Blutdruckregulation bei Kindern und Jugendlichen mit Typ 1 Diabetes mellitus

Habilitationsschrift

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Zusammenfassung

Die Entwicklung eines Diabetes mellitus Typ1 (T1DM) ist mit einem stark erhöhten Risiko für die spätere Entwicklung kardiovaskulärer und mikrovaskulärer Begleiterkrankungen verbunden. Obwohl diese Begleiterkrankungen meist erst im Erwachsenenalter klinisch Bedeutung gewinnen, mehren sich Hinweise, dass ihre Entwicklung bereits mit dem Zeitpunkt der Manifestation des T1DM im Kindesalter ihren Anfang nimmt. Als Hauptrisikofaktoren für die Entwicklung der kardiovaskulären und mikrovaskulären Begleiterkrankungen gelten neben der T1DM-assoziierten, chronischen Hyperglykämie vor allem Störungen der Blutdruckregulation, insbesondere die der Form der arteriellen Hypertonie (HTN). So sind Störungen der Regulation des Blutdrucks („Blood pressure“, BP) mit einem höheren Auftreten mikrovaskulärer Komplikationen, wie der diabetischen Nephropathie und Retinopathie vergesellschaftet.

Um das Ausmaß und den Krankheitswert von Störungen der Blutdruckregulation bei Kindern und Jugendlichen mit T1DM zu verstehen, wurden ausgesuchte Daten aus dem deutschsprachigen Register für die Verlaufsbeobachtung von Patienten mit Diabetes (DPV-Register) auf mögliche Korrelationen hin betrachtet. Das DPV-Register umfasst inzwischen Dokumentationsdaten von nahezu 90% der an T1DM erkrankten Kinder und Jugendlichen aus Deutschland, Österreich, Luxemburg und Teilen der Schweiz. Im DPV-Register werden die aus heutiger Sicht wesentlichen diabetes-relevanten Daten erfasst. Hierzu gehören: Basisdaten, diabetes-spezifische Parameter, Parameter mit Bezug zu assoziierten Erkrankungen oder Folgeerkrankungen und zusätzliche Medikamente. Diese Daten werden lokal erhoben, dokumentiert und anonymisiert. Die anonymisierten Daten werden zweimal jährlich an das Institut für Epidemiologie und medizinische Biometrie der Universität Ulm versandt und dort zentral auf ihre Qualität hin überprüft.

Bei der Auswertung des DPV-Registers konnten im Wesentlichen folgende Erkenntnisse gewonnen werden:

1. Die Prävalenz der arteriellen Hypertonie (Gelegenheitsblutdruck) ist in der Zeit von 2008 bis 2019 bei Kindern mit T1DM und gleichen Altersquerschnitten deutlich angestiegen.
2. Bei Kindern, die bereits vor Erreichen der Pubertät BP Werte im Bereich der obersten Quartile (> 75. Perzentile) aufweisen, zeigt die spätere Entwicklung zur einer manifesten arteriellen Hypertonie die mit Abstand höchste Dynamik.

Darüber hinaus müssen mehrere wichtige Einflussfaktoren bei der Beurteilung von Gelegenheitsblutdruckwerten berücksichtigt werden:
1. Es finden sich ausgeprägte jahreszeitliche Schwankungen mit höheren BP Werten im Winter.
2. Bei der manuellen BP Messung wird vom Untersucher der Messwert häufig gerundet, wobei nachweislich die Werte meist abgerundet werden. Dadurch könnten Patienten mit BP Werten in einem oberen Grenzbereich, denen bei Dokumentation exakter Werte eine antihypertensive Medikation bereits empfohlen worden wäre, diese mit dem Risiko der Entwicklung vermeidbarer Gesundheitsschäden erst deutlich verspätet erhalten.
3. Für die Gelegenheitsblutdruckwerte gibt es zudem verschiedene Referenzwerte. Diese unterscheiden sich erheblich in ihren Grenzwerten, wodurch sich die Häufigkeit der Diagnosestellung einer HTN bis zum Faktor zwei unterscheiden kann.

Da die Messung des Gelegenheitsblutdruckes nur eine Momentaufnahme darstellt ermöglichen 24 Stunden Blutdruckprofile (ABPM) eine wesentlich genauere Einschätzung der Blutdruckregulation. Aus dem DPV-Register bei Kindern mit T1DM konnten inzwischen 2105 Blutdruckprofile mit folgendem Ergebnis ausgewertet werden: Die Kinder und Jugendlichen mit T1DM zeigen eine Verringerung der nächtlichen BP Absenkung und dadurch vor allem nachts erhöhte BP Werte, was als sogenanntes „Dipping“ bezeichnet wird.

Der Pulsdruck (PP) ist die Differenz zwischen dem systolischen und dem diastolischen BP und ist ein Parameter zur Beurteilung der Steifigkeit einer Gefäßwand. Der PP wird inzwischen als eigenständiger Risikofaktor für Kardiovasopathien angesehen und gewinnt daher zunehmend an Bedeutung als prognostischer Parameter für die Entwicklung diabetischer Komplikationen. Unter diesem Aspekt wurde die Regulation des PP bei Kindern mit T1DM des DPV Registers mit folgenden Ergebnissen ausgewertet:
1. Der PP als Gelegenheitsmessung ist bei T1DM erhöht.
2. Im ABPM findet sich ein inverses Dipping des PP.
3. Der stärkste Anstieg des PP erfolgt in den ersten Jahren nach Manifestation des T1DM.

4. Bei T1DM lässt sich schon im Kindesalter eine vorzeitige Versteifung der Gefäßwand nachweisen, nach kurzer Diabetesdauer und in einer Phase mit noch stabiler Stoffwechseleinstellung.

Bei 82 Kindern mit einem T1DM und 29 gesunden Kindern einer Kontrollgruppe wurde zudem die optisch stimulierte Blutflussgeschwindigkeit in der Arteria cerebri posterior bestimmt. Die Kinder mit T1DM zeigten im Vergleich zur Kontrollgruppe eine erhöhte Dämpfung und somit erste Zeichen einer endothelialen Dysfunktion. Auch diese Veränderungen treten trotz verhältnismäßig stabiler Stoffwechseleinstellung bereits kurze Zeit nach der Diagnosestellung auf.

Die vorliegenden Arbeiten zeigen, dass sich Veränderungen der Blutdruckregulation bei T1DM schon im Kindes- und Jugendalter nachweisen lassen. Diese hypertensiven Veränderungen sind mit Frühzeichen diabetischer Folgeerkrankungen vergesellschaftet.
Störungen in der Regulation des Pulsdruckes und erste Zeichen der endothelialen Dysfunktion treten schon nach kurzer Diabetesdauer und interessanterweise bereits in einer Phase auf, die durch eine kontinuierlich stabile Stoffwechseleinstellung gekennzeichnet ist. Dies deutet daraufhin, dass die chronische Hyperglykämie nicht als einziger Pathogenitätsmechanismus betrachtet werden muss. Möglicherweise sind die Veränderungen auch Folge der therapeutisch verursachten, bisher leider unvermeidbaren chronischen Hyperinsulinämie. Somit könnten sowohl die Regulationsstörungen des PP als auch die endotheliale Dysfunktion Folge der therapeutisch bedingten peripheren Insulinresistenz sein.

Abkürzungsverzeichnis

4th Report	4th report on the diagnosis, evaluation and, treatment of blood pressure in children and adolescents
AAP	American Academy of Pediatrics
AASI	ambulanter arterieller Steifigkeitsindex
ABPM	ambulatory blood pressure monitoring (Blutdruckprofile)
AGPD	Arbeitsgemeinschaft Pädiatrische Diabetologie
BP	blood pressure (Blutdruck)
CGM	continous glucose monitoring (kont. Glukose Monitoring)
CRAE	central retinal arteriolar equivalent
CVD	cardiovascular disease (Kardiovasopathien)
DBP	diastolic blood pressure (diastolischer Blutdruck)
DM	Diabetes mellitus
DPV	Diabetesregister für Prospektive Verlaufsbeobachtung
DR	diabetische Retinopathie
ISPAD	International Society for Pediatric and Adolescent Diabetes
KIGGS	Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland
LV	linksventrikulär
MA	Mikroalbuminurie
MAP	mean arterial pressure (arterieller Mitteldruck)
PP	pulse pressure (Pulsdruck)
SBP	systolic blood pressure (systolischer Blutdruck)
T1DM	Typ 1 Diabetes mellitus
T2DM	Typ 2 Diabetes mellitus
TDP	terminal digital preference (Präferenz der letzten Ziffer)

Abbildungsverzeichnis

Gliederung

1. Einleitung

1.1 Hintergrund

Die Erkrankung an einem Diabetes mellitus geht mit einem deutlich erhöhten Risiko für kardiovaskuläre Erkrankungen (CVD) einher. Dieses erhöhte Risiko für Kardiovasopathien manifestiert sich unter anderem an einer erhöhten Prävalenz für Myokardinfarkte: Bei Menschen mit Diabetes ist die Wahrscheinlichkeit, einen Myokardinfarkt zu erleiden, höher als bei Menschen ohne Diabetes, die bereits zuvor einen Myokardinfarkt erlitten und damit nachweislich eine fortgeschrittene Atherosklerose entwickelt hatten (Abb. 1) [1].

Abbildung 1

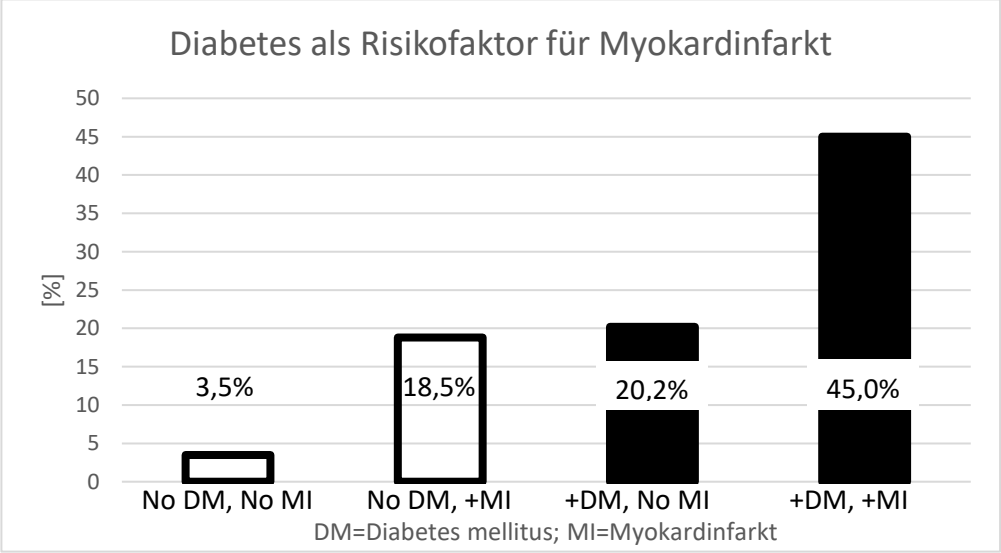

Abb. 1: Rate der Myokardinfarkte bei Patienten mit und ohne Diabetes mellitus bzw. vorherigen Myokardinfarkten. Nach *Haffner et al. N Engl J Med. 1998* [1]

Eine mögliche Erklärung für das erhöhte CVD-Risiko bei T1DM liegt in einer beschleunigten Alterung des Gefäßsystems. Bei Patienten mit Diabetes mellitus findet sich eine um 15-20 Jahre vorzeitige Alterung der Gefäße, „vascular aging“ (Abb. 2) und damit eine beschleunigte Entwicklung der Atherosklerose [2] bzw. der diabetischen Makroangiopathie. Das vermehrte Auftreten von Myokardinfarkten und Apoplexen bei DM stellt die Endpunkte dieser diabetischen Makroangiopathie dar [1].

Abbildung 2

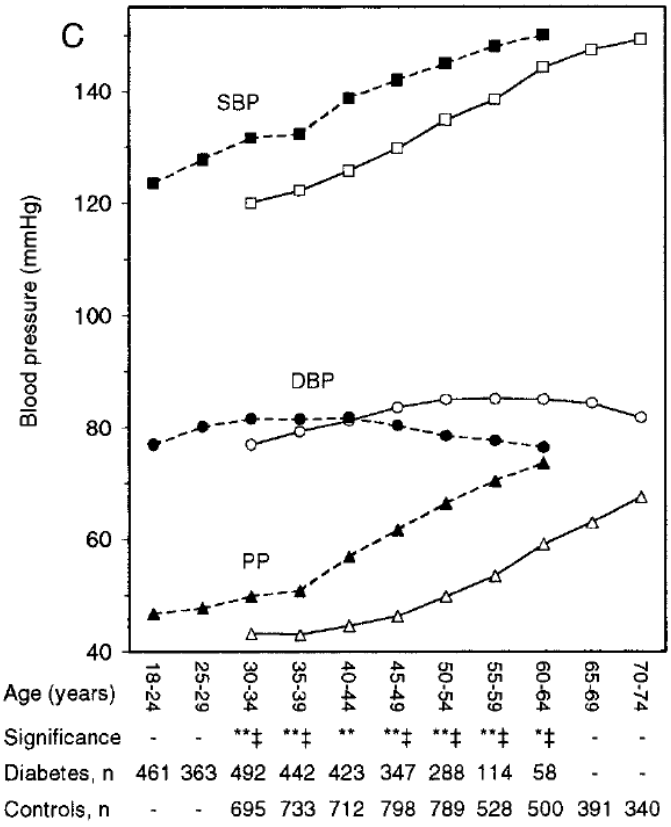

Abb. 2: Altersspezifische Blutdruckindizes von Patienten mit ●und ohne ○Diabetes mellitus. SBP syst., DBP diast. Blutdruck, PP Pulsdruck. *Rönnback et al. Circulation 2004* [2]

Myokardinfarkte und Apoplexe werden in der Regel erst im Erwachsenenalter klinisch manifest. Allerdings setzte sich seit der Jahrtausendwende die Erkenntnis durch, dass die pathophysiologischen Prozesse, die zur Atherosklerose führen, bereits im Kindesalter beginnen. Die Bogalusa Heart Study und die Young Finn Study konnten übereinstimmend diesen frühen Beginn der Entwicklung zur Atherosklerose nachweisen: Beide Studien wurden bei jungen Erwachsenen durchgeführt, die durch Unfälle / Verbrechen ums Leben gekommen sind, zuvor aber als klinisch gesund galten. Obwohl die Patienten klinisch unbeeinträchtigt waren, fanden sich bei ihnen bereits Zeichen einer beginnenden Atherosklerose, wie fatty streaks und erste fibröse Plaques. Geschwindigkeit und Ausmaß dieser Entwicklung war eindeutig mit der Anzahl der vorbeschriebenen Risikofaktoren vergesellschaftet. Als Hauptrisikofaktoren konnten arterielle Hypertonie, chronische Hyperglykämie bzw. manifester Diabetes mellitus, Dyslipidämie und Rauchen identifiziert werden [3,4].

Kinder und Jugendliche mit Diabetes mellitus Typ 1 haben bereits aufgrund ihrer Grunderkrankung einen nicht veränderbaren Risikofaktor. Durch das Auftreten

zusätzlicher Risikofaktoren wie der arteriellen Hypertonie wird bereits im Kindesalter die Gefäßalterung zusätzlich beschleunigt, womit sich das Risiko für spätere kardiovaskuläre Komplikationen weiter erhöht. Schon 10-20 Jahre nach Diabetesmanifestation versterben 25 % Patienten mit T1DM an kardiovaskulären Komplikationen, ab einer Erkrankungsdauer von 20 Jahren sind die Kardiovasopathien sogar die häufigste Todesursache [5] (Abb. 3). Diese Erkenntnisse unterstützen die Beobachtung, dass die Entwicklung der diabetischen Makroangiopathie bereits im Kindesalter beginnt.

Abbildung 3

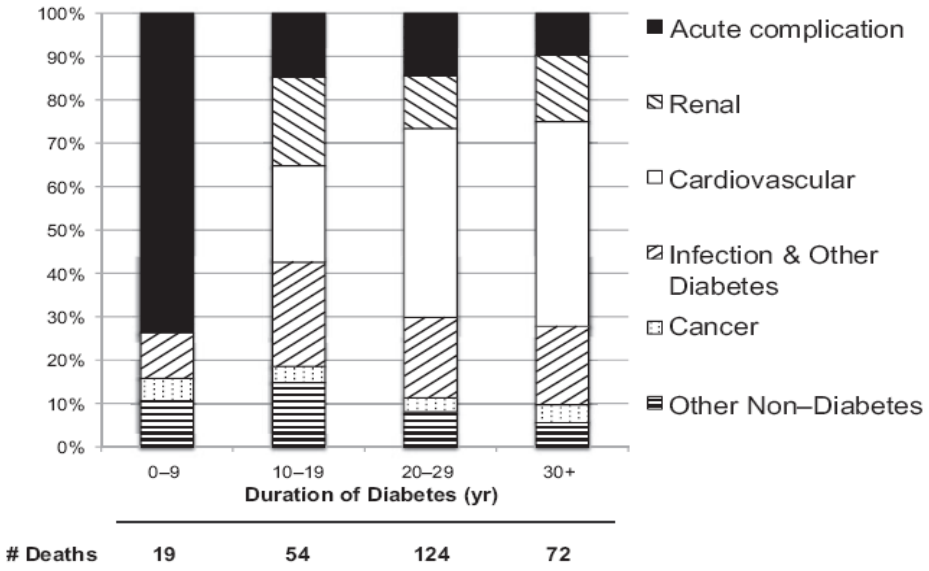

FIG. 1. Distribution of underlying causes of death within 10-year intervals of type 1 diabetes duration. Ten deaths where the cause of death was unknown were excluded.

Abb. 3: Verteilung der Todesursachen ehemaliger pädiatrischer Patienten mit T1DM. *Secrest et al. Diabetes 2010* [*5*]

Die Kombination von chronischer Hyperglykämie und arterielle Hypertonie fördert jedoch nicht nur die Entwicklung einer diabetischen Makroangiopathie, den Veränderungen an den großen Gefäßen, sondern schädigt auch die kleineren Gefäße und führt zur Entstehung einer diabetischer Mikroangiopathie. Diese manifestiert sich vor allem als diabetische Retinopathie und Nephropathie. Im Kindesalter lassen ebenfalls erste Zeichen der diabetischen Mikroangiopathie nachweisen: So konnten Gallego et al. bei Kindern und Jugendlichen mit T1DM zeigen, dass das kumulative Risiko einer diabetischen Retinopathie bei erhöhten Blutdruckwerten deutlich erhöht ist. Nach 15 Jahren Diabetesdauer hatten alle

Patienten mit SBP über der 90. Perzentile eine Retinopathie, von den Kindern mit normotensiven BP Werten waren nur 60% betroffen (Abb. 4) [6].

Abbildung 4

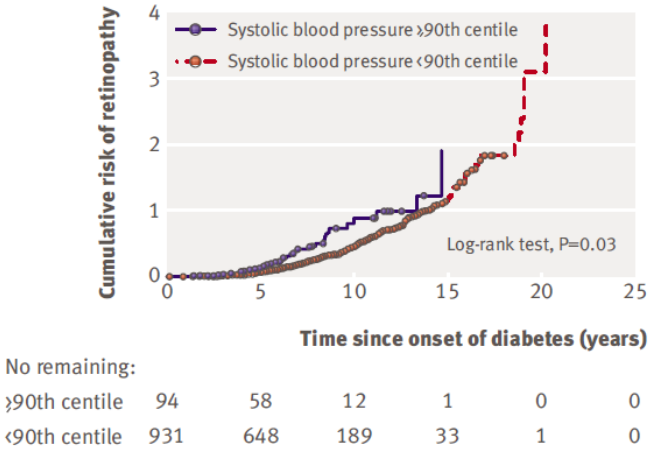

Abb. 4: Kumulative Wahrscheinlichkeit des Auftretens einer diabetischen Retinopathie in Abhängigkeit des SBP. *Gallego et al. BMJ 2008* [6]

Auswertungen des DPV-Registers (Diabetesregister für Prospektive Verlaufsbeobachtung; Deutschland und Österreich) [7] und des T1D Exchange Clinical Registry (USA) [8] konnten zeigen, dass erhöhte Blutdruckwerte bei Kindern und Jugendlichen mit T1DM als unabhängiger Risikofaktor für die Entwicklung einer Mikroalbuminurie eingestuft werden müssen und langfristig einer diabetischen Nephropathie Vorschub leisten.

Die Entstehung der Folgeerkrankungen wird wesentlich durch die chronische Hyperglykämie beeinflusst, erhöhte Blutdruckwerte beschleunigen die Ausbildung der Folgeerkrankungen aber erheblich. Folglich fordern die nationalen Leitlinie der Arbeitsgemeinschaft Pädiatrische Diabetologie (AGPD) der Deutschen Diabetesgesellschaft [9] und die internationale Leitlinie der International Society of Pediatric and Adolescent Diabetes (ISPAD) [10] für Kinder und Jugendliche mit T1DM eine möglichst normoglykäme Stoffwechseleinstellung, regelmäßige Blutdruckmessungen und die Optimierung der Blutdruckwerte in den normotensiven Bereich.

Bis anfangs der 2000er Jahre gab es nur wenige Untersuchungen zur Blutdruckregulation bei Kindern und Jugendlichen mit T1DM. Die bis dahin veröffentlichten Studien basierten in der Regel auf nur kleinen Kohorten, unterlagen häufig einem Studieneffekt und hatten somit nur eine eingeschränkte Aussagekraft. Es fehlten jedoch Untersuchungen an großen Patientenpopulationen unter

Alltagsbedingungen, die die aktuelle Situation der Blutdruckregulation bei Kindern und Jugendlichen mit T1DM abbildeten.

1.2 Fragestellung

Die hier vorgestellten Arbeiten sollten dazu beitragen, die Blutdruckregulation bei Kindern und Jugendlichen mit Diabetes mellitus und den potentiellen Einfluss auf die Entwicklung diabetischer Folgeerkrankungen besser zu verstehen. Basierend auf dem umfangreichen DPV-Register werden nahezu populationsbezogen die Möglichkeiten und Grenzen der Gelegenheitsblutdruckmessung, der 24-Stunden-Blutdruckprofile und des Pulsdruckes sowie die Assoziationen zur diabetischen Nephropathie, Retinopathie und endothelialen Dysfunktion untersucht und diskutiert.

2. Methodik

2.1 Patienten

Unsere Untersuchungen basieren auf dem DPV-Register (Diabetesregister für prospektive Verlaufsdokumentation), das seit Anfang der 1990-er Jahre an der Universität Ulm entwickelt wurde. Inzwischen beteiligen sich 498 Behandlungszentren aus Deutschland, Österreich, Luxemburg und der Schweiz an der Initiative, davon 305 pädiatrische Zentren. Im DPV-Register sind ca. 90% der Kinder und Jugendliche mit Typ 1 Diabetes in Deutschland (Österreich: 80%) dokumentiert, so dass die Erfassung nahezu vollständig ist [11].
Die Zentren erheben die Daten lokal, diese werden im Behandlungszentrum durch die Software anonymisiert und 2 x jährlich nach Ulm gesandt. Es werden die aus heutiger Sicht relevanten Diabetes-Daten erfasst: Basisdaten (Größe, Gewicht, BMI, Gelegenheitsblutdruck, Blutdruckprofile), diabetes-spezifische Parameter (HbA1c Wert, nüchtern BZ, Art der Insulintherapie, Insulinbedarf), Parameter mit Bezug zu assoziierten Erkrankungen oder Folgeerkrankungen (Schilddrüsenparameter, Autoantikörper wie TPO-, Zöliakie-AAK, Albumin im Urin, Fundoskopie) und zusätzliche Medikamente (Antihypertonika, L-Thyroxin und Thyreostatika, Statine, Psychotika). Zur Qualitätssicherung erfolgt in Ulm eine Plausibilitätskontrolle, bei Inkonsistenz oder Inplausibilitäten erfolgt die Korrektur oder Bestätigung durch das behandelnde Zentrum [12]. Die Entwicklung des Registers wurde von der Ethik Kommission der Universität Ulm genehmigt.
Die erhobenen Daten werden gemeinsam ausgewertet und publiziert.

2.2 Berechnung von SDS und LMS-SDS Werte des Blutdruckes

Ähnlich wie Körperhöhe und Körpergewicht ist auch der Blutdruck eine dynamische Größe und verändert sich bei Kindern und Jugendlichen mit zunehmendem Alter und Körperhöhe. Daher können die absoluten Blutdruckwerte bei Kindern unterschiedlichen Alters oder Körperhöhe nicht direkt miteinander verglichen werden, sondern müssen auf Perzentilen bezogen werden.
Alternativ kann der Standard Deviation Scores (SDS, im englischen Schrifttum auch als z-score bezeichnet) berechnet werden, der für die Unterschiede bezüglich des Geschlechts, des Alters und der Körperhöhe korrigiert. Der SDS gibt die Abweichung des Messwertes vom Mittelwert (MW) der Vergleichspopulation (VP) an:

SDS = (Messwert – MW VP): Standardabweichung (SD) VP

Liegt der individuelle Messwert unter dem MW der Vergleichspopulation, so ist der SDS-Wert negativ, bei Abweichung nach oben ist er positiv. Werte zwischen -2 und +2 gelten als normal.

Häufig ist die Vergleichspopulation nicht normal verteilt. Für diese Schiefe der Verteilung kann mittels der LMS Methode [13] korrigiert werden.

Der LMS-SDS errechnet sich folgendermaßen:

LMS-SDS = {[Y/M(t)] L(t)-1} / [L(t) x S(t)]

Hierbei ist Y der Messwert, M der Median S der Variationskoeffizient und L ein Maß für die Schiefe der Verteilung. Bezogen auf die Blutdruckwerte ist Y der gemessene Blutdruckwert des Kindes, L(t), M(t) und S(t) entsprechen den geschlechtsspezifischen Referenzwerten von L, M und S bezogen auf die Körperhöhe des Kindes.

Aufgrund der schiefen Verteilung unserer Vergleichspopulationen haben wir die SDS-Werte als LMS-SDS Werte berechnet und verwendet [14].

3. Gelegenheitsblutdruck

3.1 Hintergrund

Als Gelegenheitsblutdruckwert wird ein Blutdruckwert bezeichnet, der routinemäßig in der Ambulanz, der Praxis oder bei stationärer Aufnahme bestimmt wird. Die Leitlinien zur Behandlung von Kindern und Jugendlichen mit T1DM schreiben regelmäßige Messungen des Gelegenheitsblutdruckes möglichst bei jeder Vorstellung vor [9,10]. Die Messungen sollen in sitzender Position nach mindesten 5-minütiger Ruhe bei aufliegendem Arm mit adäquater Manschettengröße durchgeführt und auf 2 mm Hg abgelesen werden. Der dokumentierte Blutdruckwert sollte aus 2-3 Einzelmessungen berechnet werden. Die meisten pädiatrischen Diabeteszentren verwenden inzwischen automatisierte oszillometrische Messmethoden.
Nach den Leitlinien sollte der Blutdruck unterhalb der 90. Perzentile bezogen auf die Körperhöhe liegen. Werte zwischen der 90. und 95. Perzentile werden als Prähypertension bezeichnet und sollten zunächst eine Änderung der Lebensgewohnheiten nach sich ziehen (Lifestyle Intervention). Wenn sich der Blutdruck nach 6 Monaten nicht normalisiert hat, sollte eine antihypertensive Medikation eingeleitet werden. Bei Blutdruckwerten über der 95. Perzentile (manifeste arterielle Hypertonie) sollte parallel zur Lifestyle Intervention sofort eine antihypertensive Medikation begonnen werden. Die Leitlinien empfehlen primär den Einsatz von ACE-Inhibitoren [9,10].

3.2 Prävalenz erhöhter Gelegenheitsblutdruckwerte

Eine Auswertung des DPV-Registers von 868 Kindern und Jugendlichen mit T1DM ergab 2008, dass der Gelegenheitsblutdruck bei 4% der Patienten unter 16 Jahren und bei 13,9% der Patienten über 16 Jahren erhöht war verglichen mit den europäischen Referenzwerten von 1991 [16]. Bis 2013 ist die Prävalenz erhöhter Blutdruckwerte deutlich angestiegen: In einer Querschnittsuntersuchung der DPV-Daten an 46737 Patienten fanden sich bei 20,4% der Kinder unter 10 Jahren, bei 21,5% der Kinder zwischen 10 und 15 Jahren und bei 18,9% der Jugendlichen von 15-20 Jahren erhöhte BP-Werte [17]. 2019 (DPV-Querschnittsuntersuchung an 74677 Patienten) zeigte sich ein weiterer Anstieg auf entsprechend 30,7%, 31,4% und 28,4% [18] bezogen auf die Referenzwerte der deutschen KIGGS-Daten [19]. Für die letzten 13 Jahre kann somit eine erhebliche Zunahme der Patienten mit

arterieller Hypertonie festgestellt werden. Der Anstieg ist in den jüngeren Altersgruppen besonders stark ausgeprägt.
(Knerr I, Dost A, Lepler R et al., Diabetes Care 2008 [15], Dost A, Molz E, Krebs A et al., Ped Diabetes 2014 [16], Dost A, Bechtold S, Fink K et al., Diabetes Care 2020 [17])

3.3. Gelegenheitsblutdruckwerte im zeitlichen Verlauf (Tracking der Blutdruckwerte)

Störungen der Blutdruckregulation im Kindesalter führen häufig zur Ausbildung einer manifesten arteriellen Hypertonie im Erwachsenalter. Wir untersuchten daher welchen Einfluss die Blutdruckregulation bei Kindern vor der Pubertät (präpubertär) auf die spätere Blutdruckregulation als Jugendliche oder junge Erwachsene (postpubertär) hat. Daher wurde die Entwicklung der Blutdruckregulation bei 868 Patienten mit T1DM des DPV-Registers ausgewertet. Dieses sogenannte Tracking ergab, dass die Erhöhung des Blutdruckes im präpubertären Alter um 1 LMS-SDS den Blutdruck postpubertär um systolisch 0,43 LMS-SDS und diastolisch um 0,38 LMS-SDS erhöhte [15].
Gemäß den initialen Blutdruckwerten im Kindesalter (präpubertär) erfolgte eine Einteilung der Werte in Quartilen. Hierbei zeigte sich, dass die Kinder, die initial die niedrigsten Blutdruckwerte hatten (unterste Quartile, <25%), auch später die geringsten Blutdruck LMS-SDS Werte aufwiesen, gefolgt von den Kindern der beiden mittleren Quartilen (25-75%). Die Kinder mit den höchsten Blutdruckwerte präpubertär (oberste Quartile, >75%) boten auch postpubertär die höchsten Blutdruckwerte (Abb. 5) [15].

Abbildung 5

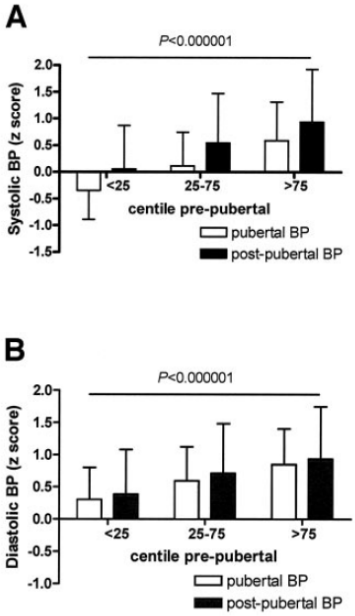

Abb. 5: Anstieg der Blutdruck LMS-SDS Werte von präpubertät zu postpubertär, abhängig von der Quartile des präpubertären Blutdruckes. *Knerr I, Dost A, et al. Diabetes Care 2008* [15]

Dies bedeutet, dass sich bei den Kindern, die bereits bei Manifestation des Diabetes bzw. im präpubertären Alter erhöhte Blutdruckwerte aufweisen, die stärkste Dynamik und damit das größte Risiko für die Entwicklung einer arteriellen Hypertonie im jungen Erwachsenalter findet. Daher müssen diese Kinder besonders eng beobachtet werden und bei Ihnen frühzeitig eine weitergehende Diagnostik und Therapie eingeleitet werden.
(Knerr I, Dost A, Lepler R, et al., Diabetes Care 2008 [15])

3.4 Probleme und Grenzen der Gelegenheitsblutdruckmessung

3.4.1 Hintergrund

In den Leitlinien sind regelmäßige Messungen des Gelegenheitsblutdruckes fest verankert [9,10]. Allerdings stellt die Messung des Gelegenheitsblutdruckes nur eine Momentaufnahme dar, die durch die Situation des Arztbesuches verfälscht werden kann.
Zusätzlich müssen bei der Erhebung der Blutdruckwerte einige Einflussfaktoren beachtet und bei der Interpretation berücksichtigt werden. Wir haben anhand des DPV-Registers überprüft, welche Rolle diese Faktoren bei Kindern und Jugendlichen mit Diabetes mellitus spielen.

3.4.2 Saisonale Schwankungen der Blutdruckwerte

Für den Blutdruck sind saisonale Schwankungen mit höheren BP-Werten in den Wintermonaten beschrieben worden [20]. Wir überprüften, ob sich solche jahreszeitlichen bedingten Änderungen der Blutdruckregulation auch bei Patienten mit Diabetes mellitus nachweisen lassen. Bei 162135 Patienten des DPV-Registers (62589 T1DM und 99546 T2DM) fanden sich deutliche saisonale Schwankungen des Gelegenheitsblutdruckes mit höheren Werten in den Wintermonaten: SBP +2,28 mm Hg (T1DM) bzw. +2,48 mm Hg (T2DM), DBP entsprechend +1,24 mm Hg bzw. +0,64 mm Hg (Abb. 6). Diese Schwankungen ließen sich sowohl für Patienten mit Typ 1 als auch Typ 2 Diabetes konstant über einen Zeitraum von 10 Jahre nachweisen (Abb. 7). Bei Frauen und bei Kindern und Jugendlichen mit T1DM waren die Unterschiede besonders stark ausgeprägt, bei Patienten mit T2DM fand sich dagegen keine Abhängigkeit von Geschlecht oder Alter [20].

