M, Feldhahn L, Freff M, Hilgard D, Krone B, Papsch M, Schumacher A, Schwab KO, Schweiger H, Wolf J, Bollow E, Holl RW: The association between socio-economic status and diabetes care and outcome in children with diabetes type 1 in Germany: The DIAS study (diabetes and social disparities). Pediatr Diabetes 20(5): 637- 644; 2019
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Publikation von weiteren Ergebnissen der DIAS- Studie (Studie 3) nach Antragstellung zur kumulativen Promotion

5. **Müller-Godeffroy E,** Mönkemöller K, Lilienthal E, Heidtmann B, Becker M, Feldhahn L; Freff M, Hilgard D, Krone B, Papsch M, Schumache A, Schwab KO, Schweiger H, Wolf J, Bollow E, Holl R: Zusammenhang von Bildungsstatus und Diabetesoutcomes: Ergebnisse der DIAS-Studie bei Kindern und Jugendlichen mit Typ-1-Diabetes in Deutschland. Diabetologie und Stoffwechsel 16(03): 211- 218; 2021
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Kongressbeiträge im Zusammenhang mit der Promotion

DDG 2008	Müller-Godeffroy E, Treichel S, Wagner VM: Untersuchung psychosozialer Parameter bei Kindern und Jugendlichen mit Typ 1 Diabetes und Insulinpumpentherapie (Poster)
MAPE 2013	Müller-Godeffroy E, Wagner VM, Ziegler A: Psychosoziale Auswirkungen einer Insulinpumpen-Therapie in Familien von Kindern und Jugendlichen mit Diabetes mellitus Typ 1 – eine prospektive randomisierte Studie (Vortrag)
Ispad 2017	Wagner V, Müller-Godeffroy E, Ziegler A: Psychosocial Benefits of Insulin Pump Therapy in Children and their Families (Vortrag)
Ispad 2017	Mueller-Godeffroy E, Vonthein R, Ludwig-Seibold C et al.: Quality of life and family burden in type 1 diabetes children and adolescents on continuous subcutaneous insulin infusion versus multiple daily injections:a multicenter randomized controlled trial (EPoster)
DGKJ/ DGSPJ 2019	Müller-Godeffroy E, Mönkemöller K, Lilienthal E et al.: Sozialstatus, Diabetesoutcomes und Diabetesversorgung bei Kindern und Jugendlichen mit Typ-1 Diabetes in Deutschland: Die Ergebnisse der DIAS-Studie (Diabetes and Social Disparities) (Vortrag)

Weitere Publikationen

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