Abbildung 6

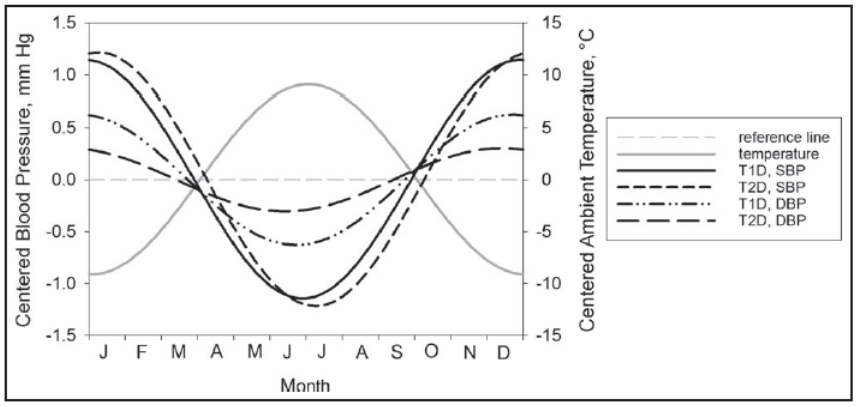

Abb. 6: Saisonales Muster der systolischen (SBP) und diastolischen (DBP) Blutdruckwerte bei Patienten mit Typ 1 und Typ 2 Diabetes mellitus. *Hermann JM, Rosenbauer J, Dost A., et al. J Clin Hypertens (Greenwich) 2015* [20]

Abbildung 7

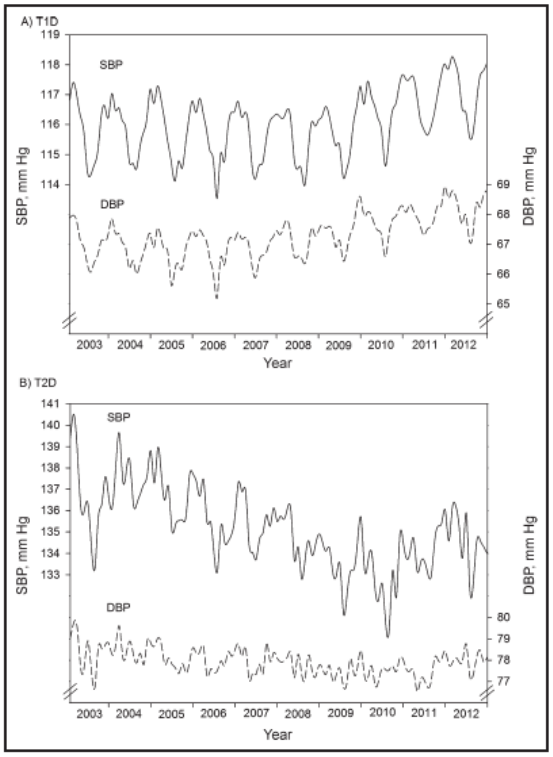

Abb. 7: Verläufe von 2003-2012 der systolischen (SBP) und diastolischen (DBP) Blutdruckwerte bei Patienten mit Typ 1 (oben) und Typ 2 (unten) Diabetes mellitus. *Hermann JM, Rosenbauer J, Dost A., et al. J Clin Hypertens (Greenwich) 2015* [20]

(Hermann JM, Rosenbauer J, Dost A, et al. J Clin Hypertens (Greenwich) 2015 [20]

3.4.3 Rundungsfehler (Terminal Digital Preference; TDP)

Die Messung des Gelegenheitsblutdruckes soll nach 5 Minuten Ruhe in aufrecht sitzender Position gemessen und auf 2 mm Hg genau abgelesen werden. Der Bestimmung des Blutdruckwertes sollten 2-3 Messung zugrunde liegen. Häufig erfolgt bei der manuellen BP-Messung jedoch eine Rundung der Messwerte auf die nächsten 5 mm Hg oder sogar 10 mm Hg (Abb. 8). Diese Tendenz wird als Terminal Digital Preference (TDP) bezeichnet, als Präferenz der letzten Ziffer.
TDP fand sich bei 55% der in DPV dokumentierten Messungen des Gelegenheitsblutdruckes (494301 Messungen bei 47373Patienten mit T1DM und entsprechend 86277/44025 T2DM). In Zentren, die überwiegend Patienten mit T1DM betreuen, meistens pädiatrische Zentren, trat TDP seltener auf und verringerte sich im Beobachtungszeitraum von 14 Jahren. In den T2DM Zentren dagegen blieb die Prävalenz von TDP nahezu konstant.

Zentren mit TDP dokumentierten niedrigere systolische (-3,6 mm Hg T1DM / -7,0 mm Hg T2DM) und erhöhte diastolische Werte (+2,2 mm Hg T1DM / +2,9 mm Hg T2DM) (Abb. 9) [21]. Dieser Bias könnte bewirken, dass Patienten mit BP Werten in einem oberen Grenzbereich, denen bei Dokumentation exakter Werte eine antihypertensive Medikation bereits empfohlen wäre, diese aufgrund des Rundungsfehlers erst verspätet erhalten. Nietert et al. schätzen diese Dunkelziffer auf 6,8% bei einer TDP Prävalenz von 50%. D.h. fast 7% der hypertensiven Patienten erhalten fälschlicherweise keine antihypertensiven Medikamente und sind somit einem erhöhten Risiko vermeidbarer Schäden ausgesetzt [22]. Bei den im DPV-Register dokumentierten Blutdruckmessungen liegt die TDP Prävalenz mit 55% sogar etwas höher. Daher kann vermutet werden, dass die Rate einer fälschlichen Unterversorgung mit Antihypertensiva bei den Patienten des DPV-Registers ähnlich hoch sein wird.

Abbildung 8

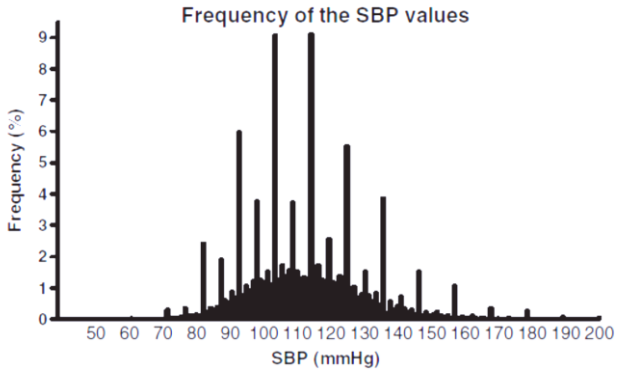

Abb. 8: Terminal Digital Preference der systolischen Blutdruckwerte. Es ist deutlich zu erkennen, dass die Messwerte gehäuft mit den Ziffern 0 und 5 enden. *Dost A et al., Diabetic Med 2009* [21]

Abbildung 9

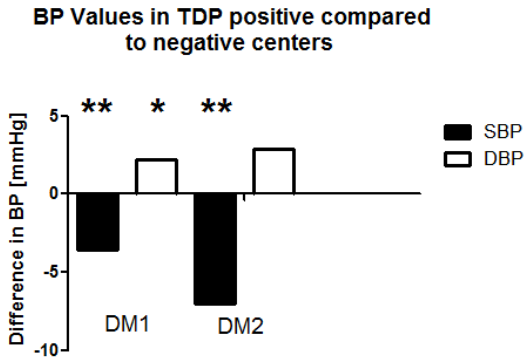

Abb. 9: Einfluss der Terminal Digital Preference (TDP) auf die Blutdruckwerte. TDP positive Zentren messen den systolischen Blutdruck bei Patienten mit T1DM um durchschnittlich 3,6 mm Hg niedriger, bei T2DM um durchschnittlich 7,0 mmHg. *nach Dost A et al., Diabetic Med 2009* [21]

(Dost A, Hofer S, Herbst A, et al. Diabetic Med 2009 [21])

3.4.4 Referenzwerte

Die Beurteilung von Blutdruckwerten und deren Einstufung als pathologisch erfolgt anhand von Referenzwerten, die an Vergleichspopulationen erstellt worden sind. 1991 wurden erstmals europäische Referenzwerte für den Gelegenheitsblutdruck bei Kindern und Jugendlichen veröffentlicht. Diese basierten jedoch lediglich auf einer Synopse von sechs Studien, die teilweise bereits mehrere Jahre zuvor durchgeführt worden waren [16]. 2004 wurde der “4th Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents” von der National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents veröffentlicht (4^{th} report) [23]. Diesen Referenzwerten liegt eine Querschnittsuntersuchung US-amerikanischer Kinder und Jugendlichen zugrunde. Seit 2007 stehen deutsche Referenzwerte zur Verfügung, die 2011 aktualisiert wurden und auf der Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KiGGS) des Robert Koch Institutes basieren (KIGGS Wellen 1 und 2) [19]. 2017 veröffentlichte die American Academy of Pediatrics neue Referenzwerte, die basierend auf dem 4th Report jetzt nur noch Kinder und Jugendliche ohne Übergewicht und Fettsucht berücksichtigen (AAP 2017) [24]. Diese neuen Referenzwerte führen zu einem Absenken der Schwellenwerte für die Diagnose einer arteriellen Hypertonie bei Kindern und Jugendlichen.

Wir haben untersucht, welchen Einfluss die jeweiligen Referenzwerte auf die Prävalenz der arteriellen Hypertonie bei Kindern und Jugendlichen mit T1DM haben. Dazu wurden die im DPV-Register dokumentierten Blutdruckwerte von 74677 Patienten (52,8% Jungen, medianes Alter 16 Jahre, mediane Diabetesdauer 5,3 Jahre) ausgewertet und die Prävalenz der arteriellen Hypertonie unter Verwendung der drei Referenzwerte AAP 2017 [24] KIGGS 2011 [19] und 4th Report 2004 [23], bestimmt: Nach den AAP 2017 Referenzwerte betrug die Prävalenz der arteriellen Hypertonie bei unseren Patienten 44,1%, nach KIGGS 29,5% und nach 4th Report 26,5%. Es besteht eine deutliche Altersabhängigkeit: < 10 Jahren AAP 2017 Prävalenz 31,4%, KIGGS 30,7%, 4th Report 19,6%, 10-15 Jahre AAP 2017 30,9%, KIGGS 31,2% 4th Report 22,4% und >15 Jahren AAP 2017 53,2%, KIGGS 28,4%, 4th Report 30,0%. Von den Jugendlichen >15 Jahren wurden 59,1% der Jungen und 46,3% der Mädchen bei Verwendung von AAP 2017 als hypertensiv klassifiziert,

dagegen nur 21,1% bzw. 26% der Jungen und 36,7% bzw. 34,4% der Mädchen bei Verwendung von KIGGS bzw. 4th report (Abb. 10).

Abbildung 10

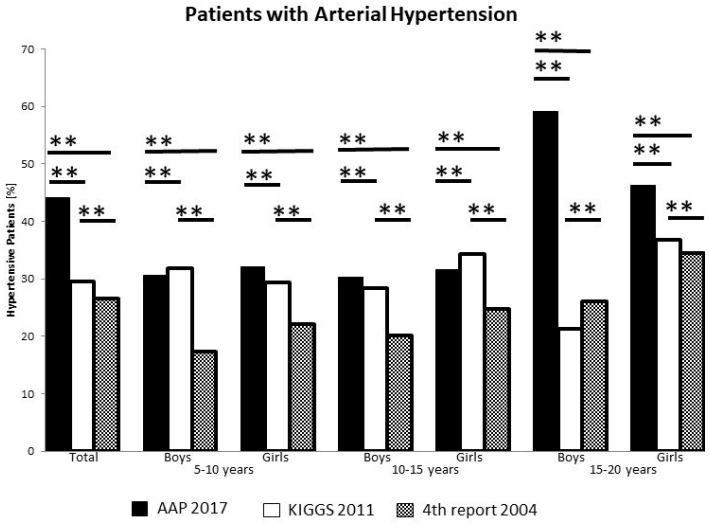

Abb. 10: Prävalenz der arteriellen Hypertonie im gesamten Kollektiv und in den Untergruppen. Es sind deutliche Unterschiede in der Prävalenz in Abhängigkeit der verwendeten Referenzwerte zu erkennen, besonders bei den Jungen >15 Jahre*. Dost A, et al. Diabetes Care 2020* [17]

Diese Daten bestätigen die Erfahrung, dass alleine die Auswahl der Referenzpopulation bzw. der Referenzwerte einen maßgeblichen Einfluss auf die Prävalenz der arteriellen Hypertonie hat. So werden nach AAP 2017 fast 60% der Jungen über 15 Jahren als hypertensiv diagnostiziert, nach KIGGS und dem 4th Report mit 30% jedoch nur die Hälfte.

(Dost A, Bechtold S, Fink K, et al. Diabetes Care 2020 [18])

4. 24-Stunden Blutdruckprofile (Ambulatory Blood Pressure Monitoring; ABPM)

4.1 Hintergrund

In der täglichen klinischen Routine erfolgt die Überprüfung der Blutdruckregulation als Messung des Gelegenheitsblutdruckes. Diese Messung kann bereits wertvolle Hinweise auf das Vorliegen einer arteriellen Hypertonie bei Kindern und Jugendlichen mit T1DM geben. Allerdings konnten wir zeigen, dass die Bestimmung und Beurteilung des Gelegenheitsblutdruckes verschiedenen Einflussfaktoren unterliegen und dass dadurch die Aussagekraft eingeschränkt wird. Zusätzlich kann die Zuverlässigkeit der Gelegenheitsblutdruckmessung durch eine eventuelle Praxis- oder Weißkittelhypertonie beeinträchtigt sein.

Daher empfehlen die Fachorganisationen der Kinderdiabetologie (AGPD, ISPAD) und Kinderkardiologie (AAP), die Diagnose einer arteriellen Hypertonie möglichst durch die Ableitung von 24-Stunden Blutdruckprofilen zu sichern. Dies sollte nach den Leitlinien der AGPD erfolgen, wenn sich innerhalb von 3 Monaten mindestens zweimalig ein auffälliger Blutdruckwert > 95. Perzentile bzw. absolut über 130/80 mm Hg findet oder bei Vorliegen einer Mikroalbuminurie [9]. Die ISPAD empfiehlt bei T1DM allgemein die Ableitung eines ABPM zur Bestätigung der Diagnose einer arteriellen Hypertonie [10].

Nur durch die Ableitung von ABPM kann die Blutdruckregulation über 24 Stunden und vor allem die nächtliche Blutdruckregulation beurteilt werden, die durch die punktuelle Messung des Gelegenheitsblutdruckes nicht erfasst wird. Bei einer Untersuchung von 75 Jugendlichen und jungen Erwachsenen mit T1DM konnten Lurbe et al. zeigen, dass die nächtlichen Blutdruckwerte bei 14 Patienten (18,6%) erhöht waren [25].

Mehrere Beobachtungen haben in den letzten Jahren bewirkt, dass bei Kindern und Jugendlichen mit T1DM häufiger ABPM abgeleitet werden: Erstens die zentrale Rolle, die die arterielle Hypertonie bei der Entstehung der diabetischen Folgeerkrankungen spielt. Zweitens die Tatsache, dass Gelegenheitsblutdruck-messungen nur eine Momentaufnahme der Blutregulation darstellen. Drittens, ABPM korreliert besser mit den Endpunkten, den manifesten Endorganschäden [26].

Wir haben bereits frühzeitig (2008) die im DPV-Register dokumentierten ABPM ausgewertet und überprüft, welche Assoziationen zu den Frühzeichen diabetischer Folgeerkrankungen bestehen.

4.2 Prävalenz pathologischer ABPM

2008 erfolgte die erste Auswertung der im DPV-Register dokumentierten ABPM von 2105 Kindern und Jugendlichen mit T1DM. Die Prävalenz pathologisch erhöhter Blutdruckwerte (> 95. Perzentile) betrug tags 5,1% SBP, 4,3% DBP und 5,7% MAP, nachts 14,6% SBP, 14,7% DBP und 19,0% MAP. Das Dipping, die nächtliche Absenkung des Blutdruckes, war bei 49,1% (SBP) und bei 17,5% bzw. 64,9% (DBP) der Patienten verringert (abhängig, ob der cut off für Non-Dipping des DBP bei 10% oder 20% angesetzt wurde) [14] (Abb. 11). Entsprechend waren 2008 die Blutdruckwerte tagsüber nur leicht erhöht (SBP +0,06, MAP +0,11 LMS-SDS bzw. der DBP sogar leicht erniedrigt (-0,12 LMS-SDS), wogegen die nächtlichen Blutdruckwerte deutlich erhöht waren (SBP +0,51, DBP +0,58, MAP +0,8 LMS-SDS) (Abb. 12) [14].

Abbildung 11

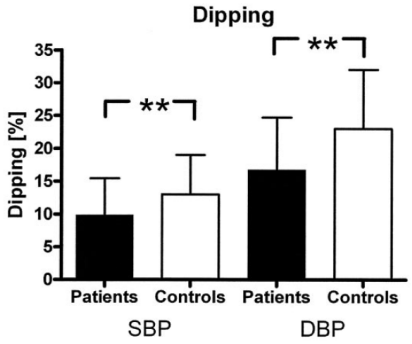

Abb. 11: Dipping [%] (SBP, DBP) der Kinder mit T1DM verglichen mit der nicht-diabetischen Vergleichskohorte. *Dost A, et al. Diabetes Care 2008* [14]

Abbildung 12

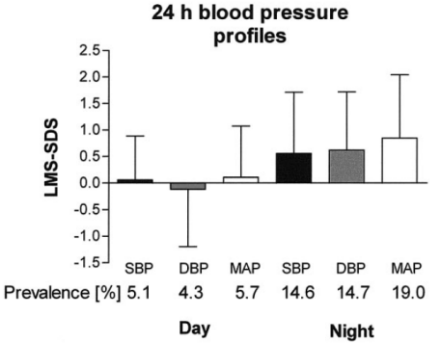

Abb. 12: Abweichung der LMS-SDS Werte (SBP, DBP, MAP) der Kinder mit T1DM von den Werten der nicht-diabetischen Vergleichskohorte. *Dost A, et al. Diabetes Care 2008* [14]

Ähnliche Werte fanden sich 2017, hier betrugen die Abweichungen bei der Auswertung der Blutdruckprofile von 3529 Kindern und Jugendlichen entsprechend tagsüber SBP +0,06, DBP -0,22 und MAP +0,08 LMS-SDS, nachts SBP +0,55, DBP +0,58, MAP +0,83 LMS-SDS (Abb. 13). Das Dipping war bei den Kindern mit T1DM mit einer Absenkung des BPs um 9,8% SBP, 16,5% DBP und 12,4% MAP als grenzwertig einzustufen und entsprach der Untersuchung von 2008.

Abbildung 13

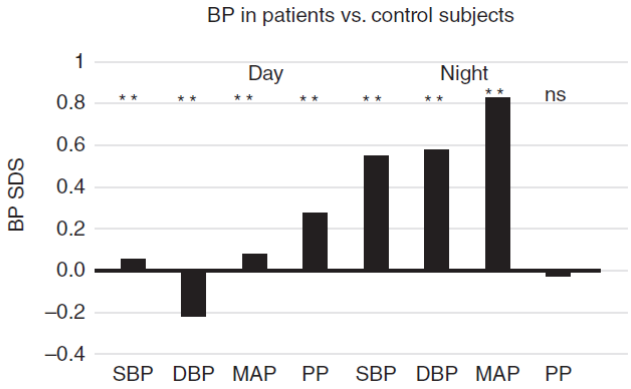

Abb. 13: Abweichung der LMS-SDS Werte (SBP, DBP, MAP, PP) der Kinder mit T1DM von den Werten der nicht-diabetischen Vergleichskohorte. *Dost A, et al. Ped Diabetes 2017* [27]

Unsere Untersuchungen zeigen reproduzierbar für den Zeitraum von 2008-2017, dass die Blutdruckregulation bei Kindern und Jugendlichen mit T1DM gestört ist. Besonders die nächtliche BP-Regulation ist betroffen, sowohl qualitativ bei einer erhöhten Prävalenz der arteriellen Hypertonie als auch quantitativ in Form erhöhter LMS-SDS-Werte.

(Dost A, Klinkert C, Kapellen TM, et al. Diabetes Care 2008 [14]*, Dost A, Bechtold-Dalla Pozza S, Bollow E, et al. Ped Diabetes 2017* [27]*)*

4.3 Assoziationen mit Frühmarkern diabetischer Komplikationen (Mikroalbuminurie und diabetische Retinopathie)

Veränderungen der Blutdruckregulation, insbesondere die arterielle Hypertonie, wurden bei Diabetes mellitus als Risikofaktoren für makrovaskuläre und mikrovaskuläre Komplikationen beschrieben. Bei Jugendlichen und jungen Erwachsenen mit T1DM geht das Auftreten einer persistierenden Mikroalbuminurie (MA) mit dem Anstieg des nächtlichen SBP einher [25].

Dies deckt sich mit der Beobachtung, dass Nephropathien nicht-diabetischer Genese ebenfalls mit vor allem nächtlichen Störungen der Blutdruckregulation assoziiert sind [28] und diese Veränderungen bereits als erstes Zeichen einer renalen Funktionsstörung bei T1DM gewertet werden könnten [29].

Bei unserer Untersuchung an 1670 Kindern und Jugendlichen mit T1DM fand sich 2008 eine deutliche Assoziation zwischen erhöhtem nächtlichen DBP und reduziertem diastolischem Dipping einerseits und einer persistierenden

Mikroalbuminurie andererseits. 2017, 9 Jahre später, ließ sich bei 186 von 2569 Patienten (7,5%) eine persistierende Mikroalbuminurie nachweisen. Die Patienten mit Mikroalbuminurie wiesen zwar tags und nachts höhere SBP-, DBP- und MAP-Werte auf, die Unterschiede in der Blutdruckregulation waren aber nachts besonders stark ausgeprägt (Abb.14) [27].

Abbildung 14

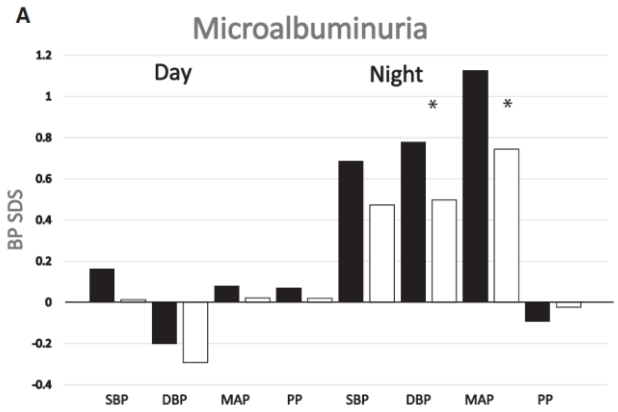

Abb. 14: LMS-SDS Werte (SBP, DBP, MAP, PP) der Kinder mit T1DM mit und ohne MA. *Dost A, et al. Ped Diabetes 2017* [27]

Erfreulicherweise tritt die diabetische Retinopathie (DR) im Kindesalter selten auf. 2017 waren im DPV-Register bei 2323 Kinder und Jugendlichen mit T1DM Befunde von ABPM und Fundoskopie dokumentiert, bei 38 der 2323 Patienten fand sich eine beginnende DR (1,6%). Die DR war mit erhöhten Blutdruckwerten assoziiert, diese Assoziationen waren wiederum nachts besonders stark ausgeprägt (Abb. 15) [27].

Abbildung 15

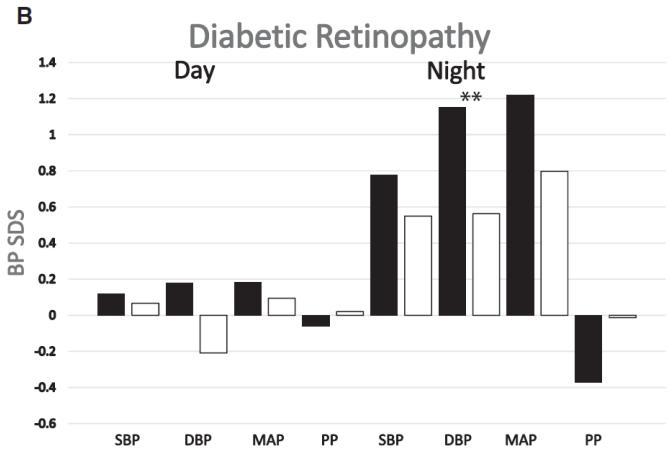

Abb. 15: LMS-SDS Werte (SBP, DBP, MAP, PP) der Kinder mit T1DM mit und ohne DR. *Dost A, et al. Ped Diabetes 2017* [27]

(*Dost A, et al. Diabetes Care 2008* [14], *Dost A, et al. Ped Diabetes 2017* [27])

5. Pulsdruck

5.1 Hintergrund

Neben den klassischen Blutdruckparametern (systolischer, diastolischer Blutdruck und arteriellem Mitteldruck) wurde in den letzten Jahren die wichtige Rolle des Pulsdruckes (PP) in der Entstehung der Atherosklerose erkannt. Als Pulsdruck wird die Differenz zwischen systolischem und diastolischem Blutdruck bezeichnet. Er wird im Wesentlichen von drei Faktoren beeinflusst: Dem Schlagvolumen des linken Ventrikels, der Compliance der Gefäße und der Reflexion der Pulswelle durch die Gefäßwand. Somit kann der Pulsdruck als indirektes Maß der Flexibilität bzw. Steifigkeit der Gefäßwand, vor allem der großen herznahen Gefäße gewertet werden [30]. Bei Erwachsenen mit T1DM laufen die Gefäßalterung und damit die Versteifung der Gefäße beschleunigt ab [2]. Diabetes mellitus wurde in der Framingham Studie bei Erwachsenen als wichtiger Risikofaktor für einen erhöhten Pulsdruck und damit für eine kardiovaskuläre Erkrankung identifiziert [31].
Es gibt nur wenige Untersuchungen zum Pulsdruck bei Kindern und Jugendlichen. Der American National Health and Nutritional Survey (NHANES) von 2012 beschrieb ein höheres Risiko für einen gesteigerten Pulsdruck für Jungen und für adipöse Kinder [32]. Bei deutschen Kindern ohne Diabetes mellitus mit prähypertensiven Blutdruckwerten (90.-95 Perzentile) lag der Pulsdruck zwischen den Werten der Kinder mit normotensiven und denen mit hypertensiven Blutdruckwerten [33]. Für Kinder mit Diabetes mellitus, vor allem T1DM, lagen lange Zeit keine Untersuchungen zur Regulation des Pulsdruckes vor.

5.2 Pulsdruck im Rahmen von Gelegenheitsblutdruckmessungen

Wir haben 2014 bei 46737 Patienten des DPV Registers die Pulsdruckwerte auf der Basis von Gelegenheitsblutdruckmessungen bestimmt. Der PP war bei 67% der Kinder und Jugendlichen mit T1DM erhöht. Es bestand eine Korrelation mit Alter, männlichem Geschlecht, Diabetesdauer, Insulindosis, Körperhöhe und BMI. Erstaunlicherweise war der Zusammenhang mit dem HbA1c-Wert zu vernachlässigen. Der PP steigt mit zunehmender Diabetesdauer an, der steilste Anstieg fand sich jedoch in den ersten 2-4 Jahren der Erkrankung, danach bleibt der PP weitgehend stabil bzw. fällt bei den Jungen sogar wieder leicht ab (Abb. 16).

Abbildung 16

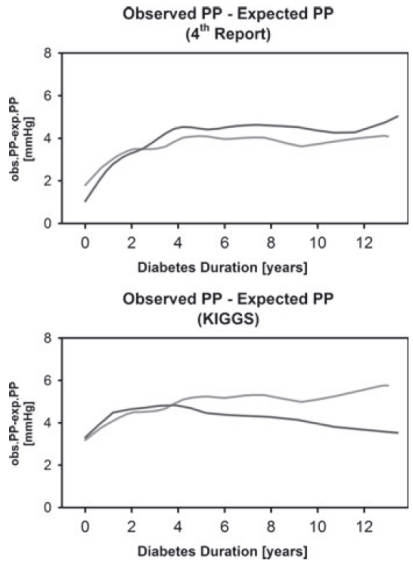

Abb. 16: Pulsdruck im zeitlichen Verlauf bei Jungen und Mädchen bezogen auf die Referenzwerte des 4th report und KIGGS
Dost A, et al. Pediatric Diabetes 2014 [16]

Daher scheint nicht, wie zunächst vermutet, die chronische Hyperglykämie Ursache des Anstiegs sein. Bei Kindern und Jugendlichen kommt es in den ersten Jahren der Erkrankung in der Regel zu einer partiellen Remissionsphase, die durch eine sehr stabile Stoffwechselsituation mit nahezu normoglykämen Blutzuckerwerten und damit mit niedrigen HbA1c-Werten gekennzeichnet ist [16].
Wir müssen den Anstieg des Pulsdruckes vielmehr als Nebenwirkung der Insulintherapie werten: Die subkutane Gabe von Insulin führt zu einer Hyperinsulinämie, die der Insulinresistenz bei T2DM ähnelt und fördert die Entwicklung von Übergewicht und krankhafter Fettsucht. Patienten mit T1DM entwickeln häufig Übergewicht, so auch die Patienten unserer Untersuchung, deren BMI um 0,52 SDS gegenüber gesunden nicht-diabetischen Kindern (Referenzwerte der Arbeitsgemeinschaft Adipositas, AGA) [34] erhöht war. Für Verwandte ersten Grades von Patienten mit Typ 2 Diabetes konnte ein Zusammenhang zwischen Insulinresistenz und endothelialer Dysfunktion nachgewiesen werden, obwohl die Probanden noch normoglykäme Blutzuckerwerte aufwiesen [35]. Bei Patienten mit manifestem T2DM zeigte sich eine ähnliche Assoziation zwischen Insulinresistenz, Insulintherapie und der arteriellen Versteifung [36]. Die Erhöhung des PP als Ausdruck der Gefäßversteifung muss somit als wahrscheinliche Folge der therapeutisch notwendigen und bisher leider unvermeidbaren chronischen Hyperinsulinämie und der damit verbundenen peripheren Insulinresistenz gesehen werden.
(Dost A, Molz E, Krebs A, et al, Ped Diabetes 2014 [16]*)*

5.3 Pulsdruck im Rahmen von Blutdruckprofilen (ABPM)

Bei erwachsenen Patienten mit einer arteriellen Hypertonie scheint der Pulsdruck basierend auf 24 Stunden Blutdruckprofilen einen höheren prädiktiven Wert für Kardiovasopathien zu haben als der Pulsdruck basierend auf Messungen des Gelegenheitsblutdruckes [4].

Unsere Auswertung der Blutdruckprofile von 3529 Kindern und Jugendlichen mit T1DM ergab folgende Ergebnisse: Der Pulsdruck lag tags höher (+0,3 LMS-SDS), war aber nachts vergleichbar mit dem PP der Vergleichskohorte (-0,03 LMS-SDS). Bei den Kindern mit Mikroalbuminurie (MA) lag der PP geringgradig höher als bei den Kindern ohne MA, der nächtliche PP war bei den Kindern mit MA tendenziell eher erniedrigt (PP -0,13 vs. -0,03 LMS-SDS). Bei den wenigen Kindern mit einer diabetischen Retinopathie fanden sich niedrigere PP Werte (tags -0,09 vs. +0,27 LMS-SDS, nachts -0,38 vs.-0,02 LMS-SDS).

Somit scheint der PP bei unseren Patienten auf den ersten Blick nicht mit den mikrovaskulären Komplikationen assoziiert zu sein. Allerdings fand sich sowohl bei den Kindern mit MA und/oder DR ein deutlicheres inverses Dipping des PP (-5,1% bzw. -2,6%), als bei den Kindern, die keine MA bzw. DR aufwiesen (-0,8% bzw. -1,0%) [27].

Die Befunde des ABPM stehen teilweise im Widerspruch zu den Untersuchungen der Gelegenheitsblutdruckmessungen. Bei den Kindern mit MA waren die PP-Werte tags zumindest tendenziell höher als bei den Kindern ohne MA, was unseren vorherigen Ergebnissen entspricht. Die Tatsache, dass die Unterschiede bei den ABPM geringer ausgeprägt sind, liegt sicherlich an der deutlich geringeren Anzahl der Patienten (ABPM 3529 vs. Gelegenheits-BP 46737 Patienten). Es muss spekuliert werden, dass geringgradige Unterschiede aufgrund der deutlich größeren Fallzahl bei der Kohorte von 2013 (basierend auf Messungen des Gelegenheitsblutdruckes) nachweisbar gewesen sein könnten, die sich in der kleineren Kohorte von 2017 (ABPM) statistisch nicht gezeigt haben. Die ABPM-basierten PP Werte zeigten bei unseren Patienten noch keinen pathologischen Anstieg der LMS-SDS Werte, allerdings findet sich bereits ein verringertes Dipping des PP bei den Patienten mit Frühzeichen mikrovaskulärer Komplikationen. Störungen der nächtlichen Blutdruckabsenkung, das Non-dipping, wird allgemein als erstes Zeichen einer Blutdruckregulationsstörung angesehen und geht langfristig mit einem erhöhten Risiko kardiovaskulärer Erkrankungen und diabetische Mikroangiopathien einher

[37]. Das inverse Dipping, also der nächtliche Anstieg des Blutdruckes, verschärft diese Entwicklung: 10 mm Hg isolierte Erhöhung des nächtlichen SBP (entsprechend der Erhöhung des nächtlichen PP) resultiert in einem 35% höheren Risiko für CVD [38]. Dies bedeutet, dass die bei unseren Patienten beobachteten Veränderungen in der Regulation des Pulsdruckes als erstes Zeichen einer beginnenden Versteifung des Gefäßes anzusehen sind, die in dieser Frühphase noch reversibel sein können [39].
(*Dost et al. Ped Diabetes 2017* [27])

6. Zerebrovaskuläre Reagibilität

Die Entwicklung einer endothelialen Dysfunktion spielt eine entscheidende Rolle in der Pathogenese diabetischer Angiopathien. Der Pulsdruck ist ein anerkannter indirekter Marker für die Versteifung der Gefäße und damit der endothelialen Dysfunktion. Natürlich ist die ergänzende direkte Überprüfung der endothelialen Funktion erstrebenswert. Zur Beurteilung der zerebrovaskulären Reagibilität können Veränderungen der stimulierten Blutflussgeschwindigkeit in der Arteria cerebri posterior gemessen werden [40]. Wir untersuchten die Anpassung der Blutflussgeschwindigkeit auf visuelle Stimulation bei 82 Kindern und Jugendlichen mit T1DM. Hier fand sich im Vergleich zur Kontrollgruppe (n=29) eine erhöhte Dämpfung des Systems. Die vermehrte Dämpfung spricht für eine unzureichende Rückbildung der Dilatation und damit für eine funktionell vermehrte Rigidität der Gefäßwand. Die bei unseren Kindern mit T1DM (Alter 13 - 14,8 Jahre) gemessenen Dämpfungswerte (0,47 – 0,48) [41] entsprechen denen gesunder Probanden im Alter von 20-40 bzw. 40-60 Jahren (0,46 / 0,45) [40]. Kinder ohne Diabetes (Alter 13,3 Jahre) dagegen wiesen eine signifikant niedrigere Dämpfung auf (0,38) [41] und zeigten ähnliche Werte wie gesunde Jugendliche und junge Erwachsene von 10-20 Jahren (0,41) [40]. Die endotheliale Funktionseinschränkung der Kinder und Jugendlichen mit T1DM entspricht einer um 15-20 Jahren verfrüht einsetzenden endothelialen Dysfunktion. Dies ist umso erstaunlicher, da die Dämpfung bei gesunden Probanden ohne Diabetes mellitus im Alter zwischen 10 und 60 Jahren nahezu unverändert bleibt. Die um 15-20 Jahre beschleunigte Veränderung der zerebrovaskulären Reagibilität entspricht genau dem Zeitrahmen, den Rönnback et al. [2] für das beschleunigte „vascular aging“ bei T1DM beschrieben haben. Die vermehrte Dämpfung kann wie der Pulsdruck als Parameter einer zunehmenden Steifigkeit der Gefäßwand angesehen werden. Daher ist es nicht überraschend, dass sich bei unseren Untersuchungen Regulationsstörungen beider Parameter, der Dämpfung und des Pulsdrucks, nachweisen ließen. D.h. wir konnten bereits zu einem frühen Zeitpunkt der Erkrankung Hinweise auf eine endotheliale Dysfunktion nachweisen. Für uns zunächst überraschend fanden sich zwischen Kindern mit kurzer (<5 Jahren) und denen mit langer Diabetesdauer (>5 Jahre) keine Unterschiede in der Dämpfung (0,47 vs. 0,48). Dies spricht dagegen, dass Störungen der Dämpfung der für den Diabetes mellitus typischen chronischen Hyperglykämie geschuldet sind, zumal die HbA1c- Werte bei den Kindern mit längerer Diabetesdauer nur geringfügig höher

lagen (8,4% vs. 8,0%). Es bleibt vielmehr zu spekulieren, dass ähnlich wie der Pulsdruck auch die Steigerung der Dämpfung Folge der exogenen Insulingabe und der damit verbundenen peripheren Insulinresistenz ist.

(*Rosengarten B, Dost A, Kaufmann A, et al. Diabetes Care 2002* [41])

7. Diskussion

Gestützt auf die umfangreiche Datenbasis des DPV-Registers werden in der vorliegenden Arbeit wichtige Aspekte der Blutdruckregulation bei Kindern und Jugendlichen mit Typ 1 Diabetes mellitus beleuchtet. Die Ergebnisse unserer Untersuchungen können als repräsentativ angesehen werden und zeigen, dass die Blutdruckregulation bei Patienten mit T1DM schon im Kindes- und Jugendalter gestört ist. Dies gilt sowohl für die Regulation des Gelegenheitsblutdruckes als auch für die Blutdruckregulation über 24 Stunden. Im Folgenden werden die Ergebnisse unserer Untersuchungen für den Gelegenheitsblutdruck, die Blutdruckprofile, den Pulsdruck und ihre Assoziationen zu den diabetischen Folgeerkrankungen anhand der aktuellen Literatur diskutiert.

7.1. Gelegenheitsblutdruck

Die Auswertung der Regulation des Gelegenheitsblutdruckes ergab folgende Erkenntnisse: Die Prävalenz der arteriellen Hypertonie ist von 2008 bis 2019 deutlich angestiegen und kann zum Teil mit veränderten Referenzwerten erklärt werden. Unsere Untersuchung von 2008 bezog sich noch auf die alten europäischen Vergleichswerte, die eine Zusammenfassung von 6 verschiedenen Studien darstellten und populationsbasierte Querschnittsuntersuchungen gesunder Kinder waren [22]. Bei den Untersuchungen von 2013 und 2019 wurden die jeweils aktuellen Referenzwerte der KIGGS Studie genutzt, die auf nicht-übergewichtigen deutschen Kindern basieren [18]. Der Anstieg der Hypertonie Prävalenz von 2008 - 2019 kann allerdings nicht ausschließlich über eine Gewichtszunahme erklärt werden: Der BMI-SDS lag bei der ersten Untersuchung 2008 altersabhängig zwischen 0,24 und 0,6, 2013 in der Gesamtkohorte bei 0,42 und aktuell (2020) bei 0,3. Der BMI-SDS ist bei unseren Kindern somit eher gesunken. Ähnliches gilt für den Insulinbedarf und für eine eventuelle sekundäre Insulinresistenz, der Insulinbedarf ist über die Jahre ebenfalls stabil geblieben.
Auch die Fallzahlen könnten einen Einfluss auf die Hypertonie Prävalenz haben: So unterscheiden sich die Fallzahlen zwischen den Studienzeitpunkten erheblich, 2008 wurden 868 Patienten untersucht, 2013 46737 und 2019 79849 Patienten. Bei der deutlich geringeren Fallzahl 2008 könnten geringe Erhöhungen der Prävalenz als

noch nicht als signifikant eingestuft worden sein. Allerdings scheint dies den um den Faktor 2-5 höheren Anstieg der HTN-Prävalenz nicht ausreichend zu erklären. Die Untersuchungen von 2013 und 2019 beruhen beide auf einer sehr breiten Datenbasis bei der sich bei beiden Untersuchungen bereits kleinste Unterschiede statistisch gezeigt hätten.

Wenn der Anstieg der HTN Prävalenz sich nicht durch unterschiedliche Fallzahlen erklären lässt, muss diskutiert werden, ob eine arterielle Hypertonie generell bei Kindern und Jugendlichen häufiger diagnostiziert wird. D.h., ob die Prävalenz auch bei stoffwechselgesunden Kindern ohne Diabetes steigt, oder ob es sich um eine spezifische Entwicklung bei Patienten mit T1DM handelt. In den Jahren bis 2008 fand sich bei den Kindern und Jugendlichen der US-amerikanischen NHANES ein Anstieg der HTN-Prävalenz. Bei der Betrachtung der Jahre 1999-2012 konnte allerdings kein weiterer Anstieg mehr beobachtet werden, es zeigte sich sogar eine geringe Abnahme der Prävalenz um 1,3% für die manifeste Hypertonie bzw. um 2,8% für den erhöhten BP [42]. Auch Kharbanda et al. fanden über einen Zeitraum von 2 Jahren (von 2014 bis 2016) nur einen geringen Anstieg der HTN-Prävalenz um 1,1% bei Verwendung der Referenzwerte des 4th Report [44]. Bezogen auf unsere Beobachtung hieße dies, dass ein Anstieg der HTN-Prävalenz bei deutschen Kindern um ca. 10 Jahre gegenüber den USA verzögert auftritt und die Kinder und Jugendlichen mit T1DM ebenfalls davon betroffen sind. Leider sind die Daten der KIGGS Studie zur Entwicklung der HTN-Prävalenz bei deutschen Kindern von der Basisuntersuchung (2003-2006) bis zur zweiten Welle (2014-2017) noch nicht veröffentlicht. Wenn es nicht zu einem Anstieg der HTN-Prävalenz bei gesunden Kindern gekommen ist, müssen für unsere Beobachtung diabetesspezifische Gründe diskutiert werden: Wie gezeigt ist der BMI stabil geblieben. Auch die Stoffwechselsituation hat sich im entsprechenden Zeitraum (1995-2009) eher gebessert, der durchschnittliche HbA1c Wert ist um 0,6% gesunken, die Rate der extrem schlecht eingestellten Patienten (HbA1c >9%) hat sich nahezu halbiert [44]. Somit liegt weder eine Verschlechterung der Stoffwechselregulation noch ein Anstieg des BMI oder der Insulinresistenz vor, die diesen Anstieg erklären könnten.

Natürlich beeinflusst auch die Auswahl der Referenzwerte die Entwicklung der HTN-Prävalenz. Kharbanda et al. hatten bei Verwendung des 4th Reports nur einen geringen Anstieg der Prävalenz um 1,1% beschrieben, bei Verwendung der neuen US-Referenzwerte (AAP 2017) betrug dieser Anstieg 5,9% [43]. Bei Routineunter-

suchungen in der Universitätskinderklinik Oklahoma führte der Einsatz der AAP 2017 Referenzwerte erwartungsgemäß zu einer deutlichen Zunahme der Diagnose „arterielle Hypertonie“ von 9,5% (4th Report) auf 17,9% (AAP 2017) [43]. Diese Daten bestätigen unsere Beobachtung, dass die Verwendung der neuen US-amerikanischen Referenzwerte zu einer Verdopplung der Diagnose arterielle Hypertonie bei Kindern und Jugendlichen mit T1DM führt [18] und bestätigen den Einfluss unterschiedlicher Referenzwerte.

Weitere Faktoren werden für den Anstieg der HTN bei Kindern und Jugendlichen in der Gesamtbevölkerung diskutiert: Die Diagnose einer essentiellen Hypertonie wird im Kindesalter [45] häufiger gestellt. Außerdem findet sich eine verhältnismäßig hohe Rate von Jugendlichen mit grenzwertig erhöhten Blutdruckwerten (Prähypertension), die im weiteren Verlauf unbehandelt zu einer manifesten Hypertonie fortschreitet [46]. Letztlich können wir den Anstieg der Prävalenz erhöhter Gelegenheitsblutdruckwerte nicht abschließend erklären, sondern nur beschreiben.

Mehrfach erhöhte Gelegenheitsblutdruckwerte müssen auf jeden Fall eine weitere Diagnostik, insbesondere die Ableitung eines 24-Stunden Blutdruckprofiles, nach sich ziehen. Es sollte nicht aufgrund weniger Gelegenheitsblutdruckmessungen unmittelbar mit einer antihypertensiven Medikation begonnen werden, sondern die Ergebnisse der ABPM berücksichtigt werden, um insbesondere die Übermedikation bei Praxishypertonie bzw. Weißkittelhypertonie zu vermeiden.

7.2 Blutdruckprofile (ABPM)

Im Gegensatz zur Entwicklung beim Gelegenheitsblutdruck fand sich bei den ABPM von 2008 bis 2017 kein Anstieg der Blutdruck LMS-SDS Werte. Über 24 Stunden gesehen scheint die Blutdruckregulation stabil geblieben zu sein. Mit 2105 (2008) bzw. 3529 (2017) Patienten liegen diese Fallzahlen verglichen mit den Messungen des Gelegenheitsblutdruckes deutlich niedriger, sind aber unseres Wissens die größten Kohorten von Kindern und Jugendlichen mit T1DM, bei denen die Blutdruckregulation über 24 Stunden untersucht worden ist.

Leider zeigten beide Auswertungen übereinstimmend, dass vor allem die nächtliche Blutdruckregulation und das Dipping beeinträchtigt sind. Erhöhte nächtliche Blutdruckwerte und Non- bzw. Inverses Dipping erhöhen bei Patienten mit Diabetes das Risiko für kardiovaskuläre Komplikationen erheblich, Non-Dipping um 29%,

Inverses Dipping sogar um 53% [37]. Non-Dipping führt zu einer linksventrikulären Hypertrophie, einer systolischen und diastolischen Funktionsstörung und einer vermehrten arteriellen Steifigkeit. Es wird daher inzwischen als unabhängiger Risikofaktor einer linksventrikulären Dysfunktion gewertet [38]. Unerkannte Störungen der nächtlichen Blutdruckregulation erhöhen das Risiko für diabetische Komplikationen wie auch unsere Untersuchungen gezeigt haben. Die Indikation zum ABPM sollte bei Kindern und Jugendlichen mit T1DM als Risikogruppe großzügig gestellt werden, um die arterielle Hypertonie bei Kindern und Jugendlichen mit T1DM frühzeitig zu diagnostizieren und zu therapieren.
ABPM ermöglicht außerdem die Diagnose einer maskierten Hypertonie und einer Praxis- bzw. Weißkittel Hypertonie (white coat hypertension). Als maskierte Hypertonie werden normale Gelegenheitsblutdruckwerte bei pathologischem ABPM bezeichnet und wird als eigenständiger Risikofaktor für Kardiovasopathien angesehen [29]. Die Weißkittel Hypertonie (WCH) bezeichnet erhöhte Gelegenheitsblutdruckwerte bei unauffälligem ABPM [29]. Augenblicklich wird diskutiert, inwieweit die WCH mit einem erhöhten Risiko für kardiovaskuläre Erkrankungen einhergeht.

7.3 Pulsdruck und endotheliale Dysfunktion

Die Regulation des Pulsdruckes ist bei Kindern und Jugendlichen mit T1DM beeinträchtigt. Bei den Patienten des DPV-Registers ist der Pulsdruck der Gelegenheitsmessungen signifikant erhöht, bei den ABPM findet sich ein inverses Dipping des PP. Regulationsstörungen des Pulsdruckes müssen als unabhängiger Marker der zunehmenden Versteifung des Gefäßsystems eingestuft werden. Übereinstimmend mit der gestörten Regulation des Pulsdruckes konnten wir bei unseren Patienten eine Beeinträchtigung der endothelialen Funktion nachweisen: Die Dämpfung in der Arteria cerebri posterior war erhöht, das heißt nach Dilatation der Arterie aufgrund eines erhöhten Blutflusses erfolgt die Rückstellung des Gefäßes verzögert, was einer funktionellen Versteifung der Gefäßwand entspricht. Somit konnten wir anhand von zwei unterschiedlichen Parametern bereits bei Kindern und Jugendlichen mit T1DM eine endotheliale Dysfunktion zeigen. Ähnliche Befunde wurden für Kinder mit Adipositas erhoben: Bei Kindern mit schwerer Fettsucht ist der ambulante arterielle Steifigkeitsindex (AASI) deutlich erhöht. Er korreliert mit BMI und

Pulsdruck, unabhängig von SBP und DBP [47]. Da für fettsüchtigen Kinder eine periphere Insulinresistenz angenommen werden kann, deuten diese Befunde auf die Insulinresistenz als möglichen ursächlichen Faktor bei der Entstehung der endothelialen Dysfunktion im Kindesalter hin. Die Steifigkeit der Gefäßwand korreliert bei Patienten mit Typ 2 Diabetes mit der Insulinresistenz bzw. einer Insulintherapie [35]. Auch unsere Daten sprechen für die iatrogen bedingte Hyperinsulinämie als potentielle Ursache der Regulationsstörung des PP sowie der verstärkten Gefäßdämpfung als frühe Marker der endothelialen Dysfunktion.
Krebs et al. konnten zeigen, dass die Intima-Media-Dicke und damit strukturelle Veränderungen der Gefäßwand bereits bei Kindern und Jugendlichen mit T1DM mit der Höhe des Pulsdruckes korrelieren [48]. D.h. der erhöhte Pulsdruck führt zunächst zu einer funktionellen Störung des Endothels (z.B. verstärkte Dämpfung) und mittelfristig zu strukturellen Veränderungen der Gefäßwand (Zunahme der Intima-Media-Dicke). Bei Kindern und Jugendlichen mit erhöhten BP-Werten in der Adoleszenz steigt das Risiko für eine Atherosklerose der Carotiden an, bei Normalisierung der Blutdruckwerte im Erwachsenenalter kann dieses Risiko wieder gesenkt werden [39]. D. h die Veränderungen am Endothel sind initial noch reversibel und eröffnen in der Adoleszenz und dem jungen Erwachsenenalter ein therapeutisches Fenster mit der Möglichkeit einer erfolgreichen Intervention.
Sowohl Pulsdruck als auch endotheliale Dysfunktion werden durch eine periphere Insulinresistenz verstärkt. Insofern könnte die Insulinpumpentherapie, bei der mit niedrigeren Insulindosen eine gleiche Stoffwechselgüte erzielt werden kann, langfristig zu einer Verbesserung der makro- und mikrovaskulären Komplikationen beitragen, obwohl sich die Stoffwechselsituation gemessen am HbA1c Wert langfristig nicht verbessert.

7.4 Assoziation zu mikrovaskulären Komplikationen (diabetische Nephropathie und Retinopathie)

Eine wesentliche Erkenntnis unserer Untersuchungen ist, dass bereits frühzeitig im Kindes- und Jugendalter Assoziationen zwischen der Blutdruckregulation und der Entwicklung von makro- als auch mikrovaskulären Folgeerkrankungen wie der diabetischen Nephropathie und Retinopathie bestehen. Diese Assoziationen sind

besonders stark ausgeprägt bei Störungen der nächtlichen Blutdruckregulation. Lurbe et al. beschrieben erstmalig bei Kindern mit T1DM, dass die Entwicklung einer Mikroalbuminurie mit erhöhten nächtlichen Blutdruckwerten einhergeht [25]. Wir konnten sowohl 2008 als auch 2017 diese Beobachtung an deutlich größeren Kollektiven bestätigen: Die Kinder mit Komplikationen hatten vor allem nachts höhere Blutdruckwerte.
Unsere Ergebnisse stimmen auch mit anderen Studien überein: Bei spanischen Erwachsenen war das Auftreten einer Mikroalbuminurie mit erhöhten nächtlichen SBP-Werten und gehäuftem Non-Dipping assoziiert. Entsprechend fand sich die höchste MA Prävalenz bei den Probanden mit nächtlich erhöhtem SBP und Non-Dipping. Dies war auch die Gruppe mit dem höchsten Anteil von Patienten mit Diabetes [49]. Das Auftreten einer MA war bei Kindern mit T1DM der Oxford Regional Prospective Study mit einer schlechten Stoffwechseleinstellung und erhöhtem Gelegenheits-DBP vergesellschaftet, die Progression zur Makroalbuminurie ebenfalls mit höherem HbA1c sowie erhöhten Gelegenheits-SBP und -DBP [50].

Erfreulicherweise ist die Rate der im DPV-Register dokumentierten T1DM Kinder und Jugendlichen mit einer Retinopathie sehr niedrig (1,6%), steigt aber leider im Verlauf der Erkrankung an. Gallego et al. konnten zeigen, dass sich nach 10 Jahren Diabetesdauer bei 36% der Patienten Veränderungen an der Retina nachweisen ließen. Neben einer schlechten Stoffwechseleinstellung war das Auftreten der Retinopathie mit erhöhtem Gelegenheits-SBP und DBP assoziiert. Dieser Effekt war unabhängig vom Vorliegen einer Mikroalbuminurie und kann daher nicht durch eine Störung der Nierenfunktion erklärt werden [6]. Bereits vor Manifestation struktureller Veränderungen an der Netzhaut kann der negative Effekt erhöhter Blutdruckwerte auf die Retina festgestellt werden. So fanden Schiel et al. mit Hilfe einer Flicker-Kamera einen Einfluss des diastolischen Blutdruckes auf die Dilatation retinaler Arterien [51].
Dieser Zusammenhang zwischen Blutdruckregulation und mikrovaskulären Veränderungen konnte auch bei Kindern ohne Diabetes gezeigt werden. Das Central Retinal Arteriolar Equivalent (CRAE) ist ein Maß für den Durchmesser retinaler Arteriolen. Es ist bei Kindern mit Prähypertonie bzw. manifester Hypertonie verringert und korrelierte negativ mit dem systolischen Blutdruck [52]. Kinder und Jugendliche

mit T1DM haben ein erhöhtes Risiko für Störungen der Blutdruckregulation und sind daher besonders gefährdet für Veränderungen des CRAE.

7.5. Stärken und Schwächen der DPV Daten

Die Stärke des DPV-Registers besteht darin, dass ca. 90% aller Kinder und Jugendlichen mit T1DM in Deutschland und 80% in Österreich dokumentiert sind. Wir konnten somit auf eine äußerst valide Datenbasis zurückgreifen. Die Untersuchungen basieren auf prospektiven Verlaufsbeobachtungen und Daten, die regelmäßig routinemäßig erhoben werden. Damit kann ein Studieneffekt ausgeschlossen werden, die Daten bilden vielmehr die Alltagssituation unserer Patienten ab. Die große Stärke des DPV-Registers ist die Mitarbeit von 498 pädiatrischen und internistischen Zentren aus Deutschland (n=449), Österreich (n=44), der Schweiz (n=4) und Luxemburg (n=1).
Auch wenn die Qualität der Daten durch eine zweimal jährliche zentrale Überprüfung auf Plausibilität verbessert wird, hängt die Qualität der Daten maßgeblich von der Zuverlässigkeit der Datenerhebung und -eingabe vor Ort ab, was zu einer Qualitätsminderung der Daten führen kann. Die Zentren vor Ort entscheiden eigenständig über Form und Durchführung der Insulintherapie, Art und Intensität der Blutdruckmessungen sowie über Indikation und Durchführung einer eventuellen antihypertensiven Therapie. Somit ergeben sich Unterschiede zwischen den Zentren. Dieser Multicenter-Effekt muss sicherlich als Schwäche unserer Untersuchungen angesehen werden, wie dies prinzipiell für alle Multicenter-Studien gilt.

7.6 Schlussfolgerungen

Seit der Jahrtausendwende wurde auch bei Kindern und Jugendlichen mit Typ 1 Diabetes mellitus zunehmend die Bedeutung der Blutdruckregulation für die Entwicklung und Prävention diabetischer Komplikationen erkannt. Unsere Arbeiten konnten dazu beitragen und zeigen, dass sich bereits bei den Kindern und Jugendlichen mit T1DM erhebliche Störungen in der Blutruckregulation finden: Besonders nachts weisen bereits viele Kinder hypertensive Blutdruckwerte und eine Verringerung der nächtlichen Blutdruckabsenkung auf. Diese Regulationsstörungen gehen mit einer deutlichen Erhöhung des Risikos für kardiovaskuläre Erkrankungen

und Komplikationen im Erwachsenenalter einher. Kinder und Jugendliche, bei denen bereits zu Beginn der Erkrankung hypertensive Blutdruckwerte nachweisbar sind, haben ein hohes Risiko für eine spätere arterielle Hypertonie. Daher ist es von entscheidender Bedeutung, die Diagnose erhöhter Blutdruckwerte bzw. einer arteriellen Hypertonie zu einem möglichst frühen Zeitpunkt zu stellen und rechtzeitig eine antihypertensive Therapie einzuleiten. Zur Erkennung einer gestörten nächtlichen Blutdruckregulation ist die Ableitung von Blutdruckprofilen unabdingbar. Die Indikation zum ABPM muss daher großzügig gestellt werden.
Wir konnten bereits nach kurzer Diabetesdauer und bei verhältnismäßig stabiler Stoffwechseleinstellung erste Zeichen einer vermehrten Versteifung der Gefäße und einer endothelialen Dysfunktion nachweisen. Das heißt neben den klassischen Blutdruckparametern sollte auch der Pulsdruck als Marker dieser Gefäßversteifung berücksichtigt werden. Sowohl der Pulsdruck als auch die endotheliale Dysfunktion scheinen durch eine periphere Insulinresistenz bedingt zu werden. Daher sollte eine optimale Stoffwechseleinstellung mit möglichst geringen Insulindosen angestrebt werden.
Unsere Untersuchung zeigen an einem nahezu populationsweiten Kollektiv, dass die Störungen der Blutdruckregulation auch mit vermehrten mikrovaskulären Komplikationen einhergehen, wie der diabetischen Nephropathie und Retinopathie.

7.7. Ausblick

Störungen der Blutdruckregulation erhöhen das Risiko für diabetische Folgeerkrankungen und sie beginnen im Kindesalter. Daher muss bereits ab dem Zeitpunkt der Diabetes Manifestation neben der Optimierung des Glukosemetabolismus auf die Optimierung der Blutdruckwerte geachtet werden.
Um dem negativen Einfluss zu hoher Insulindosen vorzubeugen, muss eine Hyperinsulinisierung vermieden werden. Dabei kann uns der Fortschritt in der Diabetes Technologie der letzten Jahre helfen, insbesondere die Insulinpumpen und das kontinuierliche Glukose Monitoring (CGM), die sehr gute Stoffwechselergebnisse bei deutlich geringerem Insulinbedarf ermöglichen und sich derzeit zur Standardtherapie bei Kindern und Jugendlichen mit Typ 1 Diabetes entwickeln.

Durch rechtzeitige Erkennung und Intervention von Störungen der Blutdruckregulation und Vermeidung von Hyperinsulinisierung können wir das therapeutische Fenster bei Kindern und Jugendlichen mit T1DM nutzen, in dem die Veränderungen am Endothel nur funktionell und damit reversibel sind. So können die beiden „Schurken“ der Diabetologie, die chronische Hyperglykämie und die arterielle Hypertonie, erfolgreich kontrolliert und die Prävalenz der Folgeerkrankungen reduziert werden.

8. Literatur

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9. Ehrenwörtliche Erklärung

Ich erkläre hiermit, dass mir die Habilitationsordnung der Friedrich-Schiller-Universität Jena vom 7. Januar 1997 und die Dritte Änderung der Habilitationsordnung vom 19. Dezember 2017 bekannt ist.

Ferner erkläre ich, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quellen gekennzeichnet.

Bei der Auswahl und Auswertung folgenden Materials haben mir die nachstehend aufgeführten Personen in der jeweils beschriebenen Weise unentgeltlich geholfen:

Prof Dr. med. Reinhard Holl, Institut für Epidemiologie und Medizinische Biometrie der Universität Ulm, bei der Planung und Durchführung der Auswertungen des DPV-Registers,
Esther Bollow und Katharina Fink, Institut für Epidemiologie und Medizinische Biometrie der Universität Ulm, bei den statistischen Berechnungen

Weitere Personen waren an der inhaltlich-materiellen Erstellung der Arbeit nicht beteiligt. Insbesondere habe ich hierfür nicht die entgeltliche Hilfe von Vermittlungs- bzw. Beratungsdiensten in Anspruch genommen. Niemand hat von mir unmittelbar oder mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorliegenden Arbeit stehen.

Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Ich versichere, dass ich nach bestem Wissen die reine Wahrheit gesagt und nichts verschwiegen habe.

Jena, den

Dr. med. Axel Günter Dost

10. Lebenslauf

Dr. med. Axel Dost

31.01.1964	geboren in Gießen
Schulbildung:	
1970-74	Grundschule, Kelkheim
1974-79	Bischof Neumann Schule, Königstein
1979-80	Ecole d´ Humanité, Goldern, Schweiz
1980-83	Bischof Neumann Schule, Königstein
1983	Allgemeine Hochschulreife
Wehrdienst:	
1983-84	Grundwehrdienst
Studium:	
1984-1990	Medizinstudium an der Justus-Liebig-Universität, Gießen
1986	Ärztliche Vorprüfung
1987	Ärztliche Prüfung, Teil 1
1989	Ärztliche Prüfung, Teil 2
1990	Ärztliche Prüfung, Teil 3
Promotion:	
1992	Glykierte Proteine bei Diabetes mellitus Typ1 Eine prospektive Untersuchung über zwei Jahre bei Kindern und Jugendlichen
Weiterbildung:	
1990-92	Arzt im Praktikum, Zentrum für Kinderheilkunde, Justus-Liebig-Universität, Gießen
1992-93	Weiterbildungsassistent, Zentrum für Kinderheilkunde, Justus-Liebig-Universität, Gießen
1995-00	Weiterbildungsassistent, Zentrum für Kinderheilkunde, Justus-Liebig-Universität, Gießen
06/2000	Prüfung zum Arzt für Kinderheilkunde und Jugendmedizin durch die LÄK Hessen
1990-2005	Ausbildung und Mitarbeit in der Arbeitsgruppe Diabetolgie/Endokrinologie bei Profs. Otten, Kiess, Holl und Wudy

Ausbildungsstipendium (DFG):

1993-95	Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada bei Prof. Paetkau und Prof. Pabst: Arbeiten an der Charakterisierung eines immunsuppressiven Faktors aus Colostrum.
06/2000-01/2005	Facharzt/Funktionsoberarzt im Zentrum für Kinderheilkunde und Jugendmedizin der Justus-Liebig-Universität, Gießen Schwerpunkte: Diabetologie und Endokrinologie,
07/2002-01/2005	zusätzlich Mitarbeit im Neugeborenen-Screening-Zentrum Hessen
seit 01.03.2005	Oberarzt für Allgemeine Pädiatrie, Endokrinologie, Diabetologie und Stoffwechsel an der Klinik für Kinder- und Jugendmedizin des Universitätsklinikums Jena, Friedrich-Schiller-Universität Jena
09/2005	Anerkennung zum Diabetologen DDG
02/2006	Zusatzbezeichnung Kinderendokrinologie/-diabetologie durch die LÄK Thüringen
04/2006	Weiterbildungsermächtigung für die Zusatzbezeichnung Kinderendokrinologie/-diabetologie durch die LÄK Thüringen
04/2006	Bestellung zum Prüfer für die Zusatzbezeichnung Kinderendokrinologie/-diabetologie durch die LÄK Thüringen
07/2006	Bestellung zum Prüfer für das Medizinische Staatsexamen durch das Landesprüfungsamt Thüringen
seit 2007	Co-Sprecher des Arbeitskreises der Thüringer Kinderdiabetologen
2011-2014	Mitglied des Vorstandes der Arbeitsgemeinschaft Pädiatrische Diabetologie (AGPD)
seit 07/2007	Reviewer für das Journal Pediatric Diabetes
seit 04/2012	Reviewer für das Journal Klinische Pädiatrie

seit 01/2013	Reviewer für das Journal Diabetes Care
01/2014	Co-Tagungsleiter der Tagung der Mitteldeutschen Arbeitsgemeinschaft für Pädiatrische Endokrinologie (MAPE) in Jena
11/2018	Co-Tagungsleiter der Jahrestagung für Pädiatrische Endokrinologie und Diabetologie (JAPED) in Weimar
01/2021	Co-Tagungsleiter der Tagung der Mitteldeutschen Arbeitsgemeinschaft für Pädiatrische Endokrinologie (MAPE) in Jena

11. Danksagung

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Die vorliegende Arbeit basiert auf Auswertungen des DPV-Registers. Das Register lebt von der zuverlässigen Eingabe der Daten vor Ort. Daher möchte ich allen Teilnehmern an der DPV-Initiative für ihre jahrelange Zusammenarbeit danken.

Die DPV-Initiative wäre ohne Prof. Dr. med. Reinhard Holl, Institut für Epidemiologie und medizinische Biometrie der Universität Ulm, nicht denkbar. Er war und ist mir stets ein extrem kompetenter und verlässlicher Ansprechpartner, insbesondere in der Planung und Durchführung von Auswertungen des DPV-Registers. Darüber hinaus hat er, als Oberarzt in der Kinderklinik Gießen, mein klinisches Wissen der pädiatrischen Diabetologie und Endokrinologie vertieft und mich in damals neue Therapieverfahren eingeführt. Ich danke ihm für jahrelange Unterstützung und die kontinuierliche Ermutigung.

Prof. Dr. med. Karl Otfried Schwab, Universitätskinderklinik Freiburg, danke ich für die konstruktiven, wertvollen Diskussionen und Anregungen, aus denen sich mehrere gemeinsame Projekte ergeben haben.

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12. Anhang

Dieser Arbeit zugrunde liegenden eigene Publikationen im Original:

1. Knerr I, Dost A, Lepler R, Raile K, Schober E, Rascher W, Holl RW. Tracking and prediction of arterial blood pressure from childhood to young adulthood in 868 patients with type 1 diabetes. Diabetes Care (2008) 31:726-727

2. Hermann JM, Rosenbauer J, Dost A, Steigleder-Schweiger C, Kiess W, Schöfl C, Holl RW. Seasonal variation in blood pressure in 162135 patients with type 1 or type 2 diabetes mellitus. J Clin Hypertens (Greenwich) (2016) 18;270-278

3. Dost A, Hofer S, Herbst A, Stachow R, Schober E, Müller UA, Holl RW. Factors contributing to terminal digital preference in 91 398 patients with diabetes mellitus in Germany and Austria: possible impact on therapeutic decisions. Diabetic Medicine (2009) 26:947-948

4. Dost A, Bechtold S, Fink K, Bonfig W, Wiemann D, Kapellen TM, Witsch M, Schwab KO, Holl RW. 2017 American academy of pediatrics clinical practice guideline: impact on prevalence of arterial hypertension in children and adolescents with type 1 diabetes. Diabetes Care (2020) 43:1311-1318

5. Dost A, Klinkert C, Kapellen T, Lemmer A, Naeke A, Grabert M, Kreuder J, Holl RW. Arterial hypertension determined by ambulatory blood pressure profiles. Diabetes Care (2008) 31:720-725

6. Dost A, Bechtold-Dalla Pozza S, Bollow E, Kovacic R, Vogel P, Feldhahn L, Schwab KO, Holl RW. Blood Pressure regulation determined by ambulatory blood pressure profiles in children and adolescents with type 1 diabetes mellitus: impact on diabetic complications. Ped Diabetes (2017) 18:874-882

7. Dost A, Molz E, Krebs A, Bechtold S, Kapellen T, Rohrer T, Raile K, Fritsch M, Schwab KO, Holl RW. Pulse pressure in children and adolescents with type 1 diabetes mellitus in Germany and Austria. Ped Diabetes (2014) 15:236-243

8. Rosengarten B, Dost A, Kaufmann A, Gortner L, Kaps M. Impaired cerebrovascular reactibility in type 1 diabetic children. Diabetes Care (2002) 25:408-409

Tracking and Prediction of Arterial Blood Pressure From Childhood to Young Adulthood in 868 Patients With Type 1 Diabetes

A multicenter longitudinal survey in Germany and Austria

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On behalf of the Diabetes Data Acquisition System for Prospective Surveillance (DPV) Scientific Initiative Germany and Austria

OBJECTIVE — Arterial blood pressure was followed in 868 patients with type 1 diabetes aged 6.0–19.9 years in 95 centers in Germany and Austria.

RESEARCH DESIGN AND METHODS — European blood pressure reference data for 28,043 children and adolescents were used with respect to age and sex. Data were stratified into three groups: prepubertal, pubertal, and postpubertal.

RESULTS — Up to 4% of the participants in the younger age-groups and 13.9% of the postpubertal patients exhibited blood pressure values >97th centile. Blood pressure levels correlated with A1C level and BMI *Z* score. Tracking of blood pressure revealed that children with elevated blood pressure had higher blood pressure in adolescence and young adulthood.

CONCLUSIONS — Patients with higher blood pressure in childhood showed elevated blood pressure later in life. We need to focus on the diagnosis of hypertension in children with type 1 diabetes and to study the efficacy of early intervention.

Diabetes Care 31:726–727, 2008

The objective of this survey was to follow arterial blood pressure and the prevalence of hypertension as a risk factor for cardiovascular disease (CVD) in a large cohort of young patients with type 1 diabetes. A total of 868 patients with type 1 diabetes from 6.0 to 19.9 years of age, who were treated in 95 Diabetes Centers and Pediatric Care Clinics in Germany and Austria, formed the study cohort for this report.

RESEARCH DESIGN AND METHODS

— At each of the first through fourth annual clinical visits, BMI (calculated as weight in kilograms divided by the square of height in meters), A1C, and blood pressure at rest were recorded. A1C measurements were standardized to the Diabetes Control and Complications Trial reference of 4.05–6.05% (1); blood pressure levels were measured on a single occasion in a relaxed, sitting position at the upper arm with proper cuff size using sphygmomanometer or semi-automated Dinamap (Critikon, Tampa, FL). Data were collected from 1977 to 2006 with informed consent according to the Declaration of Helsinki, using the diabetes data acquisition system for prospective surveillance (DPV), as previously described (2,3). Of 1,353 patients who had been screened, 962 were enrolled, and data sets from childhood to young adulthood were completed for 868 participants (96% Caucasian and 4% other ethnicity; age at diagnosis 5.9 ± 2.4 years; 432 female and 436 male). Patients with other diseases or permanent medication, including antihypertensive drugs, were excluded. European blood pressure reference data for 28,043 children and adolescents were used with respect to age and sex (4). German reference data for BMI, obtained from 17,275 female subjects and 17,147 male subjects in a comparable time span, were applied as reported earlier (3,5). Blood pressure and BMI values were derived using the least median of squares (LMS) Box-Cox power transformation method, which adjusts the distribution of the parameters for skewness and allows individual data to be expressed as SDS or *Z* score (6,7). Data were stratified in three groups according to age: 6.0–9.9 years (prepubertal), 10.0–15.9 years (pubertal), and 16.0–19.9 years (postpubertal). Statistical analysis was performed using Pearson correlation, Kruskal-Wallis test, and Wilcoxon's signed-rank test. A *P* value of <0.05 was considered significant. In addition, mixed multivariate models with systolic or diastolic blood pressure during adulthood as the dependent variable and blood pressure during childhood (6–9.9 years), sex, migration background, age at onset, current age, observation period, BMI, smoking status, and treatment center (random effect) as potential confounders were evaluated (SAS proc glimmix).

RESULTS

— Within these three age-groups, mean ± SD values for A1C were 7.4 ± 1.4, 7.9 ± 1.3, and 8.4 ± 1.7%; for BMI *Z* score 0.24 ± 0.73, 0.37 ± 0.78, and 0.60 ± 0.89; for systolic blood pressure (SBP) 106 ± 7, 116 ± 8, and 127 ±

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Abbreviations: CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

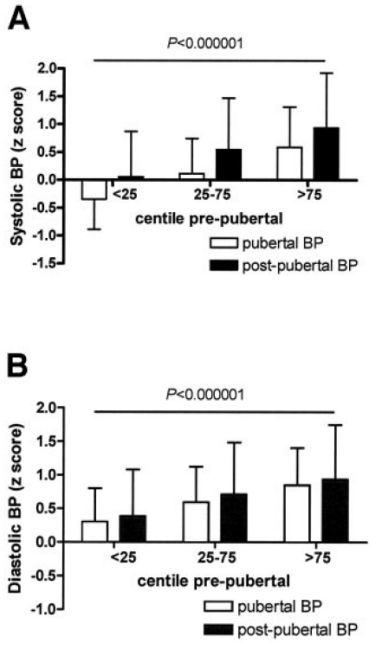

Figure 1—*Tracking of systolic* (A) *and diastolic* (B) *blood pressure (BP) from childhood to young adulthood in patients with type 1 diabetes. Prepubertal (6.0–9.9 years) blood pressure Z score quartiles are given together with mean pubertal (10.0–15.9 years) and postpubertal (16.0–19.9 years) blood pressure Z scores in 868 patients with type 1 diabetes (of whom 432 were female and 436 male). Patients were stratified according to their prepubertal blood pressure Z scores in three categories: blood pressure Z score <25th centile* (n = *217), 25th–75th centile* (n = *438), and >75th centile* (n = *213).*

11 mmHg; and for diastolic blood pressure (DPB) 65 ± 6, 68 ± 7, and 72 ± 7 mmHg. Mean blood pressure *Z* scores in the three age-groups increased with age (increases of 0.09, 0.12, and 0.52 for SBP, $P < 0.000001$, and 0.63 to 0.69 for DBP, $P < 0.0001$). In the prepubertal and pubertal age-groups, up to 4% of participants exhibited blood pressure values >97th centile. However, 13.9% of patients in the postpubertal group had blood pressure levels >97th centile. Blood pressure values correlated to A1C level and BMI *Z* score ($r = 0.2148$ and 0.3663, respectively; $P < 0.0001$).

A mixed model with adult blood pressure as the dependent variable and adjustment for sex, migration background, age at onset, current age, observation period, BMI, smoking status, and treatment center (random effect) revealed significant effects of childhood blood pressure (age 6–9.9 years) as evidence for tracking ($P < 0.000001$ for SBP and DBP) (Fig. 1). Elevation of childhood blood pressure by 1 SD increases adult blood pressure *Z* score by 0.43 (systolic) or 0.38 (diastolic).

CONCLUSIONS — In this survey, we followed blood pressure in patients with type 1 diabetes from childhood to young adulthood. Because patients with higher blood pressure in childhood, or even with hypertension, showed elevated blood pressure later in life, early intervention is feasible. The use of blood pressure determinations in patients with diabetes can, therefore, increase the prediction of a future CVD risk from childhood. It has been shown earlier, using ambulatory profiles of 24-h blood pressure, that daytime and nocturnal blood pressure is more pronounced in the course of type 1 diabetes compared with that in healthy control subjects (8). Although we can only imagine the beneficial effects of lowering blood pressure in the hypertensive individuals, preventing the development of atherosclerosis early in life is mandatory because morbidity and mortality of CVD are increased up to 10-fold in patients with type 1 diabetes (9). In our study, blood pressure values correlated significantly with A1C level and BMI *Z* score, which also exhibit adverse longitudinal changes in patients at risk for CVD (1,10). Similarly, progression of carotid intima-media thickness, a measure of atherosclerosis, is strongly associated with age, blood pressure, and A1C in subjects with type 1 diabetes (1).

Moreover, by showing the advantages of having lower blood pressure levels early in life on blood pressure levels in young adulthood, this study provides additional evidence for the importance of monitoring blood pressure as a risk factor in young patients with type 1 diabetes. In conclusion, we need to focus on the early detection of hypertension in children with type 1 diabetes and to study the efficacy of treatment in affected individuals early in life.

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Seasonal Variation in Blood Pressure in 162,135 Patients With Type 1 or Type 2 Diabetes Mellitus

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Seasonal variation in blood pressure (BP) has been observed in different populations. However, only few studies have focused on BP seasonality in diabetic patients. This study examined the seasonal patterns in BP in 62,589 patients with type 1 diabetes mellitus (T1DM) and in 99,546 patients with type 2 diabetes mellitus (T2DM) from the German/Austrian Diabetes Follow-up Registry. Adjusted mean BP values revealed seasonal cycles of 12 months, with higher BP in colder months. Using harmonic regression models, the estimated systolic BP difference throughout the year was 2.28/2.48 mm Hg in T1DM/T2DM (both $P<.001$). Interestingly, seasonal variation in diastolic BP was larger in T1DM than in T2DM (1.24/0.64 mm Hg, $P<.001$). A sex difference was observed in T1DM only, while age differences occurred in both types of diabetes. Correlations between BP and potentially related factors such as outdoor temperature indicated that reasons underlying BP seasonality are likely to be complex and vary by subgroup. *J Clin Hypertens (Greenwich).* 2016;18:270–278. © 2015 Wiley Periodicals, Inc.

Hypertension is a common comorbidity in both type 2 (T2DM) and type 1 (T1DM) diabetes mellitus. Patients with T2DM may have hypertension at diabetes onset, whereas patients with T1DM usually develop hypertension as a result of nephropathy, but also weight gain and arterial stiffness over the years. Depending on age, 20% to 60% of T2DM patients and up to 30% of T1DM patients are affected by hypertension.[1] Since high blood pressure (BP) is one of the main risk factors for cardiovascular events and microvascular complications,[1] current European guidelines (2013 European Society of Hypertension/European Society of Cardiology [ESH/ESC] guidelines for the management of arterial hypertension) recommend a systolic BP (SBP) <140 mm Hg and a diastolic blood pressure (DBP) <85 mm Hg for patients with diabetes.[2]

Various epidemiologic studies observed that BP levels vary by season.[3] Higher BP during cold seasons has been described in both normotensive[4,5] and hypertensive[4,6–8] patients as well as in children and adolescents[9,10] and in adults.[11–13] However, only few studies focused on seasonal changes of BP in diabetic patients.[14,15] Thus, it remains unclear whether this cyclic behavior observed in various populations also applies to diabetic patients.

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The objective of the present analysis was to investigate whether and to what extent seasonal variation in BP exists in T1DM and T2DM patients. In addition, we examined whether seasonal patterns differ between age strata, sex, and type of diabetes. Knowledge of the extent of seasonality in BP in diabetic patients could optimize patient care and patient-self management in order to achieve BP targets, since seasonality may affect the classification of patients as normotensive or hypertensive. Furthermore, seasonal patterns in BP should be taken into consideration when setting up clinical trials.

PATIENTS AND METHODS

The DPV Registry

The Diabetes Follow-up Registry (DPV) is a German/Austrian standardized computer-based prospective observational multicenter survey for all types of diabetes. Data are collected longitudinally at 377 diabetes centers (352 in Germany and 25 in Austria, March 2013) during routine patient care and documented in an electronic health record. Anonymized data are transmitted semiannually to the University of Ulm for central validation. Data are reported back to the diabetes centers for correction of implausible and missing data.[16] The database comprises demographic and anthropometric characteristics as well as diabetes-related variables covering therapy, comorbidities, and disease outcomes.[17] The ethics committee of the medical faculty of the University of Ulm and the institutional review boards at the participating diabetes centers approved data collection.

Study Cohort

For the present analysis, all SBP and DBP values measured between January 2003 and December 2012 were extracted from DPV. According to the ESH/ESC guidelines for the management of arterial hypertension, measurements were performed by trained personnel during routine care in pediatric or internal practices using validated auscultatory semiautomatic or oscillometric sphygmomanometers. BP was measured at the heart level in a sitting position after several minutes of rest with a bladder suitable for individual upper arm width. BP measurement error was reduced by three consecutive BP readings per occasion.[2,18] SBP (DBP) values outside of the range of 50–300 (30–250) mm Hg were considered implausible and therefore excluded. If a patient had more than one BP measurement in a single month, the median value was used for this month. Patients treated with antihypertensive medication (7.6% of T1DM patients, 42% of T2DM patients) were excluded in order to avoid bias.

Altogether, 732,179 BP values of 62,589 T1DM patients and 254,639 BP values of 99,546 T2DM patients were analyzed (Figure 1). For subgroup comparisons, BP values were stratified according to sex, age (<10, 10<20, 20<30, 30<40, 40<50, ≥50 years for T1DM; <40, 40<50, 50<60, 60<70, 70<80, ≥80 years for T2DM), duration of diabetes (<5, 5<10, 10<20, 20<30, ≥30 years), and presence of hypertension (never; at some but not all of the patient's visits, at each of the patient's visits). Hypertension was determined according to European guidelines (>140/85 mm Hg)[2] for adults and according to the German KiGGS reference values for pediatric patients younger than 18 years (>95th percentile).[19] German mean monthly outdoor temperature and sunshine duration in 2003–2012 were extracted from Germany's National Meteorological Service.[20] These data were used as parametric measures of seasonality attributable to environmental variation. For 2009–2012, an index of consultations due to acute respiratory disorders, weekly released by the Robert Koch Institute,[21] was aggregated per month and used as a proxy for the frequency of acute respiratory disorders.

Statistical Methods

All statistical analyses were performed using SAS 9.4 (Statistical Analysis Software, SAS Institute Inc, Cary, NC). *P* values <.05 of two-sided tests were considered statistically significant.

In order to consider the fact that some patients had several visits within the 10-year period, linear mixed models were applied to compute monthly aggregated BP values. Least-square means for each of the 120 months of the 10-year period, adjusted for sex, age group, duration of diabetes group, and patient-specific random effect, were calculated and plotted separately for T1DM and T2DM.

Time series can be decomposed in long-term trend, seasonal variation, and irregular fluctuation. Since we were only interested in seasonal patterns, we removed the long-term effect (year of observation) based on a linear mixed model with SBP or DBP as dependent variables and year in categories as fixed effect. A patient-specific random effect with unstructured covariance matrix was included to account for repeated measurements in patients. The resulting residuals were extracted and used to model seasonal patterns.

Seasonal patterns were examined using harmonic regression models (SAS procedure NLMIXED). This approach allows estimating amplitude and phase shift of seasonal variation. Time dependence of the year-adjusted SBP and DBP values was modelled by sine and cosine terms.[22,23] Nonlinear mixed regression models additionally included the potential confounding variables of age, sex, and duration of diabetes (in categories) and patient-specific random effects with unstructured covariance matrix:

$$\begin{aligned}\text{Year-adjusted BP} = {} & \beta_0 + \beta_S \cdot \sin\left(\frac{2\pi}{12} \cdot \text{month}\right) \\ & + \beta_C \cos\left(\frac{2\pi}{12}\text{month}\right) + \beta_{\text{sex}} \cdot \text{sex} \\ & + \sum_i (\beta_{\text{agegroup}_i} \cdot \text{agegroup}_i) \\ & + \sum_i (\beta_{\text{durationgroup}_j} \cdot \text{durationgroup}_j) \\ & + \text{patient specific random effect} + \varepsilon\end{aligned}$$

The resulting coefficients of the sine and cosine term (β_S and β_C) allowed to estimate the amplitude $A = (\beta_S^2 + \beta_C^2)^{1/2}$ and the phase $\rho = \arctan\left(\frac{\beta_S}{\beta_C}\right)$ of the seasonal pattern.[22] Corresponding 95% confidence limits (CLs; lower CL–upper CL) were computed by the Delta method.[24] We used first-order interaction terms between the trigonometric functions of month and sex, age, or duration of diabetes to compare amplitude and phase shift between subgroups. Outdoor temperature was modelled in a separate harmonic regression model to compare the estimated seasonal patterns of BP and temperature.

Spearman's rank correlation coefficient (r_s) with 95% confidence interval was calculated to assess the association between monthly aggregated BP values, adjusted for year of observation, age, sex, and duration of diabetes, and potentially related influencing factors.

RESULTS

Patient characteristics can be found in Table I. A total of 52.7% of the T1DM patients and 51.8% of the T2DM patients were men. In T1DM, an average of 11.7 BP measurements (range 1–96 BP values) per patient were available, with most of the measurements obtained from patients aged 10<20 years (62.9%). A total of 25%, 8%, 5%, 21%, and 41% of all T1DM patients had 1, 2, 3, 4–10, and >10 BP measurements, respectively. The mean time between measurements was 4.3±3.6 months. In T2DM, an average of 2.6 BP measurements (range 1–53

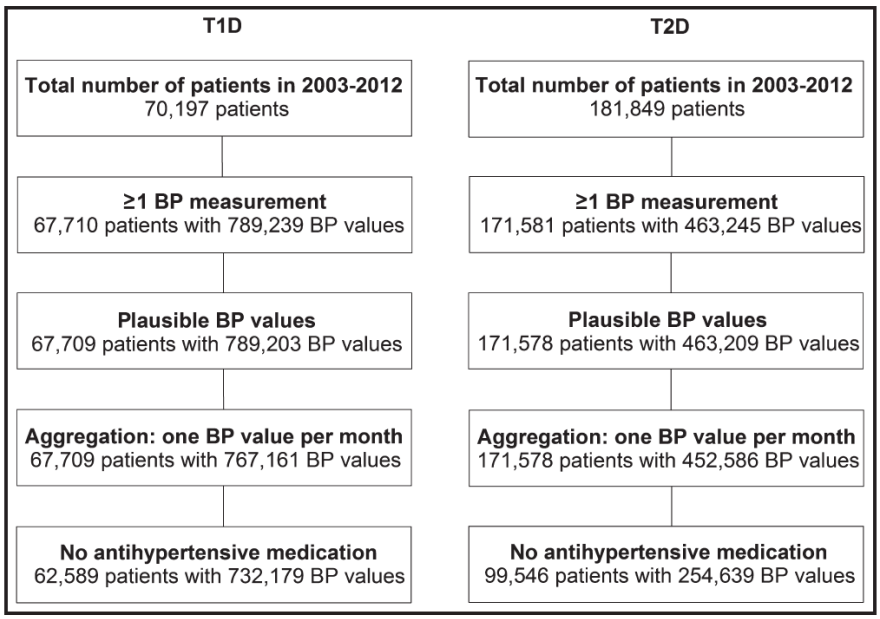

FIGURE 1. Selection of the study population. T1D indicates type 1 diabetes; T2D, type 2 diabetes; BP, blood pressure.

BP values) per patient were available, with most of the values obtained from patients 60<70 years and 70<80 years of age (each 29.1%). A total of 70%, 13%, 4%, 2%, and 11% of all T2DM patients had 1, 2, 3, 4, and >4 BP measurements, respectively. Mean duration between two BP measurements was 7.9±4.7 months. A descriptive patient summary for each of the 10 years analyzed can be found in Table SI.

Mean monthly BP, adjusted for age, sex, and duration of diabetes, indicated sinusoidal patterns for both T1DM and T2DM patients, with peaks in winter months and nadirs in summer months (Figure 2). BP values were higher and fluctuated more in T2DM compared with T1DM patients. In T1DM, subgroup analyses revealed lower BP levels in younger patients and in patients with shorter duration of diabetes, whereas the patterns observed in T2DM seemed to be less clear (not shown).

We used sine and cosine functions with 12-month periods to model BP in harmonic regression. Figure 3 depicts the yearly seasonal patterns for both types of diabetes, estimated by a harmonic regression model, with adjustments for sex, age, and duration of diabetes. All four BP patterns are inversely related to the seasonal behavior of the German outdoor temperature (Figure 3) and duration of sunshine (not shown).

Comparison of T1DM and T2DM

The estimated SBP amplitude was 1.14 (1.11–1.18) mm Hg (P<.001) in T1DM patients and 1.24 (1.17–1.31) mm Hg (P<.001) in T2DM patients (Table II), ie, an estimated difference of 2.28 mm Hg and 2.48 mm Hg, respectively, between summer and winter. The estimated overall difference in SBP amplitude between T1DM and T2DM was significant (−0.10 [−0.18 to −0.02] mm Hg, P=.0107). Stratification by sex revealed that the difference remained significant in men (difference −0.29 [−0.40 to 0.18] mm Hg, P<.001), but not in women (difference 0.08 [−0.03 to 0.19] mm Hg, P=.1621).

In contrast to SBP, seasonal variation in DBP was significantly stronger (P<.001) in T1DM patients than in T2DM patients (Table II). The association was confirmed for both men and women. Due to this finding, we analyzed the variation of peripheral pulse pressure (PP) (Table II). Overall, PP amplitude was significantly lower in T1DM than in T2DM (0.52 [0.49–0.56] v. 0.94 [0.88–1.00]; difference: −0.42 [−0.49 to −0.35], all P<.001), with this difference being more pronounced in men than in women.

In agreement with the time series plots, the lowest model-based SBP estimates were observed in summer months (T1DM: June 28th [26th–29th]; T2DM: July 8th [4th–12th]) and the highest values in winter months. Minimum DBP values were observed in June (T1DM: June 22nd [20th–25th]; T2DM: June 13th [3rd–22nd]). According to this, seasonal behavior of SBP was more simultaneous with DBP in T1DM patients than in T2DM patients. Overall, the phase shift difference between T1DM and T2DM patients was significant for both SBP (P<.001) and DBP (P=.011).

Subgroup Comparisons in Patients With T1DM

Subgroup comparisons were conducted to reveal differences in amplitude and phase shift between sex, age

TABLE I. Patient Characteristics and Distribution of BP Values

		T1DM		T2DM
Patients, No.		62,589		99,546
Men, %		52.7		51.8
Age at onset, y		10.2 (6.0–15.1)		57.8 (48.0–67.5)
Normotensive, %[a]		35.8		42.8
Hypertensive, %[a]		9.5		39.7
BP values, No.		732,179		254,639
BP values stratified by sex, %	Male	52.0	Male	51.6
BP values stratified by age group, %	<10 y	25.7		
	10≤20 y	62.9		
	20≤30 y	3.0		
	30≤40 y	2.2	<40 y	4.3
	40≤50 y	2.5	40≤50 y	8.1
	≥50 y	3.7	50≤60 y	17.9
			60≤70 y	29.1
			70≤80 y	29.1
			≥80 y	11.5
BP values stratified by duration of diabetes group, %	<5 y	56.4	<5 y	32.4
	5≤10 y	27.4	5≤10 y	24.9
	10≤20 y	12.4	10≤20 y	28.9
	20≤30 y	2.1	20≤30 y	9.8
	≥30 y	1.7	≥30 y	4.0

Abbreviations: BP, blood pressure; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. Data shown are numbers of patients, median with upper and lower quartiles, or percentages. [a]At each of the patient's visits.

groups, duration of diabetes groups, and presence of hypertension (Figure 4). Within T1DM patients, age- and duration-adjusted BP amplitude was higher in women than in men (SBP: 1.27 vs 1.03, DBP: 0.69 vs 0.57, both $P<.001$). Accordingly, PP amplitude was also significantly higher in women (0.11 [0.05–0.18], $P<.001$). SBP amplitude was highest in patients 50 years and older. Children and adolescents (younger than 20 years) were more sensitive to seasonal DBP changes than patients in middle age. Amplitude of SBP was nearly similar at all durations of diabetes, but DBP amplitude decreased with increasing duration of diabetes. Patients categorized as hypertensive (BP ≥140/85 mm Hg for adults, >95th percentile of the German KiGGS reference values for pediatric patients younger than 18 years) at none/each of their visits had the lowest/highest BP amplitude. There were no seasonal BP phase shifts between sexes, age groups, or duration of diabetes groups (all $P>.05$).

Subgroup Comparisons in Patients With T2DM

In contrast to T1DM patients, no significant sex differences in BP amplitudes were observed in T2DM patients (Figure 4, SBP: $P=.223$; DBP: $P=.988$; PP: $P=.109$). In order to examine premenopausal and postmenopausal women separately, we repeated the analysis stratified by younger than 50 and 50 years and older. Sex differences remained insignificant in both age groups. Patients aged 60<70 years had significantly stronger seasonal variation in both SBP and DBP than all other age groups (all $P<.05$) except patients younger than 40, whereas duration of diabetes had no effect on BP amplitude. Patients with hypertension at some/each of their visits had significantly higher SBP variation than patients without hypertension (both $P<.001$). There were no significant time shifts in seasonal BP phases between sexes, age, or duration groups (all $P>.05$).

As a result of the seasonal variation in BP, the proportion of patients classified as hypertensive varied throughout the year. In T1DM patients, hypertension was least prevalent in July (23.3%) and most prevalent in February (30.3%). In T2DM patients, the proportion of hypertension varied between 44.5% in July and 50.3% in March. We additionally examined the proportion of hypertension in summer (June to August) and winter (December to February) among patients who had BP values in both seasons. In both types of diabetes, hypertension was less prevalent in summer than in winter months (T1DM: 23.5% vs 31.1%, T2DM: 51.7% vs 55.8%).

Seasonal Variation in BP and Potentially Related Factors

From 2003 to 2012, German mean monthly outdoor temperature was highest in July (18.3°C) and lowest in January (0.5°C). Mean sunshine duration was longest in June (223 hours) and shortest in December (43 hours). Spearman's rank correlation (Table III) indicated a strong inverse correlation between monthly aggregated adjusted BP and outdoor temperature or sunshine duration (all $P<.001$). Correlation coefficients were lowest for DBP in T2DM patients. The aggregated

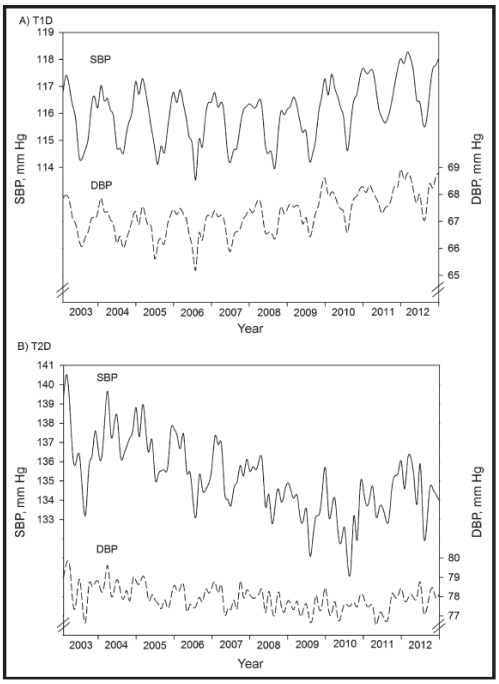

FIGURE 2. Systolic blood pressure (SBP) and SBP time series for patients with type 1 diabetes (T1D) and type 2 diabetes (T2D). Monthly aggregated SBP (solid line) and diastolic blood pressure (DBP) values (dashed line), adjusted for age, sex, and duration of diabetes in (A) T1D patients (A) and T2D patients (B). Years 2003–2012. Note the different axis scales.

index of consultations because of acute respiratory diseases was highest in February and lowest in July, with some years having a second or third period with high values. Nevertheless, correlation coefficients indicated a strong positive association between respiratory diseases and BP (all $P<.001$).

Since German mean temperature may not be fully representative for all participating diabetes centers, we ran harmonic regression models (adjusted for age, sex, and duration of diabetes) in order to compare BP amplitudes between South-Eastern Germany (continental climate) and North-Western Germany (lower variation in temperature throughout the year due to maritime influence). Neither SPB nor DBP amplitude differed significantly between the two regions for both types of diabetes (SBP difference within T1DM patients: 0.01 [−0.06 to 0.08] mm Hg, $P=.80$; SBP difference within T2DM patients: 0.15 [−0.03 to 0.33] mm Hg, $P=.10$).

Patients Taking Antihypertensive Medication

Those 5120 patients with T1DM and 72,032 patients with T2DM that were excluded in the previous analyses for taking antihypertensive medication (Figure 1) were analyzed using separate harmonic regression models, adjusted for age, sex, and duration of diabetes. In T1DM, patients with antihypertensive medication had an estimated overall SBP amplitude of 0.98 (0.64–1.32) mm Hg ($P<.001$). DBP amplitude was estimated to be 0.47 (0.27–0.68) mm Hg ($P<.001$). In T2DM patients taking antihypertensive medication, SBP amplitude was 0.84 (0.71–0.98) mm Hg and DBP amplitude was 0.27 (0.19–0.34) mm Hg (both $P<.001$),

DISCUSSION

In this large observational study based on more than 160,000 patients, BP varied seasonally in both T1DM and T2DM patients, with higher values in winter months and lower values in summer months. Our findings are in line with results from Liang and

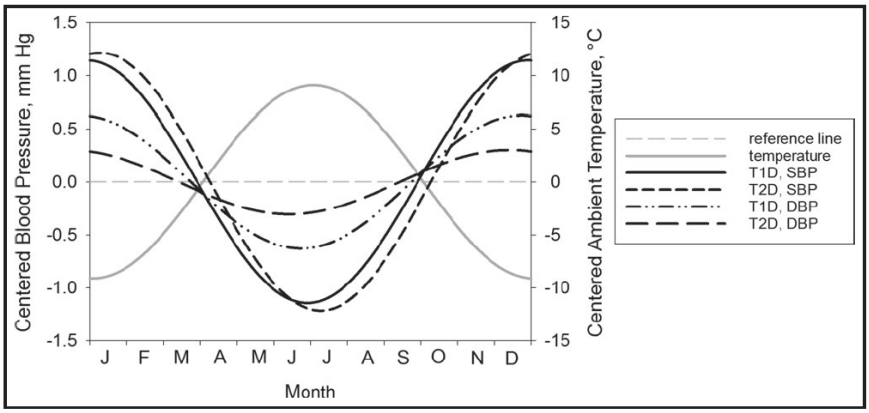

FIGURE 3. Seasonal pattern in systolic blood pressure (SBP) and diastolic blood pressure (DBP), estimated by harmonic regression models (adjusted for sex, age, and duration of diabetes). SBP in type 1 diabetes (T1D): solid black line; SBP in type 2 diabetes (T2D): short dashed line; DBP in T1D: dash dotted line; DBP in T2D: long dashed line; outdoor temperature: solid grey line. Reference line (grey dashed line) indicates no seasonal variation.

TABLE II. Estimated SBP and DBP Amplitudes

		T1DM		T2DM		Difference T1DM vs T2DM	
		Amplitude	*P* Value	Amplitude	*P* Value	Amplitude	*P* Value
SBP	Overall[a]	1.14 (1.11–1.18)	<.001	1.24 (1.17–1.31)	<.001	−0.10 (−0.18 to −0.02)	.011
	Female[b]	1.26 (1.20–1.31)	<.001	1.18 (1.08–1.28)	<.001	0.08 (−0.03 to 0.19)	.162
	Male[b]	1.02 (0.97–1.07)	<.001	1.31 (1.21–1.41)	<.001	−0.29 (−0.40 to −0.18)	<.001
DBP	Overall[a]	0.62 (0.60–0.65)	<.001	0.32 (0.27–0.37)	<.001	0.30 (0.25 to 0.36)	<.001
	Female[b]	0.68 (0.65–0.72)	<.001	0.32 (0.25–0.39]	<.001	0.37 (0.29 to 0.45)	<.001
	Male[b]	0.57 (0.53–0.60)	<.001	0.33 (0.26–0.39)	<.001	0.24 (0.17 to 0.32)	<.001
PP	Overall[a]	0.52 (0.49–0.56)	<.001	0.94 (0.88–1.00)	<.001	−0.42 (−0.49 to −0.35)	<.001
	Female[b]	0.58 (0.53–0.63)	<.001	0.87 (0.78–0.96)	<.001	−0.29 (−0.40 to −0.19)	<.001
	Male[b]	0.47 (0.42–0.52)	<.001	1.01 (0.92–1.10)	<.001	−0.54 (−0.64 to −0.44)	<.001

Abbreviations: DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. Amplitudes estimated by harmonic regression model based on blood pressure (BP) values adjusted for long-term trends (year of measurement). Overall summer-winter difference is twice the amplitude. [a]Adjusted for age, sex, and duration of diabetes. [b]Adjusted for age and duration of diabetes.

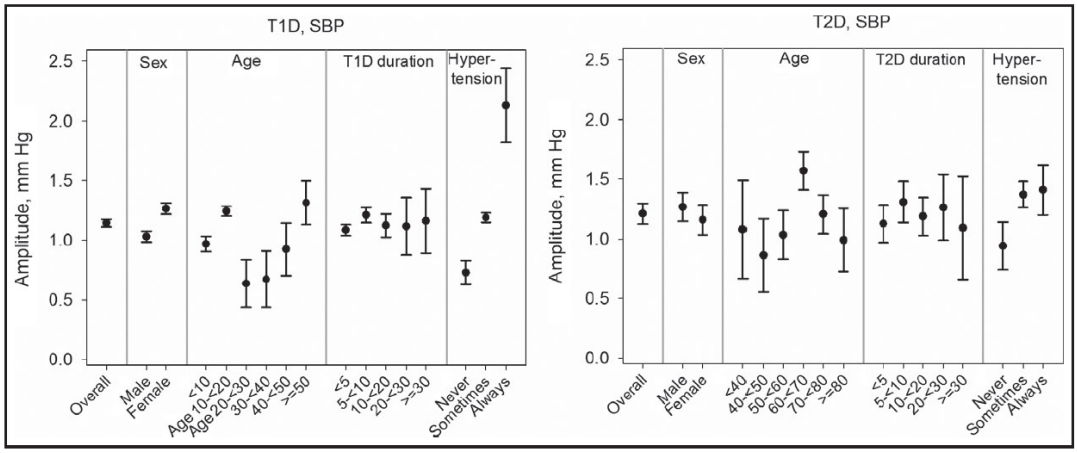

FIGURE 4. Seasonal pattern in systolic blood pressure (SBP) and diastolic blood pressure (DBP) by subgroup. SBP amplitudes with 95% confidence interval for type 1 diabetes (T1D) and type 2 diabetes (T2D), adjusted for sex and/or age and/or duration of diabetes. Overall summer-winter changes are twice the amplitudes.

TABLE III. Spearman Correlations Between BP and Potentially Influencing Factors

	T1DM		T2DM	
	SBP	DBP	SBP	DBP
Outdoor temperature, °C	−0.875 (−0.911 to −0.825)	−0.864 (−0.903 to −0.810)	−0.802 (−0.858 to −0.727)	−0.476 (−0.603 to −0.324)
Sunshine duration, h	−0.792 (−0.851 to −0.715)	−0.800 (−0.857 to −0.725)	−0.658 (−0.749 to −0.543)	−0.499 (−0.623 to −0.352)
Index of consultations[a]	0.849 (0.745–0.913)	0.792 (0.656–0.879)	0.726 (0.556–0.837)	0.411 (0.143–0.622)

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. [a]Due to acute respiratory disorders. All *P*<.001. Correlations are based on monthly aggregated blood pressure (BP) values, adjusted for year of observation, age, sex, and duration of diabetes.

colleagues,[15] who analyzed seasonal variation in BP in a Taiwanese T2DM cohort with a mean age of 66.7 years. They found that both SBP and DBP were inversely correlated with the average monthly outdoor temperature, resulting in higher BP values in winter. In contrast, Wada and colleagues[14] observed seasonal variation in SBP but not DBP in 430 Japanese patients with T2DM and early nephropathy (mean age

64.8 years). However, their negative finding could be due to the smaller sample size and the different methodical approach: They divided 1 year into four seasons instead of 12 months. In fact, we also observed weaker seasonality and more irregular fluctuation for DBP than for SBP in T2DM patients.

Interestingly, we observed no sex differences in T2DM, whereas seasonality was stronger in women than in men with T1DM. Sex differences in BP seasonality still seem controversial. Some recent studies based on various cohorts have observed no significant sex effect,[6,12] whereas others have reported either higher BP changes in men[7] or in women,[11,25,26] or sex effects depending on age.[27] In pubertal girls, higher insulin resistance caused by increased estrogen levels might be a risk factor for arterial stiffness and therefore explain sex differences in BP seasonality in T1DM. However, in T2DM patients, stratification by premenopausal and postmenopausal women did not alter our results. Moreover, in contrast to other studies,[3,13,25] advancing age was not clearly associated with higher summer-winter differences of BP. Children and adolescents with T1DM as well as T2DM patients aged 60<70 years were more sensitive to BP changes than expected when assuming a monotonically increasing association. The latter finding is in line with an Israeli study in elderly patients with hypertension that observed stronger BP seasonality in patients 65 to 75 years compared with older patients.[6] The former finding may be explained by the fact that most studies are limited to either children and adolescents or to adults, and therefore inhibit a comparison in a wider age range. Patients categorized as hypertensive had higher BP variation than normotensive patients.

Additional analyses indicated that both T1DM and T2DM patients taking antihypertensive medication have lower BP variation throughout the year than patients not taking antihypertensive medication. It could be supposed that patients taking antihypertensives have better control of their BP and slightly adjust their medication throughout the year and therefore have lower seasonal BP variation.

Potential Reasons for BP Seasonality

Estimated overall SBP/DBP changes from summer to winter were 2.28/1.24 mm Hg in T1DM patients and 2.48/0.64 mm Hg in T2DM patients, at differences in a mean outdoor temperature of approximately 18°C. These changes were lower than those reported in Japanese (approximately 25°C yearly temperature differences),[28–30] Taiwanese (subtropical monsoon climate,[15] Chinese (various temperate zones),[13] and Iraqi (hot summer season)[31] adult study cohorts, but comparable to results observed in studies with similar climatic conditions.[4,10,26] A German study in both healthy and sick children and adolescents aged 3 to 21 years reported an SBP decrease of 0.12 mm Hg with each 1°C increase in outdoor temperature,[10] which corresponds to our estimation. It was previously proposed that, paradoxically, seasonal BP differences are lower in countries with cold winters than in countries with mild winters,[32] possibly attributable to better thermal efficiency standards leading to more constant indoor temperature.[33] It is still under discussion to what extent indoor and outdoor temperature affects BP.[32,34]

Nevertheless, BP seasonality is likely to be a complex phenomenon, with various factors influencing summer to winter changes. Several studies have suggested that seasonal BP changes could be modulated by changes in the serum/blood concentration of 25-hydroxyvitamin D3, since the shorter duration of sunshine in winter months may cause a deficiency in vitamin D.[35] In our study, we found strong inverse correlations between BP and hours of sunlight. However, patients likely spend plenty of time indoors. Therefore, sunshine duration should be considered as a parametric measure of environmental seasonality rather than a measure of the exposure of patients to sunlight alone. Our analyses suggested that the seasonal pattern of BP was not simultaneous with the prevalence of acute respiratory infections, indicating that BP seasonality is likely to be affected by further physiologic markers as well as by lifestyle and environmental factors. A large Austrian study revealed decreased body mass index, total cholesterol, and triglyceride levels in summer months compared with winter months in different age groups, both for men and women.[27] Holiday season, increased physical activity, and decreased dietary fat intake could contribute to lower BP values in summer as well.[36,37] Choi and colleagues[38] observed a seasonal variation for the association between ambient air pollution and BP. Our observation of amplitude and phase shift differences between type of diabetes, sex, or age groups suggest that the reasons for BP seasonality differ between those groups.

Clinical Relevance

The randomized controlled Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial[39] investigating the effect of BP-lowering therapy in T2DM patients (mean baseline age 66 years) found an average SBP/DBP lowering of 5.6/2.2 mm Hg over the duration of follow-up (mean 4.3 years). The seasonal SBP/DBP differences we observed in patients with T2DM were about one half to one third of the BP intervention effect observed in the ADVANCE study. Moreover, the percentage of patients classified as hypertensive (BP >140/85 mm Hg) varied throughout the year. Therefore, BP seasonality should be considered when antihypertensive medication is adjusted, particularly in high-risk patients and in countries that exhibit high summer to winter BP changes.[40] Knowledge of BP seasonality in addition to accurate BP measurement and avoidance of terminal digit preference reduces misdiagnoses and prevents unnecessary costs as well as potential consequences of untreated hypertension.[41] Patients should be trained in self-monitoring of BP and in

talking with their physician about adjusting the dose of their medication to achieve target BP values.[42] Furthermore, BP differences throughout the year should be taken into account when conducting clinical trials.

Strengths and Limitations of the Study

Studies focusing on BP seasonality in diabetic patients are rare. Our study included both T1DM and T2DM patients and contrasted seasonal patterns of both types of diabetes. The large sample size permitted the analysis of monthly data instead of four seasons. In addition, age and sex subgroup comparisons could be performed. However, we acknowledge some limitations of our study. Although adherence to guidelines is mandatory for reimbursement in Germany, BP measurements are likely to have varied between patients. We have no information about the exact time of day BP was measured, and whether the measurement was taken by a nurse, a technician, or a physician. Furthermore, we considered only German mean temperature and duration of sunshine rather than patient-level data. These may not fully represent all participating diabetes centers and patients. Nevertheless, climatic distinctions within Germany are rather small and therefore unlikely to significantly change results. While many pediatric T1DM patients were continuously documented over several years, patients with T2DM more often had shorter observation times and therefore lower numbers of BP measurements. Thus, the patient composition regarding sex, age, and duration of diabetes varied slightly over the 10-year period studied. We addressed this issue by adjustments. In addition to amplitudes, we reported BP phases as calendar dates to further examine differences in seasonal patterns. However, especially in T1DM patients, BP time series exhibit dents in January or February, which could not be modelled or explained by ambient temperature, sunshine duration, or acute respiratory infections.

CONCLUSIONS

We found clear BP seasonality in both T1DM and T2DM patients. The range of seasonal changes varied among age groups in both types of diabetes, while sex differences were observed in T1DM only.

Disclosures: The authors declare that there are no conflicts of interest relevant to this article.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Patient characteristics stratified by year

Letters: Original Observation

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Factors contributing to terminal digital preference in 91 398 patients with diabetes mellitus in Germany and Austria: possible impact on therapeutic decisions

Correct blood pressure measurement is crucial for the appropriate management of diabetes. The accuracy of blood pressure (BP) readings may be negatively influenced by systematic errors such as terminal digital preference (TDP)—an observer's tendency to record BP values using particular digits. Considering that TDP can interfere with diabetes treatment, the German-Austrian bi-national diabetes databank DPV was used to study factors contributing to its practice.

In total, 580 578 BP readings from 91 398 patients (51.7% male) were documented at 286 centres participating in the DPV initiative. There were 49 4301 measurements in 47 373 patients with Type 1 diabetes and 86 277 in 44 025 patients with Type 2 diabetes.

Total TDP for the digits '0' and '5' was 55 ± 50% (mean ± SD) (Figure 1). These were documented more frequently in small treatment and rehabilitation or non-academic and outpatient centres. Lower TDP was practised in paediatric or Type 1 diabetes treatment centres in Austria and West Germany compared with the centres in East Germany. During the last 14 years, TDP increased with age and declined in Type 1 diabetes (all χ^2-test, $P < 0.0001$) but not in Type 2 diabetes management centres.

Mean systolic blood pressure was significantly reduced in centres positive for TDP by a value of 3.6 ± 0.7 mmHg (TDP ≥ 30%) ($P < 0.0001$), while mean diastolic BP was increased by 2.2 ± 0.8 mmHg ($P = 0.004$). In centres where Type 2 diabetic patients were treated, this difference is even more striking for systolic blood pressure (SBP) (−7.0 ± 2.0 mmHg on average, $P = 0.0007$). However, mean diastolic blood pressure (DBP) did not significantly differ between treatment centres (2.9 ± 2.1 mmHg, $P = 0.17$, all χ^2-test).

TDP is common practice in German diabetes treatment centres, with marked inter-centre differences depending on the type of diabetes managed. In contrast, regional differences indicate that paediatric centres are less likely to practise TDP. It is worth noting that the Type 1 diabetic patients documented in DPV are mainly paediatric or still receive care at paediatric diabetes centres.

The DPV was initially developed to meet the needs of paediatric diabetes treatment centres and is widely used by paediatric diabetologists in Germany. Thus, the documentation of paediatric patients with Type 1 diabetes is extensive and encompasses an estimated 70% [1] of patients in this group, most of whom are treated at rather small and comprehensive but well-equipped specialized centres.

The decrease in TDP observed during the last 13 years is mainly as a result of improved BP measurements at Type 1 diabetes centres. Although DPV is used at many of these centres, information on the BP device has so far not been documented. However, it can be assumed that, in hospital associated centres in particular, sphygmomanometric devices have been replaced by other automated BP measuring systems.

In our investigation, Austrian centres had no TDP and the frequency of the digits '0' and '5' was exactly 20%, as expected. Therefore, in Austria BP reading is better than in Germany. However, only five big paediatric centres in Austria presently participate in DPV, three of which are paediatric departments of university teaching hospitals, equipped with automatic BP devices.

Centres positive for TDP recorded significantly lower systolic blood pressure readings for patients with Type 1 and Type 2 diabetes. Based on this, a relevant number of patients who would have received anti-hypertensive medication in a TDP-negative centre were not treated.

Similarly, higher TDP but not DBP levels are associated with small but significantly lower SBP measurements in US practices [2]. Although the data from the USA, Germany and Austria suggest that TDP has significant implications on the assessment and treatment of high SBP, these investigations fail to establish if high TDP is causally related to lower SBP measurements.

Our data confirm the findings of Nietert *et al.*, which state that patients' DBP measurements were not related to TDP levels in practice [2]. Hitherto, we cannot explain the different associations between TDP, SBP and DBP. Nietert *et al.* also estimate that in an average practice of 1000 patients with a 50% TDP rate, approximately 68 patients who should be prescribed an anti-hypertensive drug currently go untreated because TDP is practised [2].

According to Wingfield *et al.*, mortality was higher in people with blood pressure recorded just below a treatment threshold, whose BP was presumably higher and who would have benefited from anti-hypertensive medication [3]. Considering that TDP

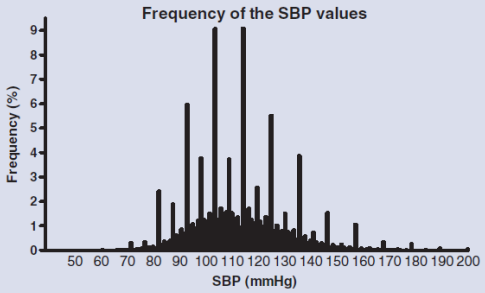

FIGURE 1 Frequency of the SBP values.

is associated with inadequate BP management, appropriate reading should be fostered through the training of academic and non-academic employees as well as by using automated BP devices.

Competing interests

Nothing to declare.

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Deterioration of glycaemic control associated with anti-insulin antibodies likely induced by health supplements

Anti-insulin antibodies generated in insulin-treated individuals with diabetes sometimes induce instability in glycaemic control or insulin resistance [1–4]. Such antibodies can also arise in individuals who have not previously received insulin and can provoke hypoglycaemia. This latter pathological condition, termed insulin autoimmune syndrome (IAS), is thought to be attributable to drug-related autoimmunity [5,6]. Various drugs, including health supplements, have been associated with the induction of IAS [5,6]. We here describe a Type 2 diabetic patient whose control deteriorated, associated with the development of anti-insulin antibodies possibly induced by the ingestion of health supplements.

A 65-year-old Japanese woman was admitted to Kobe University Hospital in April 2007 because of the deterioration of glycaemic control. She was first diagnosed with Type 2 diabetes in 1995 and was instructed to begin diet and exercise therapy, but she failed to adhere to the treatment regimen. In August 2000, she visited a hospital because of general fatigue and her glycated haemoglobin (HbA_{1c}) was 13.3%. She was admitted to hospital and prescribed human regular insulin for 11 days (total dose of 310 U). Thereafter, she was seen regularly by a primary care physician, adhered well to diet and exercise therapy and was prescribed oral glucose-lowering drugs. Her glycaemic control was relatively stable (HbA_{1c} 6.5–8.0%) during treatment with acetohexamide (500 mg/day). In May 2006, she started to take health supplements containing methylsulphonylmethane, glucosamine, and chondroitin sulphate for osteoarthritis as well as coenzyme Q10 and blueberry extracts for cosmetic reasons. Without any other change in lifestyle or eating habit, her HbA_{1c} gradually increased after September 2006 (Fig. 1). Acetohexamide was changed to glimepiride (2 mg/day) in December 2006, but glycaemic control did not improve. Her height and weight on admission were 156 cm and 59 kg, with no notable change in weight over the previous year.

On admission to our hospital in April 2007, plasma glucose and serum insulin levels after overnight fast and 2 h after breakfast were 9.2 mmol/l and 23 μU/ml and 19.4 mmol/l and 38 μU/ml, respectively. HbA_{1c} was 11.1%. She tested negative for anti-glutamic acid decarboxylase (GAD), anti-insulin receptor, anti-nuclear and anti-DNA antibodies. Serum growth hormone, cortisol, glucagon, catecholamines, thyroid hormones, transaminases and creatinine were normal. Although she had not been prescribed insulin since 2000, a high titre of anti-insulin antibodies (insulin binding ratio of 84.8%; free insulin concentration of 10 μU/ml) was detected. Scatchard analysis revealed that the affinity of the antibodies (K_1 = 0.234×10^{-8} mol/l) was relatively low and that their binding activity ($R_1 = 1.92 \times 10^{-8}$ mol/l) was slightly high. Human leukocyte antigen (HLA) typing of DRB1 yielded *0405/1501, which does not confer susceptibility to IAS [5].

The patient had stopped taking all supplements just before admission. The titre of anti-insulin antibodies decreased gradually thereafter, as did her HbA_{1c} (Fig. 1). The dose of glimepiride was reduced and, in May 2007, both voglibose and metformin were added to the treatment regimen. The titre of the anti-insulin antibodies and HbA_{1c} decreased further, with an

2017 American Academy of Pediatrics Clinical Practice Guideline: Impact on Prevalence of Arterial Hypertension in Children and Adolescents With Type 1 Diabetes

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OBJECTIVE

In 2017, the American Academy of Pediatrics introduced a new guideline (2017 Clinical Practice Guideline of the American Academy of Pediatrics [AAP 2017]) to diagnose arterial hypertension (HTN) in children that included revised, lower normative blood pressure (BP) values and cut points for diagnosing high BP in adolescents. We studied the impact of the new AAP 2017 on prevalence of HTN in children with type 1 diabetes mellitus (T1DM).

RESEARCH DESIGN AND METHODS

Up to September 2018, 1.4 million office BP measurements in 79,849 children and adolescents (aged 5–20 years) with T1DM were documented in the DPV (Diabetes Prospective Follow-up) registry. BP values of the most recent year were aggregated, and BP values of 74,677 patients without antihypertensive medication were analyzed (median age 16 years and diabetes duration 5.3 years, 52.8% boys). BP values were classified according to AAP 2017 and the references of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) (2011) and the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (fourth report) (2004).

RESULTS

Of the patients, 44.1%, 29.5%, and 26.5% were hypertensive according to AAP 2017, KiGGS, and fourth report, respectively. Differences in prevalence of HTN were strongly age dependent: <10 years, AAP 2017 31.4%, KiGGS 30.7%, fourth report 19.6%; 10 to <15 years, AAP 2017 30.9%, KiGGS 31.2%, fourth report 22.4%; and ≥15 years, AAP 2017 53.2%, KiGGS 28.4%, fourth report 30.0%. Among teenagers ≥15 years, 59.1% of boys and only 46.3% of girls were classified as hypertensive by AAP 2017 but only 21.1%/26% of boys and 36.7%/34.4% of girls by KiGGS/fourth report, respectively.

CONCLUSIONS

Classification of BP as hypertension depends strongly on the normative data used. Use of AAP 2017 results in a significant increase in HTN in teenagers ≥15 years with T1DM, particularly in boys. AAP 2017 enhances the awareness of elevated BP in children, particularly in patients with increased risk for cardiovascular disease.

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In 2017, the American Academy of Pediatrics introduced new guidelines (2017 Clinical Practice Guideline of the American Academy of Pediatrics [AAP 2017]) to diagnose arterial hypertension (HTN) in children and adolescents (1). Extensive data have shown for a long time that a substantial number of children and adolescents with HTN are treated insufficiently or even not at all (1). AAP 2017 incorporates new data on adverse consequences of high blood pressure (BP) in children and contains lower normative BP data and single-value cut points for adolescents. This new guideline is being discussed controversially, as other associations did not follow these recommendations.

Patients with diabetes are at a high risk of developing HTN, diabetic macroangiopathy, and cardiovascular disease. These conditions already start in childhood and adolescence. Previously, we have shown that prevalence of HTN (2) and intima-media thickening (3) are increased in pediatric patients with type 1 diabetes mellitus (T1DM) and are associated with a higher risk for diabetic microvascular complications such as diabetic retinopathy and nephropathy (4). All guidelines for pediatric diabetology recommend regular BP monitoring and strict BP control. However, there is a strong controversy as to what extent BP should be lowered: risk for cardiovascular disease might increase if BP control is too tight, as low BP may cause a J-shaped curve effect with a minimal risk at BP at 130/80 mmHg in subjects with high cardiovascular risk, such as patients with diabetes and hypertension. In a review of 15 reports, Chrysant and Chrysant (5) concluded that in adult patients with T2DM and HTN, lowering glycosylated hemoglobin to <7.0% and BP to <130/80 mmHg did not add any additional benefit and may even be detrimental to patients' health. Other authors show a significant reduction of the risk for stroke and myocardial infarction with intensive BP control, "the lower the better" (6). So, 2017 AAP has revived this discussion with the focus on pediatric patients.

Our objective was to study the impact of the new 2017 AAP on diagnosis and treatment of HTN in pediatric patients with T1DM in Germany, Austria, and Luxembourg.

RESEARCH DESIGN AND METHODS

The study population for the present analysis was selected from the multicenter DPV (Diabetes Prospective Follow-up) registry. Currently, 456 specialized diabetes centers from Germany ($n = 414$), Austria ($n = 38$), Switzerland ($n = 3$), and Luxemburg ($n = 1$) prospectively document demographic and clinical data of patients with any type of diabetes. Approximately 90% of the pediatric patients with T1DM in Germany and Austria are documented in the DPV registry. As previously described, participating DPV centers transfer locally collected and pseudonymized data semiannually to the University of Ulm, Ulm, Germany, for central analysis and quality assurance. In case of inconsistency or implausibility, data are reported back to the centers for verification or correction. Ethics approval of the DPV initiative has been obtained from the ethics committee of the University of Ulm. Data collection has been approved by the local/national review boards of each participating center (7).

From January 1995 to September 2018, office BP measurements of 77,158 pediatric patients (5–20 years of age) with T1DM were documented in the DPV registry. A total of 74,677 patients did not receive antihypertensive medication and were included into the analysis (Fig. 1).

The patients are all diagnosed with T1DM and visit the diabetes clinic on a regular basis, at least every 3 months, with BP measurements as part of the routine check-up. BP levels were measured in a relaxed, sitting position at the upper arm with proper cuff size using a sphygmomanometer or semiautomated Dinamap (Critikon, Tampa, FL). BP error was reduced by three consecutive readings per occasion as previously described (8). BP values documented during the most recent year of follow-up were aggregated for each individual patient.

BP was classified using normative data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) (9), the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents from 2004 (fourth report) (10), and the new 2017 AAP guideline.

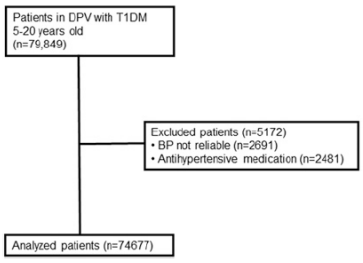

Figure 1—Flowchart for the inclusion of the patients into the investigation.

Overt HTN was defined as BP >95th percentile or, for absolute values, systolic BP (SBP) >140 mmHg/diastolic BP (DBP) >90 mmHg for KiGGS and fourth report or >130/80 mmHg for AAP 2017—whatever was lower.

Height and BMIs were compared by SDS values based on the cohort of healthy German children of KiGGS (11).

For adjustment for different laboratory methods, local HbA_{1c} values were mathematically standardized to the Diabetes Control and Complications Trial reference range (4.05–6.05%) using the "multiple of the mean" transformation method (2).

Statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC). The χ^2 test was used to analyze group differences, and multiple testing was performed with the Wilcoxon test. Data are presented as medians and interquartile range (25th–75th percentile) or as percentage as appropriate; $P < 0.05$ (two sided) is considered significant and $P < 0.01$ highly significant.

RESULTS

Characteristics of the Study Population

The median age of the children and adolescents (52.8% male) included in this investigation was 16.0 years, median diabetes duration 5.3 years, and median HbA_{1c} 7.9% (62.8 mmol/mol). Our patients had a median height SDS of 0.08 and BMI SDS of 0.3 and required a median insulin dosage of 0.84 units/kg body wt/day (Table 1) Boys were older than girls, had shorter diabetes duration, and had lower BMI SDS, height SDS, and HbA_{1c} than girls (all $P < 0.0001$, χ^2 test). Insulin dosage did not differ between the sexes (P 0 0.05) (Table 1).

Based on AAP 2017, 44.4% of our pediatric patients with T1DM were classified as hypertensive, but by KiGGS from 2011 or fourth report from 2004, only 29.5% or 26.5% of our pediatric patients with T1DM were classified as hypertensive, respectively (all $P < 0.0001$, χ^2 test) (Table 2 and Fig. 2).

Boys Versus Girls

The rate of HTN was higher in boys according to the AAP 2017 guidelines

Table 1—Basic characteristics of the study population and the subgroups

Parameter	Total	Boys	Girls	$P_{m\ vs.\ f}$	5–10 years	10–15 years	15–20 years	$P_{5–10\ vs.\ 10–15\ years}$	$P_{5–10\ vs.\ 15–20\ years}$	$P_{10–15\ vs.\ 15–20\ years}$
n	74,677	39,414	35,263		9,341	21,168	44,168			
Male sex	52.8				50.9	52.1	53.5			
Age (years)	16.0 (12.7–17.6)	16.1 (12.8–17.6)	15.9 (12.5–17.6)	**<0.00001**	8.0 (6.6–9.1)	12.9 (11.6–14.0)	17.5 (16.6–18.4)			
BMI SDS	0.30	0.17	0.45	**<0.00001**	0.28	0.2	0.35	**<0.00001**	**<0.00001**	**<0.00001**
	−0.3 to 0.9	−0.4 to 0.8	−0.2 to 1.0		−0.3 to 0.9	−0.4 to 0.82	−0.3 to 0.9			
Height SDS	0.08 (−0.6 to 0.8)	0.07 (−0.6 to 0.8)	0.08 (−0.6 to 0.8)	**<0.00001**	0.17 (−0.5 to 0.9)	0.14 (−0.6 to 0.8)	0.02 (−0.7 to 0.7)	**0.002**	**<0.00001**	**<0.00001**
Insulin dosage (units/kg body wt/day)	0.84 (0.7–1.0)	0.85 (0.7–1.1)	0.84 (0.7–1.0)	0.05	0.69 (0.6–0.8)	0.85 (0.7–1.0)	0.88 (0.7–1.1)	**<0.00001**	**<0.00001**	**<0.00001**
Age at diabetes onset (years)	9.1 (5.5–12.3)	9.3 (5.6–12.8)	8.8 (5.5–11.8)	**<0.00001**	5.1 (3.2–6.9)	8.5 (5.3–11.0)	10.7 (7.0–13.6)	**<0.00001**	**<0.00001**	**<0.00001**
Diabetes duration (years)	5.3 (2.4–8.9)	5.1 (2.3–8.7)	5.6 (2.6–9.1)	**<0.00001**	2.3 (0.8–4.3)	4.2 (1.6–7.3)	6.8 (3.8–10.5)	**<0.00001**	**<0.00001**	**<0.00001**
HbA_{1c} (%)	7.9 (7.1–9.1)	7.9 (7.0–9.0)	8.0 (7.1–9.2)	**<0.00001**	7.4 (6.8–8.1)	7.9 (7.1–8.9)	8.1 (7.2–9.4)	**<0.00001**	**<0.00001**	**<0.00001**
HbA_{1c} (mmol/L)	63.1 (53.8–75.9)	62.6 (53.4–75.3)	63.6 (54.4–76.5)	**<0.00001**	57.1 (50.4–64.9)	62.4 (53.6–73.5)	65.4 (55.0–79.3)	**<0.00001**	**<0.00001**	**<0.00001**

Data are presented as median and lower–upper quartile (25–75th percentile) or as percent unless otherwise indicated. $P < 0.05$ is considered significant and $P < 0.0001$ highly significant (Wilcoxon test). Boldface values indicate significant differences. f, females; m, males.

Table 2—Absolute BP and prevalence of HTN in the study population and the subgroups

Parameter	Total	Boys	Girls	$P_{m\ vs.\ f}$	5–10 years	10–15 years	15–20 years	$P_{5–10\ vs.\ 10–15}$	$P_{5–10\ vs.\ 15–20}$	$P_{10–15\ vs.\ 15–20}$
n	74,677	39,414	35,263		9,341	21,168	44,168			
SBP (mmHg)	120 (110–128.5)	120.5 (111.5–130)	118.5 (110–126)		106 (100–112)	115 (109–122)	124 (117.5–132)			
DBP (mmHg)	70 (64–76	70 (64–75.5)	70 (65–77)		63 (59.5–68.5)	68 (62–73)	72 (67.5–79)			
AAP 2017	44.1	47.6	40.2	**<0.0001**	31.4	30.9	53.2	**0.43**	**<0.0001**	**<0.0001**
KiGGS	29.5	24.5	35.1	**<0.0001**	30.7	31.2	28.4	**0.33**	**<0.0001**	**<0.0001**
fourth report	26.5	23.3	30.0	**<0.0001**	19.7	22.4	29.9	**<0.0001**	**<0.0001**	**<0.0001**

Unless otherwise indicated, data are presented as median and lower–upper quartile (25–75th percentile) or as percentage of patients diagnosed as hypertensive. $P < 0.05$ is considered significant and $P < 0.0001$ highly significant (χ^2 test). Boldface values indicate significant differences. f, females; m, males.

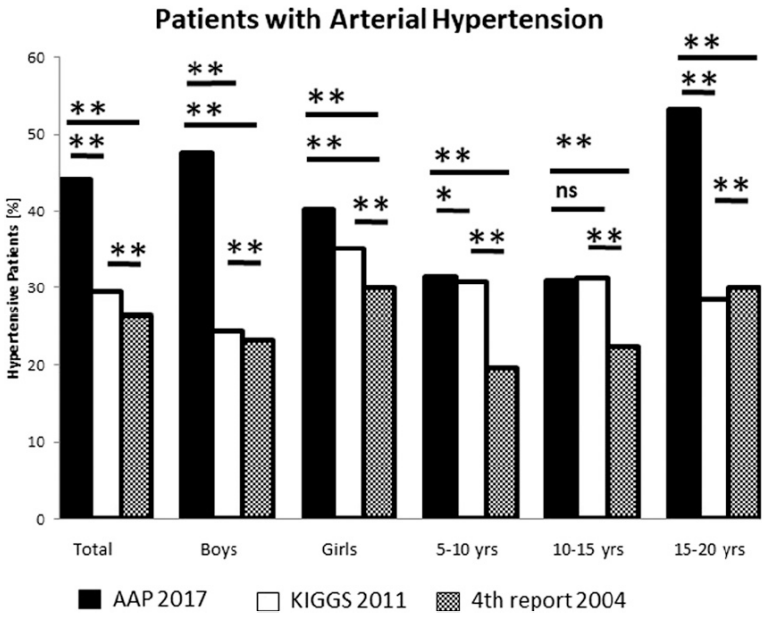

Figure 2—Rate of patients with HTN depending on the different references in the study population and the subgroups. *$P < 0.05$, **$P < 0.0001$, not significant (ns), χ^2 test. yrs, years of age.

but lower based on the older reference values: AAP 2017 47.6% (boys) vs. 40.2% (girls), KiGGS 24.5% vs. 35.1%, fourth report 23.3% vs. 30.0%, respectively (all $P < 0.0001$, χ^2 test) (Table 2 and Fig. 2).

Age

The differences are strongly age dependent: there were only slight differences in the rate of HTN between AAP 2017 (31.4%) and KiGGS (30.7%) ($P = 0.003$, χ^2 test) in children <10 years of age. In the 10–14.9 year olds, 30.9% were hypertensive according to AAP 2017 and 31.2% according to KiGGS ($P = 0.08$). Prevalence of HTN was significantly lower using the reference values of the fourth report (5–9.9 years old, 19.6%, and 10–14.9 years old, 22.4%; all $P < 0.0001$, χ^2 test).

Of the teens >15 years old, 53.2% were diagnosed as hypertensive based on AAP 2017 compared with 28.4% (KiGGS) and 30.0% (fourth Report). HTN occurred less frequently by KiGGS than by fourth report (all $P < 0.0001$, χ^2 test) (Fig. 2).

Age and Sex

With application of the newer guidelines AAP 2017 and KiGGS, HTN prevalence was quite similar in the young children <10 years of age, whereas fourth report resulted in lower rates of HTN (all $P < 0.0001$, χ^2 test) (Fig. 3).

In the 10–15 year olds, AAP 2017 and KiGGS provided similar rates of HTN, both in girls and boys. Again, HTN prevalence was lowest based on fourth report (all $P < 0.0001$, χ^2 test) (Fig. 3).

For teenagers ≥15 years of age, HTN prevalence was significantly higher by AAP 2017 compared with KiGGS and fourth report and lower by KiGGS than by fourth report. These differences were greatest in boys (all $P < 0.0001$, χ^2 test) (Fig. 3).

Prevalence of HTN was higher in girls in most age-groups. HTN was slightly more frequent in boys 5–10 years of age with use of KiGGS and dramatically increased in teenage boys >15 years of age with use of AAP 2017 (Fig. 3).

Reclassification of Being Hypertensive

A total of 10,263 children with T1DM (13.7%) were identified as hypertensive by AAP 2017 but not by KiGGS and fourth report. These patients were older (median age 17.5 years), more often male (75%), taller (median height SDS 0.28), and had longer diabetes duration (median diabetes duration 6.5 years) compared with the total cohort, whereas HbA_{1c} levels (median 8.1%), BMI SDS (0.31), and insulin demand (0.87 units/kg body wt/day) were quite similar among the two groups (total cohort: 16.0 years, 52.8% male, 0.08, 5.3 years, 7.9%, 0.3, and 0.084 units/kg body wt/day, respectively) (Table 3).

CONCLUSIONS

Prevalence of HTN varied between 26.5% and 44.1% in our pediatric patients with T1DM, depending on reference values/guidelines. With use of the new AAP 2017 guideline, HTN increased from below 30% (KiGGS and fourth report) to 44.1% in the total cohort. BP regulation seems to be altered in almost every second child with T1DM, which resembles the rate of adult hypertensive patients in the U.S. and China (12). The prevalence found in our cohort is much higher than that in healthy children without diabetes, which is estimated at 2–4% (13), and other cohorts of children with T1DM (4–7%) (14,15). Previously, we also found lower rates for HTN in children with T1DM from Germany and Austria: 2008, 4%–13.9% (prepubertal children–adolescents, respectively) (16), and 2013, 20% (based on KiGGS and fourth report) (17). Within one decade, HTN prevalence seems to have more than doubled in pediatric patients documented in DPV. This might be attributed to different factors: firstly, in older investigations the cutoff for HTN was set at the 97th percentile and has meanwhile been lowered to the 95th percentile; secondly, the occurrence of overweight, obesity, or other risk factors for HTN might have increased in our children; and thirdly, a greater awareness of HTN has led to more regular and tighter BP monitoring in patients with T1DM.

However, all these observations are based on office BP only and not on ambulatory BP monitoring (ABPM). Therefore, white coat hypertension cannot be ruled out, which is reported to be present in up to 22% of the patients (18) and might play a role in the rise in office HTN over time. ABPM might also detect isolated nocturnal hypertension or masked hypertension; both have been identified as independent risk factors for CVD (19).

The increase in HTN attributed to use of 2017 AAP is strongly age dependent: in children <15 years of age, HTN differs only slightly between AAP 2017 and KiGGS, but in teens >15 years of age the implementation of AAP 2017 led to a significant increase of HTN prevalence: from <30% to 53.1%. From the age of 13 years onward, AAP 2017 uses adult cutoff levels of 130/80 mmHg to diagnose HTN, whereas KiGGS and fourth report stick to the 95th percentile up to an absolute cutoff level of 140/90 mmHg. In

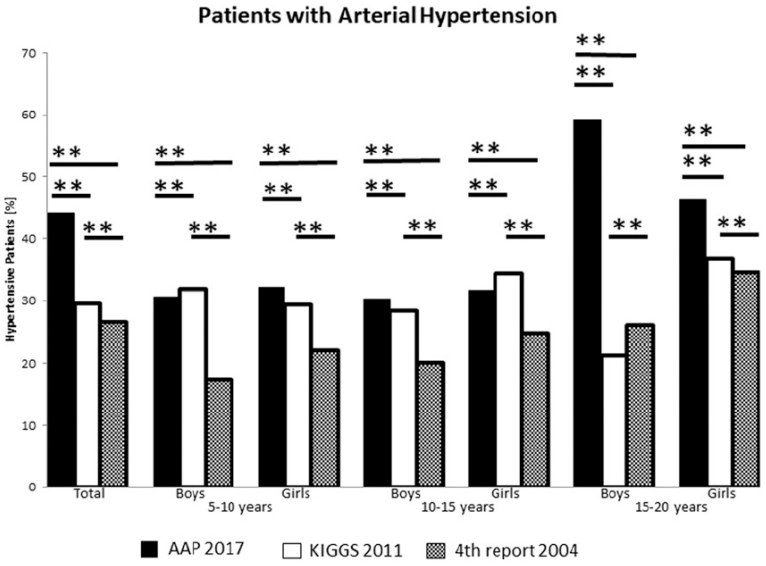

Figure 3—Rate of patients with HTN depending on the different references in the study population and the subgroups. $^{**}P < 0.0001$, χ^2 test. years, years of age.

adolescents, the 95th percentile can reach absolute BP values >130/90 mmHg and, therefore, patients might be classified as nonhypertensive by KiGGS and fourth report but as hypertensive by AAP 2017. In our patients, this upward reclassification particularly affects teenage boys >15 years of age.

AAP 2017 and 2011 KiGGS BP references are based on normal weight children to exclude the influence of overweight and obesity, whereas the references of the fourth report are strictly population based and include overweight children as well. The 90th and 95th percentiles for BP are found to be 2–6 mmHg lower in KiGGS than in fourth report (10) and might explain the lower prevalence of HTN with use of the fourth report references, as children with T1DM tend to be overweight (BMI SDS 0.27). However, the increase of HTN within the last decade cannot be attributed to an increase of obesity, as the rates of overweight (11.3% vs. 10%) and obesity (5.3% vs. 3%) remained stable from 2003 (20) to 2015 (21) among children with T1DM in Germany and Austria.

Children with T1DM in the U.K.-based Clinical Practice Research Datalink (CPRD) aged >10 years had a higher risk of HTN than younger children (22), and thus teenage children, particularly with T1DM, are identified as a population at high risk for HTN.

In the total cohort, HTN is more frequent in boys than in girls. This sex gap is quite small among younger children, <15 years of age, and BP is even more often elevated in younger girls. The more recent guidelines, AAP 2017 and KiGGS (2011), showed similar HTN prevalence in younger children <15 years of age. Based on fourth report, prevalence of HTN was higher in girls for all age-groups, again hinting at overweight as the possible cause, as BMI SDS is higher in girls with T1DM.

Prevalence of HTN skyrockets up to nearly 60% in teenage boys ≥15 years of age if AAP 2017 is used but remains lower in boys than in girls based on KiGGS and fourth report. Teenage girls >15 years were also far more often classified as hypertensive by AAP2017. This implies that BP levels of teenage patients, particularly boys, must fall between the cutoffs of AAP 2017 (130/80 mmHg) and KiGGS/fourth report (95th percentile up to the absolute BP of 140/90 mmHg). In the KiGGS cohort of healthy German boys and girls, BP rises similarly in both sexes until the age of 13 years. But the pubertal rise in BP is significantly more pronounced in boys, resulting in BP differences of up to 17 mmHg for SBP and 2 mmHg for DBP between boys and girls (9). The significant increase of HTN in German teenage boys >13 years seems to be primarily independent of diabetes. On the other hand, T1DM per se enhances the risk for arterial HTN, and chronic hyperglycemia is associated with HTN and cardiovascular disease. Thus, the massive increase of HTN in teenage boys documented in DPV with application of AAP 2017 seems to result from both diabetes and factors not related to diabetes.

Sharma et al. (23) studied the consequences of the new AAP 2017 on the prevalence and severity of elevated BP in healthy U.S. children from the National Health and Nutrition Examination Surveys (NHANES): children reclassified as hypertensive were more likely to be male and slightly taller than normotensive children. Our patients, whose BP was reclassified as hypertension by AAP 2017, were also more often male (75%) and taller (height SDS 0.28).

AAP 2017 is very sensitive to detect early alterations in BP regulation in T1DM and, therefore, classifies BP as hypertension earlier than KiGGS or fourth report, particularly in the teenage boys >15 years of age with T1DM documented in DPV.

Although it was not the original intent of our study, we found that the data reveal that 93.5% of the patients documented in DPV are not receiving antihypertensive medication. Based on the KiGGS references, office BP is increased in 29.5% and based on AAP 2017, 44.1%, but only 6.5% of the patients are on antihypertensive medication. There is an ongoing discussion among German pediatric diabetologists as to how to diagnose HTN in children with T1DM and when and how to treat. Thus far, there is a consensus that HTN should not be diagnosed based on a single office BP measurement, but BP >90th percentile (KiGGS) measured repeatedly at two to three different visits should prompt further investigations—mainly ABPM. The awareness of the devastating consequences of HTN in T1DM needs to be sharpened among the German pediatric diabetologists and likely among pediatric diabetologists in other countries as well.

Children with T1DM are identified to have increased risk for HTN and diabetes complications resulting from HTN (1). Thus, AAP 2017 recommends regular monitoring of office BP; routine performance of ABPM should be strongly considered to assess HTN severity and determine whether abnormal circadian patterns are present, which may indicate increased risk for target organ damage (1). This risk might be reduced if elevated BP during

Table 3—Absolute BP and prevalence of arterial HTN and risk factors in the study population and the age-groups depending on sex

		5–10 years			10–15 years			15–20 years		
	Total	Boys	Girls	*P*	Boys	Girls	*P*	Boys	Girls	*P*
n	74,677	4,755	4,586		11,019	10,149		23,640	20,528	
SBP (mmHg)	120 110–128.5	106 100–112	106 100–112	0.46	115 109–122	115 109–122	0.35	126.5 120–134	121 115–129	**<0.0001**
DBP (mmHg)	70 64–76	63 59.5–68	63.5 60–69	**0.01**	68 62–72.5	69 62.5–74	**<0.0001**	72 67–78	73 68–79.5	**<0.0001**
AAP 2017 (%)	44.1	30.6	32.2	0.12	30.33	31.5	0.06	59.1	46.3	**<0.0001**
KiGGS (%)	29.5	31.9	29.4	**0.01**	28.4	34.3	**<0.0001**	21.1	36.7	**<0.0001**
fourth report (%)	26.5	17.3	22.1	**<0.0001**	20.2	24.7	**<0.0001**	26.0	34.4	**<0.0001**
BMI SDS	0.30 −0.3 to 0.4	0.27 −0.3 to 0.9	0.29 −0.3 to 0.9	0.61	0.11 −0.5 to 0.8	0.30 −0.3 to 0.9	**<0.0001**	0.18 −0.4 to 0.8	0.57 −0.5 to 1.1	**<0.0001**
Height SDS	0.8 −0.6 to 0.8	0.17 −0.5 to 0.9	0.17 −0.5 to 0.9	**0.98**	0.17 −0.5 to 0.8	0.12 −0.6 to 0.8	**0.0002**	−0.01 −0.7 to 0.7	0.05 −0.6 to 0.8	**<0.0001**
Insulin dosage (units/kg body wt/day)	0.84 0.7–1.0	0.67 0.5–0.8	0.7 0.6–0.9	**<0.0001**	0.83 0.7–1.1	0.87 0.7–1.1	**<0.0001**	0.89 0.7–1.1	0.86 0.7–1.1	**<0.0001**

Unless otherwise indicated, data are presented as median and lower–upper quartile (25–75th percentile) or as percentage of patients diagnosed as hypertensive. $P < 0.05$ is considered significant and $P < 0.0001$ highly significant (χ^2 test). Boldface values indicate significant differences.

childhood were to resolve by adulthood (24).

The intention of the new 2017 AAP is to enhance the awareness of HTN in children and adolescents and to identify individuals at risk for HTN (25). It is the primary goal not to start antihypertensive medication in every child with high BP values right away but, rather, to identify children at risk for HTN, to initiate early diagnosis, and to start intervention if the diagnosis is confirmed, preferably by ABPM.

Conclusion

The identification of BP values as normo- or hypertensive strongly depends on the references applied. AAP 2017 results in a dramatic increase of HTN prevalence in older adolescents with T1DM, particularly in teenage boys. The implementation of AAP 2017 enhances the awareness of HTN and should prompt further evaluation. It should not result in immediate antihypertensive medication before confirmation of the diagnosis of HTN.

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Arterial Hypertension Determined by Ambulatory Blood Pressure Profiles

Contribution to microalbuminuria risk in a multicenter investigation in 2,105 children and adolescents with type 1 diabetes

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OBJECTIVE — Arterial hypertension is a key player in the development of diabetes complications. We used a nationwide database to study risk factors for abnormal 24-h blood pressure regulation and microalbuminuria in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Ambulatory blood pressure monitoring was performed in 2,105 children and adolescents from 195 pediatric diabetes centers in Germany and Austria. Individual least median squares (LMS)-SD scores were calculated for diurnal and nocturnal systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressure according to normalized values of a reference population of 949 healthy German children. The nocturnal blood pressure reduction (dipping) was calculated for SBP as well as DBP.

RESULTS — In diabetic children, nocturnal blood pressure in particular was significantly elevated (SBP +0.51, DBP +0.58, MAP +0.80 LMS-SD) and dipping of SBP DBP, and MAP was significantly reduced ($P < 0.0001$). Age, diabetes duration, sex BMI, A1C, and insulin dose were related to altered blood pressure profiles; dipping, however, was only affected by age, female sex, and A1C. The presence of microalbuminuria was associated with nocturnal DBP ($P < 0.0001$) and diastolic dipping ($P < 0.01$).

CONCLUSIONS — Our observations revealed a clear link between the quality of metabolic control and altered blood pressure regulation even in pediatric patients with short diabetes duration. Nocturnal blood pressure in particular seems to mainly contribute to diabetes complications such as microalbuminuria.

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Arterial hypertension is a major risk factor for micro- and macrovascular complications in type 1 diabetes. Diabetic vascular complications can be regarded as endpoints of a long-lasting pathological process involving metabolic and possibly genetic factors. Recently, a high age-dependent prevalence of atherogenic risk factors such as obesity, dyslipidemia, smoking, poor glycemic control, and arterial hypertension was reported in a large cross-sectional study of children and adolescents with type 1 diabetes (1).

Many studies have shown increased blood pressure in adult diabetic patients (2) and an impact of blood pressure regulation on the development of albuminuria and vice versa (3). Thus far, however, systematic investigations on blood pressure regulation and cardiovascular complications in diabetic children and adolescents have been performed in only a limited number of patients and with conflicting results. Up to 30% of children and adolescents with type 1 diabetes showed arterial hypertension in an investigation in Poland (4), whereas only 2% of the boys and 7% of the girls of a French cohort of diabetic children were hypertensive (5).

Several factors are known to influence blood pressure profile in diabetic patients, such as age, sex, body weight, diabetes duration, insulin dosage, metabolic control, and microalbuminuria (6). Ambulatory blood pressure monitoring (ABPM) permits the observation of blood pressure throughout day and night in a nonmedical environment and the quantification of circadian blood pressure variability (7). ABPM is better related to end organ damage and cardiovascular morbidity from hypertension than office blood pressure readings (8,9). Consistently, impairment of nocturnal blood pressure regulation has been reported in adolescents and young adults with type 1 diabetes (10,11). However, the contribution of increased systolic (SBP) or diastolic (DBP) blood pressure to an altered blood pressure profile and the development of end organ damage remains controversial.

Identifying factors that initiate and accelerate the development of vascular complications and controlling such factors is crucial for the prevention of these long-term consequences of diabetes. Therefore, we studied the influence of potential risk factors on the quantitative development of hypertensive blood pressure profiles and microalbuminuria in a prospective cohort of diabetic children from 195 pediatric diabetes centers in Germany and Austria.

RESEARCH DESIGN AND METHODS

— A total of 31,278 patients with type 1 diabetes under 18 years of age were consecutively registered at 195 centers for pediatrics and internal

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Abbreviations: ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; LMS, least median squares; MAP, mean arterial pressure; SBP, systolic blood pressure; SDS, SD score.

medicine using the national quality initiative DPV software (Diabetes Software for Prospective Documentation). The data were generated locally, documented, and transmitted in anonymous form to the University of Ulm for central evaluation and analysis, as described previously (1,12). A total of 5,982 24-h blood pressure recordings were obtained from January 1994 until October 2006.

Study population

Pediatric patients between 5 and 18 years of age and the most recent ambulatory blood pressure recording for each patient were included in this cross-sectional investigation. Patients with antihypertensive treatment were excluded (9.2%), and the blood pressure profiles of 2,105 children and adolescents (1,101 boys and 1,004 girls) were analyzed. Altogether, 74% of the recordings were generated in six major centers.

Control population

Normalized reference values were obtained from cross-sectional ABPM data in 949 healthy children and adolescents (464 boys and 485 girls). Their age ranged from 5 to 18 years (mean 11.1) and height from 101 to 198 cm (mean 150). Only healthy children with no history of disease affecting blood pressure and without current antihypertensive medication or other blood pressure–affecting drugs were included in this investigation, performed by the German Working Group on Pediatric Hypertension (7). Using the least median squares (LMS) method, sex-specific *L M*, and *S* reference values were calculated for 24-h and daytime and nighttime mean values of SBP DBP, and mean arterial pressure (MAP) relative to age and height. These reference values enable the calculation of SDS (SD score) values in individual patients for each of the above-mentioned AMBP recordings (see below).

Measurements

A1C values were determined in each center and standardized according to the Diabetes Control and Complication Trial reference range of 4.05–6.05% (1). BMIs were compared by SDS values based on a cohort of 34,422 healthy German children (17,147 boys and 17,275 girls) (13).

Blood pressure profiles

Ambulatory 24-h blood pressure monitoring was performed by oscillometry with adapted cuff size. Daytime blood pressure was measured every 20 min between 0800 and 2000 h, and nighttime blood pressure was recorded once per hour between 0000 and 0600 h. Each patient recorded his/her daily routine; in case of changes in active and sleeping times, blood pressure readings were individually adjusted. Only ABPM recordings with at least 75% reliable readings were further analyzed. Mean SBP DBP, and MAP were calculated separately for daytime and nighttime, as well as the nocturnal reduction of SBP and DBP (dipping). Age and sex dependency of blood pressure were corrected for using SDS values for SBP DBP, and MAP.

Because the use of pediatric ABPM reference values is comprised by the non-Gaussian distribution of 24-h blood pressure in children, we used the LMS method to calculate appropriate SDS values for ABPM. The LMS method describes the distribution of a measurement Y by its median (M), the coefficient of variation (S), and a measure of skewness (L) required to transform the data to normality. The reference values of *L M*, and *S* can be used to calculate individual LMS-transformed SDS (LMS-SDS) by the following equation (7):

$$\text{LMS-SDS} = \{[Y/M(t)]L(t) - 1\}/[L(t) \times S(t)]$$

where Y is the child's individual blood pressure value, and $L(t)$, $M(t)$, and $S(t)$ represent sex-specific reference values of *L M*, and *S* interpolated for the child's height.

The individual LMS-SDS values were compared with those of the published reference population of healthy German children (7,14). Blood pressure profiles (SBP DBP, and MAP) were considered pathological when the LDS-SDS exceeded 1.65, corresponding with the 95th percentile (7).

The nocturnal reduction of blood pressure (dipping) was calculated as (daytime BP − nighttime BP)/daytime BP, where BP is blood pressure.

The generally accepted definition of normal systolic dipping is a nocturnal SBP reduction of >10% (15), whereas pathological diastolic dipping is controversially defined as a nocturnal reduction of <10% (16) or <20% (15). Therefore, prevalence will be given for both definitions.

Albuminuria

Persistent microalbuminuria was defined according to the guidelines of the International Society for Pediatric and Adolescent Diabetology as a minimum of two positive out of three consecutive urine specimens at least 4 weeks apart (17) with an albumin excretion rate of 20–200 μg/min in timed overnight urine collections or 30–300 mg/24h in 24-h urine collections and an albumin-to-creatinine ratio of 2.5–25 mg/mmol or 30–300 mg/g in the morning spot urine. Each of the participating centers decided independently which method to use. Blood pressure profiles were compared with the urinary albumin excretion rates taken within ±3 months of the ABPM recording.

Statistical analysis

Statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC). Group-specific differences were compared using parametric testing (*t* test) after testing for Gaussian distribution (Kolmogorov-Smirnov) and otherwise by nonparameteric Wilcoxon's test.

Age (years), diabetes duration (years), sex, A1C (%), BMI-SDS, and insulin dose (insulin units per kilogram body weight per day) were compared with blood pressure LMS-SDS as independent variables by multiple linear regression analysis. Potential factors contributing to microalbuminuria were studied by stepwise multiple logistic regression analysis. We did not correct for the multiple tests. Therefore, all reported *P* values are nominal. Unless otherwise stated, data are presented as means ± SD. $P < 0.05$ was considered significant and $P < 0.01$ as highly significant.

RESULTS

Characteristics of the study population

The mean age of the children included in this investigation was 14.05 ± 2.95 years, mean diabetes duration 5.15 ± 4.02 years, mean BMI-SDS 0.49 ± 0.90, and average A1C 8.0 ± 1.8%. The subjects required an average insulin dosage of 0.83 ± 0.28 units · kg body wt^{-1} · day^{-1}.

The boys were significantly older than the girls (14.2 ± 0.09 vs. 13.9 ± 0.1 years; $P = 0.021$, Wilcoxon's test) and had a shorter diabetes duration (4.9 ± 0.12 vs. 5.4 ± 0.13 years; $P = 0.001$, Wilcoxon's test), and the girls had significantly higher BMI-SDS than the boys (0.57 ± 0.03 vs. 0.42 ± 0.03; $P < 0.0001$, Wilcoxon's test). A1C ($P = 0.06$) and insulin dosage ($P = 0.56$) did not differ between the sexes.

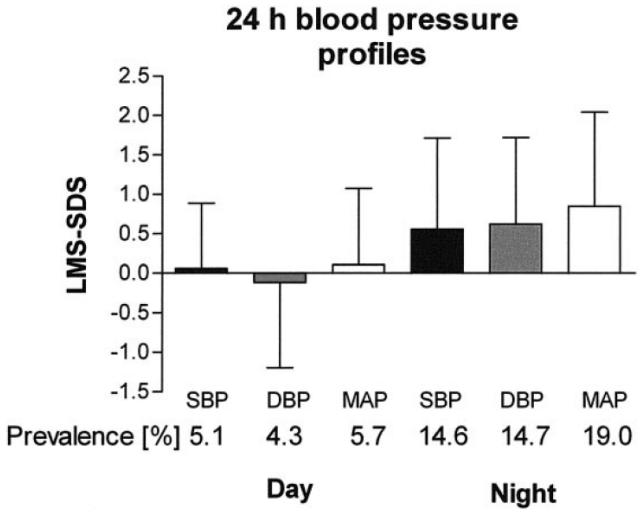

Figure 1—*Mean LMS-transformed blood pressure values in diabetic children. SBP, DBP, and MAP were significantly elevated compared with the control group (P < 0.0001), and diurnal DBP was significantly reduced (P < 0.0001). Mean LMS-SDS of the control population is represented by the baseline (LMS-SDS 0.0). Values are given as means ± SD. The prevalence of pathological blood pressure values is shown at the bottom.*

Blood pressure profiles

Daytime mean LMS-SDS in diabetic patients was higher by 0.06 ± 0.83 for SBP and by 0.11 ± 0.97 for MAP, whereas LMS-SDS for DBP was reduced by 0.12 ± 1.08, compared with the reference population ($P < 0.0001$ for all three variables) (Fig. 1). More pronounced results were found for nocturnal blood pressure: mean LMS-SDS was increased by 0.51 ± 1.20 for SBP, 0.58 ± 1.10 for DBP, and 0.80 ± 1.20 for MAP in the study population ($P < 0.0001$ for all three variables) (Fig. 1).

Mean dipping was significantly reduced in the diabetic children compared with the reference population (respectively 10.0 ± 5.7 vs. 13.0 ± 6.0% for systolic dipping and 16.8 ± 8.1 vs. 23.0 ± 9.0% for diastolic dipping; $P < 0.0001$) (Fig. 2).

The prevalence for pathological blood pressure at daytime was 5.1% for SBP, 4.3% for DBP, and 5.7% for MAP and during the night was 14.6% for SBP, 14.7% for DBP, and 19.0% for MAP (Fig. 1). Pathological dipping was found in 49.1% for SBP and in 17.5% for DBP using a cut off of 10% and in 64.9% for DBP using a cut off of 20%.

Diabetes-associated risk factors for arterial hypertension

Using multiple regression analysis, insulin dosage, female sex, BMI-SDS, A1C, and diabetes duration were significantly associated with increased blood pressure (Table 1). Increased SBP was strongly related to diabetes duration, female sex, and BMI-SDS, both for the diurnal and nocturnal values. Age and A1C were not associated with SBP. DBP was strongly related to diabetes duration, female sex, and A1C. Diurnal DBP was additionally associated with BMI-SDS and nocturnal DBP with age and insulin dosage. Diabetes duration, female sex, BMI-SDS, and insulin dose were significantly correlated with MAP, age, and A1C, however, only with the nocturnal MAP. Nocturnal blood pressure reduction was linked to age and A1C and diastolic dipping additionally to female sex and insulin dosage.

Albumin excretion and blood pressure

Twenty four–hour blood pressure profiles and data on urinary albumin excretion were available for 1,670 patients. A total of 101 patients (6.1%) had persistent microalbuminuria, which was significantly associated with nocturnal DBP ($P < 0.0001$) and impaired diastolic dipping ($P < 0.01$). SBP MAP, A1C, age, diabetes duration, sex, BMI-SDS, and insulin dose were not related to microalbuminuria.

CONCLUSIONS — In this bi-national multicenter investigation, diabetic children showed an abnormal blood pressure profile, particularly affecting nocturnal blood pressure. Mean LMS-SDS values of blood pressure in diabetic children differed from those of the control population by +0.51 to +0.80.

The prevalence of arterial hypertension in the diabetic population is 1.5 to 3 times higher than that in nondiabetic age-matched groups (18); ~75% of adult diabetic patients have blood pressure >140/90 mmHg (19). Age-related changes in blood pressure regulation were observed in both diabetic and non-

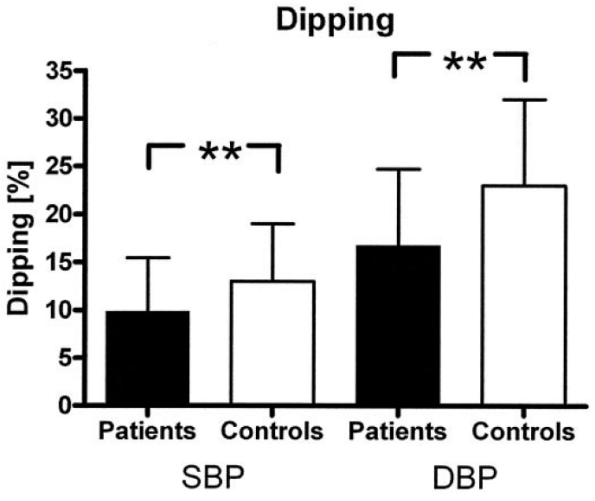

Figure 2—*Absolute dipping values in the diabetic children. SBP and DBP dipping were significantly reduced compared with that of the control population (**P < 0.0001). Values are given as means ± SD.*

diabetic subjects, but the changes seem to occur 15–20 years earlier in type 1 diabetic patients compared with control subjects, suggesting accelerated vascular ageing (20). Compared with the nondiabetic population, type 1 diabetes is associated with a deleterious blood pressure pattern in adult patients even in the absence of diabetic kidney disease (20). According to the Strong Heart Study (21), prehypertension is more prevalent in diabetic patients and the risk for cardiovascular disease is increased 2.9-fold in subjects with type 1 diabetes alone and 3.7-fold in diabetic patients with prehypertension. Our data demonstrate that this fatal development already starts in children and adolescents at an early stage of type 1 diabetes.

In particular, nocturnal arterial hypertension and nondipping seems to be associated with cardiovascular disease in the general population. Systemic arterial vascular tone is increased in patients with essential hypertension during the night compared with normotensive control subjects. This increased vascular tone might contribute to the well-known changes of arterial structure in essential hypertension and eventually lead to cardiovascular disease (22).

Nondippers experience a greater incidence of stroke and myocardial infarction than people with normal dipping (23). Because our diabetic children showed impaired nocturnal blood pressure regulation, they might have an increased risk for macrovascular complications even after short diabetes duration (24). Therefore, early detection of alterations in blood pressure regulation is crucial for adequate diabetes management and sufficient antihypertensive therapy. Performing AMBP in diabetic patients might provide valuable information on early alterations in blood pressure regulation (25).

BMI in particular influenced SBP but had no effect on blood pressure dipping, the most prominent sign of altered blood pressure regulation in these diabetic patients. Performing 24-h AMBP, Wühl et al. (7) demonstrated a significant association between SBP and BMI-SDS, accounting for ~10.7% of the total variability in SBP in healthy children and adolescents. The contribution of increased BMI on SBP variability in our patients was less pronounced, with a maximum of 5.6%. BMI was significantly associated with the SBP-SDS in children with type 1 diabetes participating in the Oxford Regional Prospective Study (26).

Table 1—*Results of the multiple linear regression analysis for SBP, DBP, and MAP values during daytime and nighttime as well as for nocturnal dipping*

	SBP			DBP			MAP		
	Estimate	95% CI	*P*	Estimate	95% CI	*P*	Estimate	95% CI	*P*
Day									
Age (years)	−0.007	−0.200 to −0.006	0.3134	0.009	−0.008 to 0.026	0.2996	−0.008	−0.023 to −0.008	0.3384
Diabetes duration (years)	0.026	0.016–0.036	**<0.0001**	0.039	0.026–0.052	**<0.0001**	0.026	0.014–0.038	**<0.0001**
Sex	−0.166	−0.236 to −0.951	**<0.0001**	−0.163	−0.255 to −0.071	**0.0005**	−0.270	−0.354 to −0.184	**<0.0001**
A1C (%)	−0.006	−0.026 to 0.015	0.5697	0.038	0.011–0.065	**0.0054**	0.015	−0.010 to 0.039	0.2364
BMI-SDS	0.138	0.099–0.177	**<0.0001**	0.082	0.031–0.133	**0.0017**	0.131	0.083–0.178	**<0.0001**
Insulin dose	0.170	0.035–0.304	**0.0136**	0.175	−0.001 to 0.351	0.0509	0.307	0.146–0.468	**0.0002**
Night									
Age (years)	0.018	−0.001 to 0.036	0.0535	0.047	0.030–0.065	**<0.0001**	0.032	0.013–0.0519	**0.0011**
Diabetes duration (years)	0.029	0.015–0.042	**<0.0001**	0.027	0.014–0.040	**<0.0001**	0.021	0.006–0.035	**0.0067**
Sex	−0.363	−0.459 to −0.265	**<0.0001**	−0.226	−0.318 to −0.134	**<0.0001**	−0.188	−0.293 to −0.829	**0.0005**
A1C (%)	0.008	−0.020 to 0.036	0.572	0.081	0.054–0.107	**<0.0001**	0.056	0.026–0.086	**0.0003**
BMI-SDS	0.237	0.183–0.291	**<0.0001**	0.029	−0.022 to 0.080	0.2690	0.080	0.021–0.139	**0.0078**
Insulin dose	0.272	−0.088 to 0.456	**0.0037**	0.323	0.148–0.498	**0.0003**	0.393	0.194–0.594	**0.0001**
Dip									
Age (years)	−0.177	−0.270 to −0.084	**0.0002**	−0.215	−0.347 to −0.083	**0.0014**			
Diabetes duration (years)	0.006	−0.065 to 0.076	0.8722	0.049	−0.051 to 0.149	0.3347			
Sex	0.007	−0.492 to 0.506	0.9772	−0.808	−1.512 to −0.104	**0.0245**			
A1C (%)	−0.183	−0.328 to −0.039	**0.0127**	−0.430	−0.633 to −0.226	**<0.0001**			
BMI-SDS	0.045	−0.233 to 0.324	0.7488	0.332	−0.060 to 0.725	0.0970			
Insulin dose	−0.325	−1.272 to 0.622	0.5017	−1.682	−3.020 to 0.345	**0.0137**			

P < 0.05 is indicated in bold. Sex is coded as 0 for female and 1 for male.

Elevated BMI is associated with peripheral insulin resistance, leading to higher insulin requirements similar to a type 2 diabetes–like metabolic situation. Metabolic syndrome is a frequent finding in type 1 diabetes and increases with inadequate glycemic control (27). Even short-term hyperglycaemia of 48 h may disturb vascular function; therefore, prolonged and repeated episodes of hyperglycemia could lead to permanent vascular dysfunction (28). Both, hyperglycemia and hyperinsulinemia stimulate different pathophysiological pathways, which result in altered blood pressure regulation and endothelial dysfunction.

In our diabetic children, female sex predisposed to early blood pressure alterations, probably due to an increased weight gain and a higher risk for insulin resistance during puberty. Adolescent nondiabetic girls are less insulin sensitive than boys but compensate for decreased sensitivity by increasing their insulin secretion (29). Thus, an elevated BMI is probably a major cause for higher insulin resistance in pubertal girls with type 1 diabetes (30). Increased insulin resistance resulting in hyperinsulinemia and hyperglycemia and elevated BMI substantially contributes to the increased rate of arterial hypertension in diabetic girls.

Alterations in nocturnal blood pressure regulation contribute to microalbuminuria and might enhance the development of diabetic nephropathy even in children with type 1 diabetes. Development of microalbuminuria is linked to insufficient blood pressure control and a progressive increment of glucose values in nondiabetic with mild hypertension (31,32). The Oxford Regional Prospective Study confirmed the link between microalbuminuria and arterial hypertension in children followed from diagnosis of type 1 diabetes. In young adults with type 1 diabetes, an increase in SBP during nighttime preceded the development of microalbuminuria. The risk of microalbuminuria for diabetic subjects with a normal pattern of nocturnal blood pressure was 70% lower than that for patients with an abnormal pattern (33). In accordance, our cross-sectional data suggest that impairment of blood pressure regulation begins at nighttime with a higher prevalence than microalbuminuria. However, office blood pressure measurement did not rise before the onset of microalbuminuria (26,27).

Therefore, metabolic state, body weight, and insulin dosage need to be optimized at the onset of diabetes in order to avoid negative impact on blood pressure regulation and vasculature. Age, female sex, and diabetes duration also affected blood pressure regulation as nonmodifiable risk factors. However, these factors classify patients at a higher risk for arterial hypertension requiring special monitoring.

In conclusion, our data suggest that ABPM might be a valuable tool in monitoring pediatric patients with type 1 diabetes, thus enabling vascular-directed preventive intervention at the earliest possible time.

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ORIGINAL ARTICLE

Blood pressure regulation determined by ambulatory blood pressure profiles in children and adolescents with type 1 diabetes mellitus: Impact on diabetic complications

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Background: The combination of high blood pressure and hyperglycemia contributes to the development of diabetic complications. Ambulatory monitoring of blood pressure (ABPM) is seen as standard to assess blood pressure (BP) regulation.

Objective: We evaluated 24-hour BP regulation in 3529 children with type 1 diabetes, representing 5.6% of the patients <20 years of age documented in the DPV registry, and studied the influence of BP parameters including pulse pressure (PP) and blood pressure variability (BPV) on microalbuminuria (MA) and diabetic retinopathy (DR).

Results: BP was increased in this selected cohort of children with diabetes compared to healthy German controls (standard deviation score (SDS) day: systolic BP (SBP) +0.06, mean arterial pressure (MAP) +0.08, PP +0.3; night: SBP +0.6, diastolic BP +0.6, MAP +0.8), while daytime diastolic BP (SDS −0.2) and dipping of SBP and MAP were reduced (SBP −1.1 SDS, MAP 12.4% vs 19.4%), PP showed reverse dipping (−0.7 SDS). Children with microvascular complications had by +0.1 to +0.75 SDS higher BP parameters, except of nocturnal PP in MA and diurnal and nocturnal PP in DR. Reverse dipping of PP was more pronounced in the children with MA (−5.1% vs −0.8%) and DR (−2.6% vs −1.0%). BP alteration was stronger in girls and increased with age.

Conclusion: There is an early and close link between 24-hour blood pressure regulation and the development of diabetic complications not only for systolic, diastolic, and mean arterial BP but also for the derived BP parameter PP and BPV in our selected patients.

KEYWORDS

blood pressure profiles, blood pressure variability, diabetic complications, pulse pressure, type 1 diabetes mellitus

1 | INTRODUCTION

Increased blood pressure (BP) significantly contributes to the development of diabetic complications. Particularly, impaired nocturnal BP regulation is associated with microalbuminuria (MA) in children and adolescents type 1 diabetes (T1DM) from Germany and Austria and therefore a risk factor for diabetic nephropathy.[1] However, the earlier investigations studied only systolic, diastolic, and mean arterial BP, as well as dipping, but neglected the derived BP parameter such as pulse pressure (PP) and blood pressure variability (BPV). Within recent years, these parameters have been recognized as independent risk factors for cardiovascular disease (CVD).[2] Two of 3 of the children with type 1 diabetes from Germany and Austria showed isolated systolic arterial hypertension and therefore increased PP.[3] This investigation is based on office BP readings and might therefore be influenced by white coat effect or prior exercise. In adults, PP determined by ambulatory monitoring of blood pressure (ABPM) seems to be a more reliable predictor of CVD than simple office PP.[4] Spanish patients with CVD had increased PP and blood glucose levels, their nocturnal PP increased by 3.5% and resulted in reverse dipping. In

patients without CVD nocturnal PP decreased by 0.8% and showed physiological dipping.[5] The nocturnal decrease of BP in general but particularly of the PP seems to be of high predictive value for CVD.

Altered BPV contributes to the development and progression of arterial hypertension[6] and cardiovascular mortality increases with diurnal systolic BP (SBP).[7] In children with arterial hypertension, the variability of SBP and diastolic BP is mainly influenced by SBP.[8] However, the data on PP and BPV in children is scarce, particularly in children with T1DM.

We therefore studied 24-hour BP regulation, PP, and BPV in children with type 1 diabetes from 427 centers in Germany and Austria.

2 | OBJECTIVES

(1) Is there a difference in BP and PP regulation and BPV between children with and without type 1 diabetes in a historic group?

(2) If so, does the circadian regulation of BP, PP, and/or BPV differ?

(3) Is the regulation of BP, PP, and BPV related to early signs of diabetic complications like MA and diabetic retinopathy (DR)?

3 | METHODS

DPV (Diabetes Software for Prospective Documentation) is an electronic documentation system for patients with diabetes broadly used in Austria and Germany. On the basis of this continuous diabetes data acquisition system for prospective surveillance, a prospective multicenter survey was designed. Data documentation started in 1995 and comprises demographic, anthropometric, and diabetes-related characteristics of patients with type 1 diabetes. Standardized documentation is primarily used as a quality control system.

The data are generated locally, extracted automatically, and transmitted in anonymous form to the University of Ulm, Germany, for central evaluation and analysis, as described previously.[1] Inconsistent data are reported back to the participating centers for confirmation or correction and are then reentered into the cumulative database.

3.1 | Study population

As of March 2015, a total of 63 296 patients with type 1 diabetes younger than 20 years were documented in the DPV registry. Of them, 1992 were on antihypertensive medication and were excluded from this investigation. Twenty-four hours BP profiles (ABPM) were available in 3529 (1883 males and 1646 females) of the remaining 61 304 patients and were included in the analysis (Figure 1).

The patients were grouped according to their age: <10 years (prepubertal, n = 344), 10 to 15 years (pubertal, n = 1351), and >15 years (postpubertal, n = 1834).

3.2 | Measurements

Body mass indexes (BMIs) were compared by SDS values based on a cohort of 34 422 healthy German children (17 147 boys and 17 275 girls).[9]

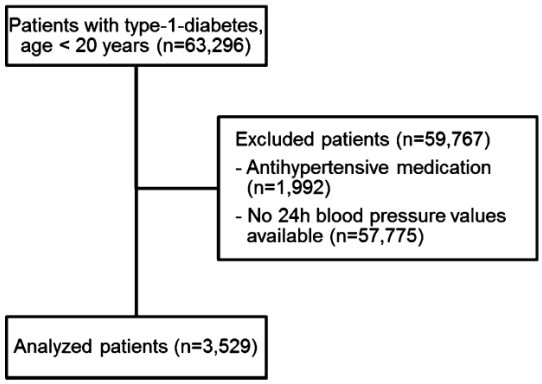

FIGURE 1 Flow chart for the inclusion of the patients into this investigation.

Hemoglobin A1c (HbA1c) values were determined in each center and standardized according to the Diabetes Control and Complication Trial reference range of 4.05% to 6.05%.[1]

Dyslipidemia is assumed if one of the following cut offs is exceeded: cholesterol >200 mg/dL, high-density cholesterol <35 mg/dL, Low-density cholesterol >130 mg/dL, or triglycerides >150 mg/dL.[10]

3.3 | BP profiles

Ambulatory 24-hour blood pressure monitoring (ABPM) was performed by oscillometry with adapted cuff size as described earlier[1]: shortly, daytime BP was measured between 0800 and 2000 h, and nighttime BP was recorded between 0000 and 0600 h. Each patient recorded his/her daily routine; in case of changes in active and sleeping times BP readings were individually adjusted. Only ABPM recordings with at least 75% reliable readings were further analyzed, resulting in the 3529 AMBP-profiles eligible for further analysis. Mean SBP, DBP, mean arterial pressure (MAP), and PP were calculated separately for daytime and nighttime, as well as the nocturnal reduction of SBP, DBP, MAP, and PP (dipping). Age and sex dependency of BP were corrected for using LMS transformed SDS values for SBP, DBP, MAP, and PP. PP was defined as the difference between SBP and DBP.

The individual LMS-SDS values were calculated based on the published reference population of healthy German children[11,12] and are further referred to as SDS.

The nocturnal reduction of BP (dipping) was calculated (daytime BP − nighttime BP)/daytime BP, expressed as percent, where BP is blood pressure. The generally accepted definition of normal systolic dipping is a nocturnal SBP reduction of >10%,[12] whereas pathological diastolic dipping is controversially defined as a nocturnal reduction of <10%[13] or <20%.[14] Reverse dipping describes the increase of nighttime BP compared with daytime BP. So far, no reference values are available for dipping of MAP and PP in healthy German children. Therefore, we calculated the expected dipping of MAP and PP based on a cross-sectional study of 949 healthy school children and adolescents aged 5 to 20 years[11] and compared them with dipping of MAP and PP in our patients.

BPV was defined as fluctuation of BP values during the individual 24-hour-ABPM and is expressed as standard deviation of SBP, DBP, and MAP, separately for daytime and nighttime. BPV was documented in 3194 patients (91% of the patients with documented ABPM). Up to now no reference values exist for BPV in German healthy children.

3.4 | Albuminuria

Persistent MA was defined according to the guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD)[15]: a minimum of 2 positive out of 3 consecutive urine specimens at least 4 weeks apart with an albumin excretion rate of 20 to 200 µg/min in timed overnight urine collections or 30 to 300 mg/24 h in 24-hour urine collections and an albumin-to-creatinine ratio of 2.5 to 25 mg/mmol for boys and 3.5-25 mg/mmol for girls in the morning spot urine. Each of the participating centers decided independently which method to use. BP profiles were compared with the urinary albumin excretion rates taken within ±3 months of the ABPM recording.

3.5 | Retinopathy

According to the ISPAD guidelines, children and adolescents with type 1 diabetes should have a retinoscopy in mydriasis annually if they are older than 10 years of age or suffer from diabetes for more than 2 to 5 years.[15] In Germany and Austria, approximately 73% of the patients (2578 of 3529 patients) had an eye examination documented within 12 months before and 3 months after ABPM. A total of 42 patients (1.6%) were documented with any kind of DR.

3.6 | Statistical analysis

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). Differences between the patients and the controls were tested by *t* test. Group-specific differences were compared using non-parametric Wilcoxon's test or χ^2 test. Age, diabetes duration, sex, HbA1c, BMI-SDS, and insulin dose were compared with BP-SDS and BP SD for BPV as dependent variables by multiple linear regression analysis. Potential factors contributing to MA and DR were studied by stepwise multiple logistic regression analysis. Unless otherwise stated, data are presented as means ± SD. $P < .05$ was considered significant and $P < .001$ as highly significant.

4 | RESULTS

4.1 | Characteristics of the study population

The mean age of the children included in this investigation was 14 years, mean diabetes duration 5 years, mean BMI-SDS 0.52, and average HbA1c 8.6% (70.1 mmol/mol). The subjects required an average insulin dosage of 0.86 units × kg body wt^{-1} × day^{-1} (Table 1).

The boys were significantly older than the girls, had a shorter diabetes duration, and significantly lower BMI-SDS. HbA1c and insulin dosage did not differ between the sexes (Table S1, Supporting Information).

4.2 | Blood pressure

Daytime SBP was slightly but significantly elevated, while DBP was even lower in the children with diabetes. Compared with the control population nocturnal BP was increased in our diabetic patients. MAP was increased in the T1DM children, at daytime only slightly. Dipping

TABLE 1 Demographic characteristics of the study population as a whole and by the presence of microalbuminuria (MA) and diabetic retinopathy (DR)

		MA (n = 2569)			DR (n = 2578)		
Parameter	Total	Yes	No	*P*	Yes	No	*P*
N	3529 (100%)	186 (7.2%)	2383 (92.8%)		42 (1.6%)	2536 (98.4%)	
Age [y]	14.3 ± 2.9	14.3 ± 2.9	14.1 ± 3.1	ns	15.8 ± 2.1	14.5 ± 2.8	**.008**
Sex [% m]	53.4	50.5	53.6	ns	47.6	53.1	ns
Migrat. [%]	8.4	11.3	9.4	ns	7.1	8.4	ns
Height [cm]	163 ± 16.2	164 ± 16.7	162 ± 2	ns	165 ± 13.3	164 ± 15.4	ns
Height-SDS	−0.06 ± 1	0.08 ± 1.1	0.07 ± 1.0	ns	−0.53 ± 1.2	0.07 ± 1.0	**.008**
Weight [kg]	59.5 ± 17.0	59.2 ± 18.6	58.4 ± 18.1	ns	63.5 ± 14.6	60.3 ± 17.2	ns
Weight-SDS	0.52 ± 1.0	0.43 ± 1.1	0.51 ± 1.0	ns	0.38 ± 1.2	0.52 ± 0.98	ns
BMI [kg/m^2]	21.8 ± 4.1	21.5 ± 4.5	21.6 ± 4.1	ns	23.1 ± 3.5	21.9 ± 4.00	ns
BMI-SDS	0.58 ± 1.0	0.43 ± 1.1	0.57 ± 1.0	ns	0.75 ± 0.9	0.58 ± 1.0	ns
Age at diagn [y]	9.2 ± 4.0	9.6 ± 4.0	9.1 ± 4.0	ns	7.3 ± 3.6	9.3 ± 4.0	**.008**
Diab duration [y]	5.1 ± 4.1	4.7 ± 4.0	4.9 ± 4.2	ns	8.5 ± 3.6	5.2 ± 4.1	**<.0001**
CT [%]	12.5	3.8	12.8	**.007**	7.1	13.3	ns
ICT [%]	67.9	67.2	66.3	ns	88.1	66.4	**.016**
CSII [%]	19.6	29.0	20.8	**.044**	4.8	20.3	**.04**

Significant differences are marked in bold.

Abbreviations: BMI, body mass index; CSII, continuous subcutaneous insulin infusion (insulin pump); CT, conventional (insulin) therapy; ICT, intensified conventional (insulin) therapy; ns, not significant; SDS, standard deviation score.

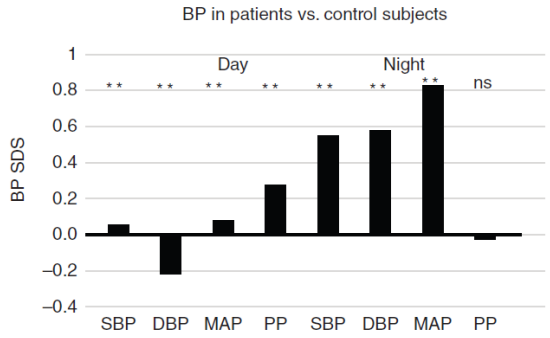

FIGURE 2 Blood pressure (BP) standard deviation score (SDS) of the diabetic subjects compared with the historic controls. The SDS values of the controls are set as "0" (shown as the thick line), the deviation SDS of the BP parameters of the diabetic subjects is shown as closed bars. $^{**}P < .001$; ns, not significant.

was lower in the patients vs the controls: SBP 9.8 ± 5.8% vs 13.0 ± 6.0% and DBP 16.5 ± 8.2% vs 23.0 ± 9.0%. Dipping SDS was significantly reduced for SBP (−1.06 ± 0.9) but elevated for DBP (0.093 ± 1.1, both $P < .001$; Wilcoxon). Dipping of MAP was significantly lower in the T1DM children than expected (DM 12.4 ± 6.9% vs 19.0 ± 0.8%, $P < .0001$) (Figure 2).

BP-SDS, dipping of DBP, and MAP were significantly higher in the girls, whereas systolic dipping was similar in both sexes (Table S2).

Nocturnal BP-SDS increased with age, daytime BP-SDS also increased with age, but significantly only for DBP and MAP, whereas dipping of all BP parameter decreased with age (Table S2).

4.3 | Pulse pressure

Compared with healthy controls diurnal PP was increased in the T1DM children but nocturnal PP did not differ.

In the T1DM children, PP increased during the night resulting in reverse dipping. However, the observed decrease in dipping of PP in our patients was lower than the expected dipping of PP based on the cohort of healthy German children (DM −0.713 ± 21.3% vs expected −1.66 ± 2.8%, $P = .009$, t test) (Figure 2).

Daytime PP-SDS was significantly higher in boys than in girls but nocturnal PP-SDS significantly lower. Dipping of PP was significantly higher in boys than in girls, the latter even showed reverse dipping of PP. PP-SDS decreased with age (Table S2).

4.4 | Blood pressure variability

Individual ABPM values fluctuated by up to 10 standard deviations (SD) (Table 4) indicating a high BPV. Daytime BPV was higher for all BP parameters than nocturnal BPV and systolic BPV was higher than diastolic BPV (Table 4).

BPV was higher in the boys than in the girls and increased with age (Table S2).

4.5 | Microalbuminuria

Urine excretion of albumin was documented in 2569 patients (73%). Of them, 186 (7.2%) showed persistent MA.

The children positive for MA were more often on intensified and less often on conventional insulin therapy. Sex, age, diabetes duration, mean HbA1c, and insulin dose did not differ between the 2 groups (Table 1, Table 2).

Blood pressure regulation was impaired in the T1DM children with MA after correction for age, sex, diabetes duration, and BMI-SDS: SDS of most BP parameters were significantly increased, only nocturnal DBP-SDS was slightly but not significantly elevated. There were no significant differences between the MA positive or negative children in terms of diurnal and nocturnal PP-SDS (Table 3, Figure 3A). Dipping of SBP and DBP was only negligibly lower in the children positive for MA. There was a trend for reduced dipping of MAP in the children positive for MA. Nocturnal PP increased in all children but significantly stronger in the children with MA (Table 3).

TABLE 2 Metabolic characteristics of the study population as a whole and by the presence of microalbuminuria (MA) and diabetic retinopathy (DR)

		MA (n = 2569)			DR (n = 2578)		
Parameter	Total	Yes	No	*P*	Yes	No	*P*
N	3529 (100%)	186 (7.2%)	2383 (92.8%)		42 (1.6%)	2536 (98.4%)	
HbA1c [%]	8.6 ± 1.9	8.8 ± 1.9	8.6 ± 1.9	ns	9.6 ± 2.3	8.5 ± 1.9	**.008**
HbA1c [mmol/mol]	70.0 ± 20.8	72.2 ± 21.1	70.3 ± 21.1	ns	81.8 ± 25.1	69.6 ± 20.7	**.008**
Insulin [IU/kg/d]	0.86 ± 0.31	0.90 ± 0.28	0.86 ± 0.31	ns	0.94 ± 0.30	0.86 ± 0.30	ns
Cholesterol [mg/dL]	183 ± 49.3	182 ± 47.0	182 ± 46.3	ns	197 ± 41.6	183 ± 50.9	**.038**
HDL [mg/dL]	57.7 ± 16.4	58.3 ± 16.9	57.9 ± 15.9	ns	54.0 ± 16.6	57.4 ± 15.4	ns
LDL [mg/dL]	85.9 ± 36.1	99.6 ± 32.7	88.8 ± 35.5	**.006**	72.8 ± 36.1	83.6 ± 35.9	ns
Dyslipidemia [%]	43.2	44.8	42.2	ns	65.7	43.1	**.032**
Antilipid med [%]	1.0	0	0.5	ns	11.9	1.0	**<.0001**
Smoking [%]	13.1	11.3	12.4	ns	18.2	13.8	ns
DR [%]	1.6	1.7	1.3	ns	100	0	-
MA [%]	7.2	100	0	-	7.7	9.4	ns

Significant differences are marked in bold.

Abbreviations: HbA1c, hemoglobin A1c; HDL, high-density cholesterol; ns, not significant; LDL, low-density cholesterol.

TABLE 3 Blood pressure (BP) parameters in the study population as a whole and by the presence of microalbuminuria (MA) and diabetic retinopathy (DR)

		MA (n = 2569)			DR (n = 2578)		
Parameter	Total	Yes	No	*P*	Yes	No	*P*
N	3529 (100%)	186 (7.2%)	2383 (92.8%)		42 (1.6%)	2536 (98.4%)	
SBP-SDS day	0.06 ± 0.8	0.14 ± 0.9	0.01 ± 0.8	ns	0.17 ± 0.8	0.07 ± 0.8	ns
DBP-SDS day	−0.22 ± 1.1	−0.03 ± 1.5	−0.29 ± 1.0	ns	0.26 ± 1.2	−0.21 ± 1.1	**.022**
MAP-SDS day	0.08 ± 1.1	0.25 ± 1.2	0.00 ± 1.0	ns	0.25 ± 0.9	0.10 ± 1.2	ns
PP-SDS day	0.28 ± 1.0	0.17 ± 1.2	0.30 ± 0.9	ns	−0.09 ± 1.0	0.27 ± 1.0	**.038**
SBP-SDS night	0.55 ± 1.2	0.65 ± 1.2	0.48 ± 1.2	ns	0.92 ± 1.2	0.55 ± 1.2	ns
DBP-SDS night	0.58 ± 1.1	0.77 ± 1.2	0.51 ± 1.1	**.036**	1.30 ± 1.3	0.55 ± 1.2	**.001**
MAP-SDS night	0.83 ± 1.2	1.1 ± 1.4	0.76 ± 1.2	**.016**	1.34 ± 1.5	0.80 ± 1.2	ns
PP-SDS night	−0.03 ± 1.0	−0.13 ± 0.9	−0.03 ± 1.0	ns	−0.38 ± 1.2	−0.02 ± 1.0	ns
Dip SBP [%]	9.8 ± 5.8	9.4 ± 6.0	9.8 ± 5.8	ns	7.7 ± 6.7	9.9 ± 5.8	ns
Dip DBP [%]	16.5 ± 8.2	15.6 ± 8.7	16.6 ± 8.3	ns	14.1 ± 9.6	16.7 ± 8.2	ns
Dip MAP [%]	12.4 ± 6.7	11.4 ± 6.8	12.4 ± 6.8	ns	10.9 ± 7.3	12.7 ± 6.9	ns
Dip PP [%]	−0.7 ± 21.3	−5.1 ± 68.9	−0.8 ± 12.3	ns	−2.6 ± 12.0	−1.0 ± 22.3	ns

Significant differences are marked in bold.

Abbreviations: DBP, diastolic BP; Dip SBP, dipping of SBP. The other BP parameters are abbreviated accordingly; MAP, mean arterial pressure; ns, not significant; PP, pulse pressure; SDS, standard deviation score; SBP, systolic BP.

Variability of daytime DBP and MAP was significantly lower in the children with persistent MA, whereas variability of the other BP parameter was similar in both groups (Table 4).

Multiple logistic regression analysis shows a significant association between MA and nocturnal MAP-SDS (OR 1.28) and a negative trend between MA and BMI-SDS (Table 5A).

4.6 | Retinopathy (DR)

Forty-two of the 2578 patients (1.6%) with documented eye examinations were positive for DR. The T1DM children with DR were older, suffered longer from diabetes, had higher HbA1c levels and were more often on intensified insulin therapy. Sex and insulin dose did not differ between the 2 groups (Table 1, Table 2).

BP levels were higher in the patients positive for DR, although significantly only for DBP resulting in a significantly lower PP in the patients with retinopathy (Table 3, Figure 3B). Dipping was only slightly but not significantly reduced in patients with DR and the proportion of patients with reverse dipping of PP was not significantly higher in the DR positive children (Table 3).

BPV did not differ between the children with DR and those without (Table 4).

DR was significantly related to diabetes duration (<2 years, OR 0.11), and nocturnal MAP and negatively to nocturnal PP (OR 0.56) in the multiple logistic regression analysis (Table 5B).

5 | DISCUSSION

5.1 | BP regulation

Blood pressure regulation is impaired in T1DM children and adolescents with elevated systolic, nocturnal diastolic BP and MAP. Diurnal DBP and nocturnal systolic dipping was lower whereas diastolic dipping was higher in the children with diabetes. These data support our earlier findings[1] which have been confirmed by other groups since then.[16,17]

5.2 | Pulse pressure

Daytime PP was higher in the patients but nighttime PP was similar to the controls. Earlier, we reported elevated daytime office PP in type 1 diabetic children from Germany and Austria[3] confirming these findings. Up to the age of 30 years, office SBP and DBP increase in parallel in patients with T1DM and the isolated increase of office SBP occurs only from the age of 30 years onwards resulting in elevated office PP after the age of 30 years.[18] The fact, that dipping of PP is reduced in our patients, particularly in girls, might be the first sign of impaired endothelial function. Hermida et al[5] found reverse dipping related to CV events in patients with arterial hypertension. In our patients, the nocturnal rise of PP was less pronounced than expected and the other PP parameters were not impaired. Assumingly our patients were too young and suffered from diabetes for a too short time to see a substantial effect of PP. It remains to speculate that their ABPM-PP will increase later and will eventually reach pathological levels.

5.3 | Blood pressure variability

BPV was lower in our children with type 1 diabetes and mild arterial hypertension compared to non-diabetic children with essential arterial hypertension from Poland[8] and healthy graduate students from Missouri, USA.[19] Reference data on BPV in healthy German children do not exist yet.

BPV increases with bodyweight and possibly with insulin resistance.[20] Adult patients with arterial hypertension have higher systolic and diastolic BP, PP, and BPV.[21] Systolic BPV correlated with fasting glucose in children and adults.[8] Patients with increased BPV have a higher risk for CVD and mortality in general and for stroke in particular.[21] Our T1DM patients have increased blood glucose and BP levels,

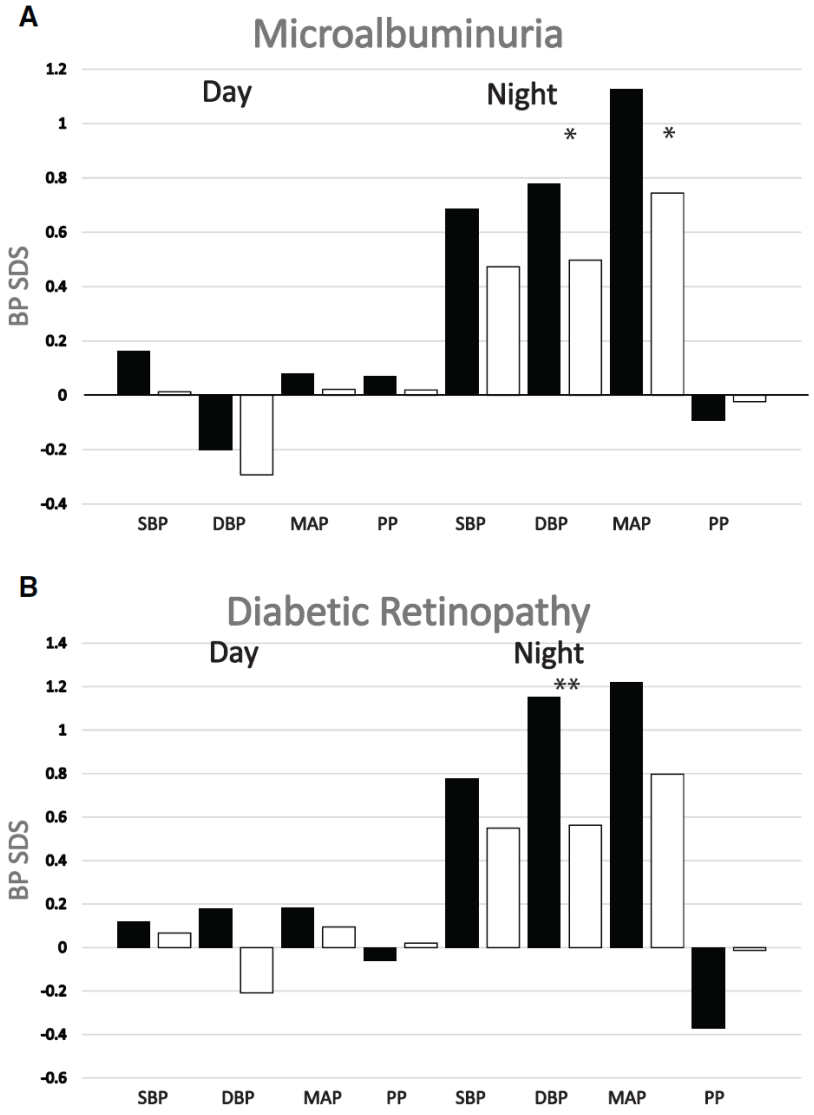

FIGURE 3 Blood pressure (BP) standard deviation score (SDS) by the presence of microalbuminuria (MA, A) or diabetic retinopathy (DR, B). Closed columns MA or DR positive, open columns MA or DR negative. Please note the higher BP SDS in the patients positive for MA or DR except of nocturnal pulse pressure (PP) for MA and diurnal and nocturnal PP for DR. $^{*}P < .05$; $^{**}P < .001$.

TABLE 4 Blood pressure variability (BPV) in the study population as a whole and by the presence of microalbuminuria (MA) and diabetic retinopathy (DR) expressed as average individual standard deviation of the parameter (SD)

		MA (n = 2322)			DR (n = 2323)		
Parameter	Total	Yes	No	*P*	Yes	No	*P*
N	3197 (100%)	174 (7.5%)	2148 (92.5%)		38 (1.6%)	2285 (98.4%)	
SD SBP day [mm Hg]	9.6 ± 5.2	8.7 ± 5.0	9.6 ± 5.3	ns	10.7 ± 4.1	9.7 ± 5.1	ns
SD DBP day [mm Hg]	8.9 ± 5.2	7.7 ± 4.4	8.9 ± 5.2	**.009**	10.4 ± 4.9	9.0 ± 5.1	ns
SD MAP day [mm Hg]	7.9 ± 5.7	6.5 ± 4.5	7.7 ± 6.0	**.042**	9.0 ± 4.2	7.9 ± 5.7	ns
SD SBP night [mm Hg]	8.2 ± 5.2	7.7 ± 4.9	8.2 ± 5.3	ns	9.2 ± 6.8	8.3 ± 5.4	ns
SD DBP night [mm Hg]	7.5 ± 5.3	6.9 ± 4.5	7.4 ± 4.9	ns	7.8 ± 3.8	7.5 ± 5.4	ns
SD MAP night [mm Hg]	6.6 ± 6.1	5.9 ± 4.8	6.4 ± 5.7	ns	6.7 ± 3.7	6.7 ± 6.5	ns

Significant differences are marked in bold.

Abbreviation: ns, not significant; SD SBP day, average individual standard deviation of diurnal BP. The other BP parameters are abbreviated accordingly.

both related to increase BPV in adults. So, the combination of these 2 "bad companions"[22] might increase the risk for high BPV and in the long run for CVD and mortality.

Surprisingly, BPV was quite low in our patients which might be due to the short diabetes duration and to a rather stable metabolic situation. Systolic BPV increases with duration of T2DM implying a

TABLE 5 Factors influencing the presence of microalbuminuria (MA) and diabetic retinopathy (DR)

	OR	95%-CI
A. Microalbuminuria		
Male gender (male vs female)	1.002	0.740-1.356
Age (<10 y vs 10-15 y)	0.733	0.410-1.311
Age (≥15 y vs 10-15 y)	0.940	0.682-1.295
Diab duration (<2 y vs >2 y)	1.146	0.809-1.625
BMI-SDS	0.867	0.737-1.020
MAP-SDS noc	1.248	1.073-1.451
B. Retinopathy		
Male gender (male vs female)	0.747	0.395-1.411
Age (<10 y vs 10-15 y)	1.182	0.142-9.800
Age (≥15 y vs 10-15 y)	2.609	1.134-6.004
Diab duration (<2 y vs >2 y)	0.206	0.048-0.894
MAP-SDS noc	1.274	1.014-1.600
PP-SDS noc	0.702	0.530-0.931

BMI, body mass index; MAP, mean arterial pressure; noc, noctural; PP, pulse pressure; SDS, standard deviation score.

progressive development of rigidity of the heart in diabetes. In newly diagnosed T2DM, systolic BPV is similar to non-diabetic subjects[23]; supporting our observation that in early stages of diabetes BPV does not necessarily increase.

5.4 | Microalbuminuria

Persistent MA according to the ISPAD definition was found in 7.2% of our patients with ABPM and was significantly lower than the MA prevalence of 17% in the total DPV cohort. Fourteen out of 75 (18.7%) adolescents and young adults from the cohort of Lurbe et al[24] developed MA within the first 5 years of T1DM and 16% of a Turkish cohort.[25] Lurbe's patients were slightly older, had higher HbA1c levels and higher overall BP,[24] the Turkish cohort from Darcan et al[25] had significantly higher HbA1c levels than our patients. Our data rather relate to the findings of the VISS study of southeastern Sweden with a rate of 15% MA after 20 years of follow up in T1DM patients.[26]

In our patients, MA was related to increased BP but not to nocturnal PP, supporting earlier reports of Lurbe et al and Darcan et al.[24,25] Multiple testing showed a clear link between nocturnal MAP and MA in our patients. This underlines the fact that altered nocturnal BP regulation seems to be a marker and forerunner of MA.

PP was not increased in the children with MA, contradicting earlier studies: mean diurnal and nocturnal PP was increased in obese, and type 2 diabetic children compared to lean children.[26] Within 5 years of diabetes, both mean nocturnal SBP and mean nocturnal DBP increased in T1DM children developing MA, whereas BP remained almost stable in the normalbuminuric group. So, PP as the difference between SBP and DBP, increased only slightly in the patients positive for MA and decreased slightly in the patients negative for MA.[24]

Our children, particularly the girls, showed reverse dipping of PP, which is possibly one of the earliest signs of altered BP regulation.

Reverse dipping was stronger in the albuminuric patients. So, reverse dipping of PP could be seen as the earliest link between BP regulation, endothelial dysfunction, and albuminuria in type 1 diabetes, leading the way for the later rise of absolute PP.

BPV of daytime diastolic and mean arterial BP was significantly lower in our children with persistent MA. Variability of the other BP parameter did not differ between children with and without first signs of diabetic complications. There might be an influence of insulin resistance on BPV.[27,28] As insulin demand is similar in our patients with or without MA, the missing difference in insulin resistance might level the higher BPV described for MA. MA correlates with elevated BP but not with BPV in middle aged T2DM patients with mild to moderate hypertension from Romania.[29] So, BPV seems to be associated primarily to BP and only secondarily to MA. As, BP is only mildly elevated in our T1DM children this fact might explain the missing link between elevated BPV and MA found in this investigation.

5.5 | Retinopathy

Only 1.6% of our patients were documented with any kind of DR after a mean diabetes duration of 5 years, similar to the overall prevalence of DR in the DPV cohort of 1.8%.

All BP parameters with the exception of PP were increased in our patients' positive for DR. In the Swedish VISS study, DR was related to elevated office SBP with higher SBP in the more severe stages of DR. Office DBP was not related to the different levels of DR.[26] Incident DR could be reduced by intensified insulin therapy, insulin pump therapy, and angiotensin receptor blockade. The progression of DR was reduced by intensified insulin therapy, ACE inhibitors, and islet cell transplantation, implying that arterial hypertension plays an important role in the development and progression of DR.[30]

The association between diabetes duration, increased nocturnal MAP and DR in multiple testing might be a first sign for the negative effect of chronic hyperglycemia and arterial hypertension on the development of DR over time.

In adult, T1DM patients from the STENO-cohort DR was significantly related to 24 hours central aortic systolic pressure, 24 hours central PP, 24 hours SBP, and long diabetes duration. Arterial damage caused by diabetes seems to be a later complication not relevant before 10 years of diabetes duration[31] which might explain the association between DR and lower PP in our patients.

Dipping of SBP, DBP, and MAP was only slightly reduced and reverse dipping of PP was only not significantly increased in the patients with DR. The lack of significance might be attributed to the fortunately small number of children positive for DR in Germany and Austria.

BPV was similar in the children positive or negative for DR. The inverse correlation between birth weight and BPV in young adults born preterm implies a possible influence of insulin resistance on BPV.[27,28] Insulin demand is similar in our patients with or without DR, so the missing difference in insulin resistance might equalize the higher levels of BPV in DR.

5.6 | LIMITATIONS

There are some limitations to our investigation. DPV is a cooperation of meanwhile 241 pediatric diabetes centers from Germany and Austria. Each center is free to decide on the diagnostic and therapeutic tools they use. Usually the centers relate to international (ISPAD) and national guidelines (DDG/AGPD). Still there is a certain variety in the use, for example, of ABPM: some centers perform them on a routine base in all patients every 12 to 24 months, the others determine ABPM only in patients with elevated office BP. The selection of our ABPM patients represents only 5.6% of the patients documented in DPV and is certainly biased with a high number of patients with elevated office BP. These patients are per se at a higher risk for diabetic complications.

The use of ABPM needs to be discussed critically as it requires additional resources in terms of manpower and finances. The equipment required needs to be bought, a nurse or technician has to install it with the patient and read out the data afterwards. Eventually, the doctor has to interpret and to discuss the results with the patient. All this reduces the time for the team to interact with the patients. On the pro-side: ABPM is considered the gold standard to evaluate BP regulation and is recommended unanimously by the American Heart Association, the ISPAD and the German Diabetes Association in case of repeatedly elevated office BP, suspected masked hypertension or in patients with increased risk for arterial hypertension and CVD such as patients with diabetes.[15,32,33]

The low number of patients with MA and DR might result from the different diagnostic approach between the centers. For example, they use different and hard to compare definitions for MA all being suggested by the ISPAD guidelines. Therefore, we classified the patients only as positive or negative for MA. According to the ISPAD guidelines, the patients had to be positive for MA at least in 2 of 3 consecutive urine specimens at least 4 weeks apart. So, we tried to reduce the number of transient MA, but cannot rule out a number of patients with transient MA. The eye examinations of many patients were done by their home ophthalmologist usually performing only fundoscopy in mydriasis, which has a high risk of overseeing the early stages of DR.

The strength of DPV is the great number of cooperating centers—the patients documented in DPV represent approximately 90% of the pediatric T1DM patients in Germany and Austria—and the fact that the data are documented prospectively under every day conditions. Naturally, these centers vary in their way to care for their patients.

6 | CONCLUSION

In earlier reports, we assumed a stepwise progression of arterial stiffness and BP: after disease onset, insulin resistance promotes endothelial dysfunction, later oxidative stress, carbonyl stress, and advanced glycation endproducts may combine to exaggerate structural changes in collagen and elastin structure and function and result in the loss of vascular elasticity.[3]

So, our patients still have relative elastic vessel walls and are just at the beginning of endothelial dysfunction. This opens an important diagnostic and therapeutic window to identify and to reduce endothelial dysfunction. The reverse dipping of PP and as well as BPV might be important early markers for progression to structural changes in the vasculature and the fact that the therapeutic window is closing.

From our personal experience, we think that ambulatory monitoring of BP seems to be a valuable tool to recognize these very early changes in BP regulation.

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Disclosures

The authors declare that there are no conflicts of interest relevant to this article.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Original Article

Pulse pressure in children and adolescents with type 1 diabetes mellitus in Germany and Austria

Dost A, Molz E, Krebs A, Bechtold S, Kapellen T, Rohrer T, Raile K, Fritsch M, Schwab KO, Holl R. Pulse pressure in children and adolescents with type 1 diabetes mellitus in Germany and Austria.
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Background: Impaired blood pressure regulation contributes to the development of diabetic complications. The influence of systolic (SBP) vs. diastolic blood pressure (DBP) is still controversial. Peripheral pulse pressure (PP), the difference between SBP and DBP, is an indicator for arterial stiffness. Only little data are available for PP in children. Therefore, we studied PP regulation in type 1 diabetic children and adolescents.
Methods: Blood pressure values of 46 737 patients with T1DM younger than 20 years are documented in the DPV database and were compared with the control populations of the '4th report on high blood pressure (4th report)' and the German KIGGS study.
Results: PP is increased in 63% (4th report) or 67% (KIGGS) of the patients, respectively. The rate of increased PP remains stable between 59 and 68%, irrespective of sex, age, and the control population. Absolute PP is elevated independently of the control population (PP T1DM 49.13 ± 11.1 vs. 4th report 45.38 ± 3 vs. KIGGS 44.58 ± 4.6 mmHg; all $p < 0.0001$, Wilcoxon test) and increases with age in both sexes. Age, male sex, diabetes duration, insulin dose, and body mass index (BMI) are independent factors contributing to elevated absolute PP levels and to the prevalence of wide PP. HbA1c is negligible negatively related to increased PP levels (multiple linear regression).
Conclusions: In T1DM increased PP is a marker for accelerated arterial stiffness and aging and should be considered as an additional risk factor in the treatment of diabetic children. Elevated PP in children with T1DM may contribute to the high risk for early development of atherosclerosis.

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Key words: blood pressure – children – type 1 diabetes mellitus – PP

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Blood pressure is a periodic phenomenon consisting of two components: steady and pulsatile. The former is a function of cardiac output and vascular resistance, while the latter represents the variations of the pressure curve around the steady component and depends mostly on large artery compliance and ventricular ejection. Both can be estimated by using combined levels of systolic (SBP) and diastolic blood pressure

(DBP): the steady component correlates with mean arterial pressure (MAP), while the pulsatile component correlates with peripheral pulse pressure (PP) (1). Reduced vascular compliance increases pulse wave velocity and leads to an unphysiological early arrival of the pulse wave during the systolic and not, like in the damped physiological state, during the diastolic phase. In consequence, SBP increases and DBP decreases, resulting in higher PP. PP describes the force that affects the endothelial wall between peak systole and low diastole and is calculated as the difference between SBP and DBP.

The Framingham study identified diabetes as a major risk factor for high PP and in consequence for coronary heart disease (CHD). CHD risk increases with lower DBP at any level of SBP $\geq$ 120 mmHg (2). Even with normotensive blood pressure PP predicts cardiovascular risk, particularly in diabetic patients (3).

In elderly patients, peripheral PP is regarded as a consequence of arterial stiffness and is related to increased cardiovascular mortality. Among non-diabetic patients, PP is significantly associated with cardiovascular and all-cause mortality, but these associations are confounded by age, MAP, and gender. In diabetic patients, this association between PP and cardiovascular mortality persists even after adjustment for age, MAP, and gender (4, 5).

The role of SBP and DBP in the development of cardiovascular disease in patients with type 1 diabetes remains controversial. PP integrates SBP and DBP as the pulsatile component of the blood flow and might therefore be a valuable parameter to resolve these inconsistencies.

Diabetes mellitus type 1 goes along with early endothelial dysfunction and arterial stiffness. As PP increases with age, elevated PP might indicate accelerated vascular aging in young diabetic patients. Children with type 1 diabetes as young as 10 years have increased arterial stiffness when compared with age-matched control subjects (6). Little is known about the factors contributing to increased arterial stiffness and PP in diabetic children and adolescents.

Therefore, we studied PP in a prospective cohort of diabetic patients under 20 years from 220 pediatric diabetes centers in Germany and Austria as well as potential factors influencing PP.

Methods

DPV (Diabetes Software for Prospective Documentation) is an electronic documentation system for patients with diabetes broadly used in Austria and Germany. On the basis of this continuous diabetes data acquisition system for prospective surveillance, a prospective multicenter survey was designed. Data documentation started in 1995 and comprises demographic, anthropometric, and diabetes-related characteristics of patients with type 1 diabetes and is used as a quality control system.

The data are generated locally, documented, and transmitted in anonymous form to the University of Ulm, Germany, for central evaluation and analysis, as described previously (7, 8). Inconsistent data are reported back to the participating centers for confirmation or correction and are then reentered into the cumulative database.

Study population

As of March 2013 a total of 790 036 blood pressure readings from 48 728 patients with type 1 diabetes younger than 20 years are documented in the DPV database. The most recent blood pressure reading for each patient was included in this cross-sectional investigation. Patients receiving antihypertensive treatment were excluded (4.1%). Therefore, the blood pressure readings of 46 737 children and adolescents (24 430 males and 22 307 females) were included in this investigation.

The patients were grouped according to their age: <10 years (prepubertal, n = 8647), 10–15 years (pubertal, n = 14 895), and >15 years (postpubertal, n = 23 195).

Control populations

Normalized reference values were obtained from the '4th Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children And Adolescents' from 2004 (9) and the "German Health Interview and Examination Survey for Children and Adolescents", a nationally representative examination survey of children and adolescents in Germany (KIGGS) from 2007 (10).

Measurements

HbA1c values were determined in each center and standardized to the Diabetes Control and Complication Trial reference range of 4.05–6.05% (11). Body mass indices (BMIs) were compared by standard deviation score (SDS) values (z-scores) based on a cohort of 34 422 healthy German children (17 147 males and 17 275 females) (12).

Blood pressure

Blood pressure levels were measured in a relaxed, sitting position at the upper arm with proper cuff size using sphygmomanometer or semi-automated Dinamap (Critikon, Tampa, FL, USA) (13).

Age and sex dependency of blood pressure were corrected for using SDS values for SBP, MAP, and DBP based on the control populations mentioned above.

Because the use of pediatric BP reference values is comprised by the non-Gaussian distribution of blood pressure in children, we used the least mean square (LMS) method to calculate SDS values for blood pressure as described earlier (8)

Pulse pressure

Peripheral PP is the difference between the systolic and the diastolic blood pressure. PP was available in 46 737 type 1 diabetic patients below 20 years without antihypertensive treatment. We tested the absolute PP and the percentage of increased PP (wide PP) in the whole study population and in the subpopulations depending on sex or age. PP is considered increased (wide) if the observed PP of the patients is higher than the 50th percentile of the reference population (4th report or KIGGS, resp.).

The difference between the observed PP and the expected PP of the control populations was plotted against the chronological age and the diabetes duration to test the influence of these parameters on PP regulation. Expected PP corresponds to the 50th PP percentile (i.e., 0 SDS) of the control populations (9, 11).

Statistical analysis

Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). The difference between the observed and expected PP levels were analyzed with the Wilcoxon signed rank test. Observed PP as independent variable was related to age (years), diabetes duration (years), sex, HbA1c (%), insulin dose (insulin units per kilogram body weight per day), and BMI-SDS by multiple linear regression analysis. Data are presented as means ± SD; $p < 0.05$ is considered significant and $p < 0.01$ is highly significant.

Results

Characteristics of the study population

The mean age of the children included in this investigation was 14.0 ± 4.2 years, mean diabetes duration 5.4 ± 4.2 years, mean BMI-SDS 0.52 ± 1.0, and average HbA1c 8.3 ± 1.8%. The subjects required an average insulin dosage of 0.85 ± 0.3 units × kg body $wt^{-1} \times day^{-1}$. Boys were slightly older than girls, had shorter diabetes duration, lower BMI-SDS, and lower HbA1c than girls. Insulin dosage did not differ between the sexes (Table 1).

Blood pressure

Blood pressure is significantly elevated in the children and adolescents with type 1 diabetes, irrespective of the control population: SBP-SDS +0.77/+0.56, MAP-SDS +0.52/+0.29, and DBP-SDS +0.39/+0.16 (4th report/KIGGS; $p < 0.0001$, *t*-test). All, SBP-SDS, MAP-SDS, and DBP-SDS were lower in boys than girls. As expected, absolute blood pressure (SBP, MAP, and DBP) but not BP-SDS increased with age, again irrespective of the reference population (Tables 2–4).

Pulse pressure

Absolute PP is significantly increased in children with type 1 diabetes by 0.37 or 0.40 SDS, respectively (4th report/KIGGS): mean observed PP 49.1 ± 11.1 mm Hg, expected PP based on the 4th report 45.4 ± 3.6 mm Hg, based on KIGGS 44.6 ± 4.6 mmHg, (all $p < 0.0001$, Wilcoxon test). PP levels are higher in males (males 50.7 ± 11.7 mmHg vs. females 47.4 ± 10.0 mmHg; $p < 0.001$, *t*-test), and increase with age, both for diabetic and non-diabetic children (Tables 2–4).

The prevalence of wide PP in the diabetic patients is 63% based on the 4th report, and 67% based on KIGGS. PP is elevated at a similar rate in girls and boys and remains stable at approximately 60–70% for all age groups (Tables 2–4).

Diabetes-associated risk factors influencing pulse pressure

The prevalence of wide PP is related to age, male sex, insulin dose, BMI-SDS, and height-SDS. PP levels are less often increased in children from Austria. Remarkably, the diabetes duration is not associated with a wide PP (Table 5, multiple regression).

Using multiple linear regression analysis, age, male sex, diabetes duration, insulin dosage, and BMI-SDS are significantly associated with increased absolute PP in diabetic children. There is a negligible negatively relationship between HbA1c and PP (Table 5).

Pulse pressure, relation to age and diabetes duration

The difference between the observed and the expected PP (PPobs-PPexp) increases significantly in the first 6 years of life of the diabetic children, particularly compared with the control subjects of the 4th report: in the diabetic children aged1 year the observed PP is even lower by 7 mmHg in females and by 10 mmHg in males than in the controls of the 4th report (PPobs-PPexp: −7 mmHg in females and −10 mmHg in males), at 6 years PP is elevated by 2 mmHg in females and by

Table 1. Basic characteristics of the study population

Parameter	Total	Boys	Girls	<10 years	10–15 years	15–20 years
n	46 737	24 430	22 307	8 647	14 895	23 195
Age (years)	14.0 ± 4.2	14.0 ± 4.2	13.9 ± 4.2	7.0 ± 2.2	12.7 ± 1.4	17.4 ± 1.3
Body weight (kg)	55.6 ± 19.9	57.2 ± 21.0	53.7 ± 18.4	26.6 ± 8.3	51.0 ± 13.1	69.2 ± 12.2
Body weight-SDS	0.42 ± 1.1	0.30 ± 1.1	0.55 ± 1.0	0.38 ± 1.1	0.36 ± 1.0	0.47 ± 1.1
BMI (kg/m^2)	21.2 ± 4.1	20.9 ± 3.8	21.6 ± 4.3	17.0 ± 2.1	20.3 ± 3.5	23.4 ± 3.5
BMI-SDS	0.52 ± 1.0	0.41 ± 0.9	0.64 ± 1.0	0.43 ± 0.9	0.42 ± 0.9	0.61 ± 1.0
Diabetes duration (years)	5.4 ± 4.2	5.3 ± 4.2	5.5 ± 4.1	2.4 ± 2.1	4.5 ± 3.4	7.1 ± 4.3
Insulin dosage (IU/kg/d)	0.85 ± 0.3	0.85 ± 0.3	0.84 ± 0.3	0.71 ± 0.3	0.86 ± 0.3	0.88 ± 0.3
HbA1c (%)	8.3 ± 1.8	8.2 ± 1.8	8.4 ± 1.8	7.7 ± 1.4	8.2 ± 1.7	8.6 ± 2.0

BMI, body mass index; SDS, standard deviation score. Body weight, body weight-SDS, BMI, BMI-SDS insulin dose, and HbA1c are higher in girls and increase with age.

Table 2. Blood pressure regulation in all diabetic patients compared with the control populations (4th report and KIGGS)

Parameter	Study population	p
n	46 737	
SBP-SDS vs. 4th report	0.76 ± 1.0	<0.0001
MAP-SDS vs. 4th report	0.52 ± 0.7	<0.0001
DBP-SDS vs. 4th report	0.39 ± 0.8	<0.0001
SBP-SDS vs. KIGGS	0.56 ± 1.2	<0.0001
MAP-SDS vs. KIGGS	0.29 ± 1.0	<0.0001
DBP-SDS vs. KIGGS	0.16 ± 1.1	<0.0001
PP observed (mmHg)	49.1 ± 11.0	—
PP exp in 4th report (mmHg)	45.4 ± 3.6	—
PP exp in KIGGS (mmHg)	44.6 ± 4.6	—
PP incr vs. 4th (%)	63	<0.0001
PP incr vs. KIGGS (%)	67	<0.0001
PP obs–exp vs.4th report (mmHg)	3.7 ± 10.3	<0.0001
PP obs–exp vs. KIGGS (mmHg)	4.5 ± 10.2	<0.0001
PP-SDS vs. 4th	0.37 ± 1.0	<0.0001
PP-SDS vs. KIGGS	0.41 ± 1.2	<0.0001

SDS, standard deviation score. PP observed is the documented PP of the diabetic subjects, PP exp is the expected PP (50th percentile of the control population (i.e., SDS 0), either 4th report or KIGGS). PP incr is the rate of patients with increased PP compared either to the 4th report or KIGGS. PP obs–exp describes the difference between the observed and expected PP compared with the 4th report and KIGGS. The following parameters are significantly increased in diabetic children: systolic BP (SBP), mean arterial pressure (MAP), diastolic BP (DBP), pulse pressure (PP), and observed PP ($p < 0.0001$).

Table 3. Blood pressure regulation in the diabetic patients according to sex

Parameter	Boys	Girls	p
n	24 430	22 307	
SBP-SDS vs. 4th report	0.66 ± 1.0	0.87 ± 1.0	<0.0001
MAP-SDS vs. 4th report	0.41 ± 0.7	0.63 ± 0.7	<0.0001
DBP-SDS vs. 4th report	0.28 ± 0.7	0.51 ± 0.8	<0.0001
SBP-SDS vs. KIGGS	0.44 ± 1.1	0.69 ± 1.2	<0.0001
MAP-SDS vs. KIGGS	0.20 ± 1.0	0.39 ± 1.0	<0.0001
DBP-SDS vs. KIGGS	0.07 ± 1.1	0.25 ± 1.2	<0.0001
PP observed (mmHg)	50.6 ± 11.7	47.4 ± 9.9	<0.0001
PP exp in 4th (mmHg)	46.8 ± 3.9	43.8 ± 2.4	<0.0001
PP exp in KIGGS (mmHg)	46.4 ± 5.3	42.6 ± 2.3	<0.0001
PP incr vs. 4th report (%)	63	63	0.12
PP incr vs. KIGGS (%)	65	69	<0.0001
PP obs–exp vs. 4th report (mmHg)	3.8 ± 10.9	3.6 ± 9.6	0.12
PP obs–exp vs. KIGGS (mmHg)	4.2 ± 10.6	4.8 ± 9.6	<0.0001
PP-SDS vs. 4th report	0.38 ± 1.0	0.36 ± 0.9	0.22
PP-SDS vs. KIGGS	0.37 ± 1.2	0.45 ± 1.2	<0.0001

SDS, standard deviation score. PP observed is the documented PP of the diabetic subjects, PP exp is the expected PP (50th percentile of the control population (i.e., SDS 0), either 4th report or KIGGS). PP incr is the rate of patients having increased PP compared either with the 4th report or KIGGS. PP obs–exp describes the difference between the observed and expected PP compared with the 4th report and KIGGS. Absolute pulse pressure (PP) is higher in boys, whereas the deviation of BP and PP compared to the control populations (SDS values and PP obs-exp) is higher in girls than in boys for systolic BP (SBP), mean arterial pressure (MAP), diastolic BP (DBP), PP (vs. KIGGS) and $p < 0.0001$.

1 mmHg in males. Compared with the KIGGS cohort there is almost no difference at 1 year of age (PPobs-PPexp 1 mmHg in females and 0 mmHg in males), whereas PPobs-PPexp increases to 4 mmHg in both females and males at 6 years of age. In the patients older than 6 years, PPobs-PPexp remains stable between 2 and 4 mmHg compared with the 4th report and at 4 mmHg compared with KIGGS data.

Surprisingly, the major increase of PP occurs within the first 4 years of diabetes. PPobs-PPexp increases from 2 to 3 mmHg in females and from 1 to 4.5 mmHg in males compared with the controls of the 4th report. Compared to KIGGS PP of the diabetic children rises from 3 to 5 mmHg in both sexes (KIGGS). From 5 years of diabetes onwards, PPobs-PPexp remains quite stable on the same level (4th report and girls in KIGGS) or even decreases (boys in KIGGS) (Fig. 1).

Discussion

Blood pressure regulation is abnormal in diabetic children as demonstrated in this binational multicenter investigation. Compared to the American reference population, SBP is increased by 0.77 SDS, MAP by 0.52 SDS, and DBP by 0.39 SDS. Compared to the

Table 4. Blood pressure regulation in the diabetic patients according to age

Parameter	<10 years	10–15 years	15–20 years	p
n	8647	14 895	23 195	
SBP-SDS vs. 4th report	0.72 ± 0.9	0.69 ± 1.0	0.83 ± 1.1	<0.0001
MAP-SDS vs. 4th report	0.57 ± 0.7	0.46 ± 0.71	0.53 ± 0.7	<0.0001
DBP-SDS vs. 4th report	0.50 ± 0.7	0.34 ± 0.7	0.38 ± 0.8	<0.0001
SBP-SDS vs. KIGGS	0.62 ± 1.2	0.59 ± 1.1	0.52 ± 1.2	<0.0001
MAP-SDS vs. KIGGS	0.33 ± 1.0	0.30 ± 1.0	0.27 ± 1.0	<0.0001
DBP-SDS vs. KIGGS	0.18 ± 1.1	0.16 ± 1.1	0.14 ± 1.1	0.15
PP observed (mmHg)	42.7 ± 9.1	48.1 ± 10.0	52.1 ± 11.2	<0.0001
PP exp in 4th report (mmHg)	40.7 ± 2.0	44.7 ± 2.4	47.6 ± 2.6	<0.0001
PP exp in KIGGS (mmHg)	38.5 ± 1.2	43.5 ± 2.2	47.5 ± 4.0	<0.0001
PP incr vs. 4th report (%)	59	63	64	<0.0001
PP incr vs. KIGGS (%)	69	67	65	<0.0001
PP obs–exp vs. 4th report (mmHg)	2.0 ± 9.3	3.4 ± 9.7	4.5 ± 10.9	<0.0001
PP obs–exp vs. KIGGS (mmHg)	4.1 ± 8.9	4.6 ± 9.7	4.6 ± 10.9	0.02
PP-SDS vs. 4th report	0.22 ± 0.9	0.35 ± 0.9	0.45 ± 1.0	<0.0001
PP-SDS vs. KIGGS	0.44 ± 1.2	0.43 ± 1.2	0.38 ± 1.2	<0.0001

DBP, diastolic BP; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic BP; SDS, standard deviation score.
PP observed is the documented PP of the diabetic subjects, PP exp is the expected PP (50th percentile of the control population (i.e., SDS 0), either 4th report or KIGGS). PP incr is the rate of patients with increased PP compared either with the 4th report or KIGGS. PP obs–exp describes the difference between the observed and expected PP compared with the 4th report and KIGGS. Absolute PP increases with age in the study population and in controls ($p < 0.0001$). Although the differences between the age groups are significant, only PP obs–exp compared with the population of the 4th report shows this age dependency.

Table 5. Results of multiple regression analysis of the factors influencing the prevalence of wide pulse pressure compared with the control populations of the 4th report and KIGGS (A) and the absolute pulse pressure (B)

	4th report				KIGGS			
(A) Wide pulse pressure	Estimate	Standard error	*t* Value	Pr > |t|	Estimate	Standard error	*t* Value	Pr > |t|
Intercept	0.2304	0.08	2.85	0.0044	0.9686	0.08	11.79	0.004
Age	0.03009	0.003	10.91	<0.0001	−0.01651	0.03	−5.86	<0.0001
Diabetes duration	−0.00406	0.003	−1.45	0.15	−0.00324	0.03	−1.15	0.25
Sex (male)	−0.01053	0.02	−0.53	<0.0001	−0.1163	0.02	−5.82	<0.0001
HbA1c	−0.06968	0.01	−11.59	<0.0001	−0.05368	0.01	−8.89	<0.0001
Insulin dose	0.2011	0.04	5.74	<0.0001	0.1700	0.04	4.79	<0.0001
Background (G/A)	−0.04527	0.03	−1.52	0.13	−0.05679	0.03	−1.87	0.06
BMI-SDS	0.2418	0.01	22.59	<0.0001	0.2714	0.01	24.99	<0.0001
Height	−0.04964	0.01	−5.15	<0.0001	−0.03120	0.01	−3.20	0.001

(B) Absolute pulse pressure	Estimate	Standard error	*t* Value	Pr > |t|
Intercept	33.7100	0.40	84.11	<0.0001
Age	0.9120	0.01	76.59	<0.0001
Diabetes duration	−0.06543	0.01	−5.45	<0.0001
Sex (male)	3.2846	0.09	38.70	<0.0001
HbA1c	−0.3309	0.03	−12.77	<0.0001
Insulin dose	1.6353	0.15	10.89	<0.0001
Background (G/A)	0.02140	0.13	0.17	0.87
BMI-SDS	1.6794	0.05	36.97	<0.0001
Height	0.7598	0.04	18.39	<0.0001

BMI-SDS, body mass index-standard deviation score. $p < 0.05$ is considered significant.

German controls SBP was increased by 0.57 SDS, MAP by 0.29 SDS, and DBP by 0.16 SDS. The increase is more pronounced for SBP than for DBP, resulting in higher PP levels in the diabetic children.

PP is elevated in approximately two of three diabetic children and is related to age, BMI-SDS, and insulin requirement, whereas sex does not seem to have a major influence on the prevalence of wide PP. In the non-diabetic children of the American National Health and Nutrition Survey (NHANES), odds ratios for wide PP are significantly higher in boys and in obese children (14). In our study, mean BMI-SDS and HbA1c

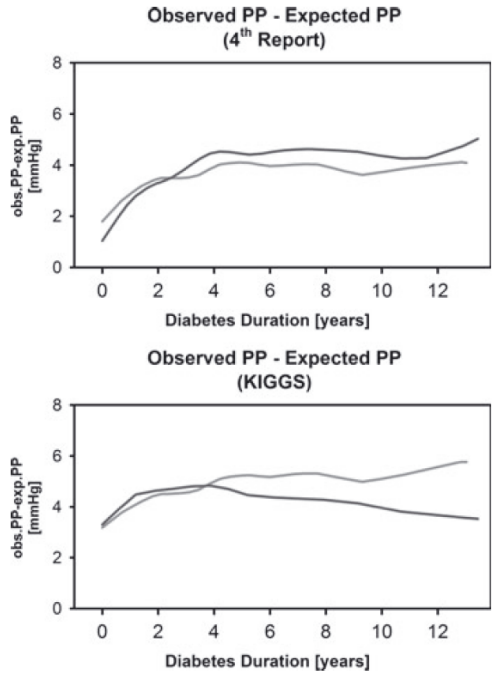

Fig. 1. Time course of the difference between the observed PP in the diabetic patients (— boys, — girls) compared with the expected values of the control populations 4th report (A) and KIGGS (B). PP increases particularly within the first 4 years of diabetes and seems to reach a plateau thereafter (4th report) or even decreases (diabetic boys compared with the control population KIGGS).

levels are higher in diabetic girls than in the boys. So, these factors seem to counteract the gender-specific difference in the prevalence of wide PP and result in an even higher rate of elevated PP in girls.

In their recently published review O´Rouke and Adij attribute the increase of PP to arterial stiffening in patients over 60 years, but to high amplification of the central pressure wave in patients younger than 40 years. They discuss that isolated systolic hypertension in young non-diabetic patients does not require aggressive treatment (15). However, we compared diabetic to non-diabetic children and adolescents on an almost nationwide scale. The age of diabetic patients ranges from 5.5 to 20 years, the controls from 3 to 17 years (KIGGS) and from 1 to 17 years (4th report), respectively, covering a similar age span. Slightly more boys than girls were included in all cohorts. Therefore, the cohorts are well matched except of the fact that the patients are diagnosed with diabetes. Therefore, the differences in PP regulation found in this investigation can be attributed to the diagnosis of type 1 diabetes.

In the diabetic children mean absolute PP is 49.1 mmHg, ranging in the subgroups from 42.7 to 52.1 mmHg, and covering exactly the range of the mean PP levels of the obese children in NHANES (48.3–51.9 mmHg) (14). Compared to a German cohort of normo-, prehyper-, and hypertensive children from Munich, mean PP of our diabetic patients range between the PP of the children with normal and hypertensive blood pressure (16).

Mean absolute PP is elevated by 4 to 5 mm Hg in the diabetic children. This difference is equivalent to half of the PP increase in adult type 2 diabetic patients in the Dutch Hoorn study. In these patients each 10 mm Hg increase of PP enhances the risk of cardiovascular death by 27% (4).

In our diabetic children both components of BP regulation, MAP and PP, are increased and might largely contribute to impaired vascular tone. Assuming that the same levels of PP correlate with the same cardiovascular risk, this would mean that the diagnosis of type 1 diabetes significantly enhances the risk for cardiovascular disease (CVD). The combination of diabetes, obesity, and increased PP is linked to a significant concentric hypertrophy of the left cardiac ventricle, associated with increased incidence of CV events and death (17).

Absolute PP is higher in boys than in girls, both in diabetic and non-diabetic individuals. This gender-related difference is also found in non-diabetic children (14, 16) and in young adults. It disappears later in life; in diabetic subjects by the age of 35–39 years and in non-diabetic subjects by the age of 55–59 years (18). Therefore, this gender-specific difference in PP regulation seems to be physiological and it is rather the convergence between the sexes that is a marker for vascular aging.

In the adult type 2 diabetic subjects of the Hoorn study, SBP increases and DBP decreases significantly stronger with age compared with the non-diabetic controls. As a result, mean PP levels are significantly higher in the diabetic patients for a given age (4). In type 1 diabetic patients PP begins to rise approximately 15 years earlier than in non-diabetic subjects indicating accelerated endothelial dysfunction and arterial stiffness (18). Increased arterial stiffness in type 1 diabetes occurs as early as childhood when compared with matched control subjects (6, 19, 20).

These pathological alterations start with the onset of diabetes, contributing to an earlier loss of vascular compliance and eventually resulting in accelerated vascular aging and diabetic macroangiopathy at a comparably young age.

In our diabetic children PP increases within the first 5–6 years of life. However, measuring blood pressure in children younger than 5 years is a real challenge and often incorrect. So, the blood pressure values in the very young children below 5–6 years and therefore the PP levels might be inaccurate and should be neglected.

Assumingly for the same reason only children of 6 years or older were included in the NHANES

survey. Here, PP increased by 0.9 mmHg in the non-obese cohort from the age-group 6–12 years to the age-group 13–17 years, and by 3.6 mmHg in the obese children, respectively (14). In our patients PP levels remained rather stable from the age of 5 years onwards indicating that age itself does not exert a major influence on PP regulation.

The significant correlation between age and PP levels in the multiple testing might be attributed to the fact that diabetes duration increases with age and that rather the years of diabetes than the chronological age seem to be crucial for the alterations in blood pressure regulation.

PP increases within the first 4 years of diabetes and reaches a plateau for the next 10 years in our cohort. This finding was quite surprising as we presumed a slower incline of the PP. *A priori* we had speculated that the cumulative effect of chronic hyperglycemia and advanced glycosylation endproducts would cause a slow and steady progressive loss of endothelial function over several years.

From the day of the diagnosis of type 1 diabetes, the patients are given insulin subcutaneously. To reach appropriate insulin levels in the liver the applied insulin doses need to be higher than the physiologically secreted amount of insulin, leading to peripheral hyperinsulinemia. In our patients high insulin doses correlate with elevated PP assuming a link between PP and insulin resistance. Balletshofer et al. found a significant association between endothelial dysfunction and insulin resistance in young normoglycemic first-degree relatives (FDRs) of type 2 diabetic subjects independent of the classic cardiovascular risk factors. Flow-associated dilation was reduced to half in insulin-resistant FDRs compared with insulin-sensitive FDRs and non-diabetic control subjects (21).

Insulin is a strong enhancer of sodium transport by upregulation of several transporters in the renal tubules. Sodium retention facilitated by hyperinsulinemia could therefore be an important factor in the pathogenesis of arterial hypertension in insulin resistance (22).

High doses of insulin cause accumulation of fat mass and eventually obesity. In our patients BMI-SDS increases with age and diabetes duration, particularly in females. Obesity, especially central obesity, is significantly linked to a higher prevalence for wide PP and to higher mean PP in NHANES (14) and in our patients. As we induce hyperinsulinemia in the type 1 diabetic children, our therapy might be one of the reasons for this early increase in PP. Factors like chronic hyperglycemia and AGE-production come into effect later within decades and eventually lead to structural changes in the vessel architecture. The delayed effect of chronic hyperglycemia on PP regulation explains the negligible correlation between PP and HbA1c in our patients.

Several factors seem to contribute to impaired PP regulation in diabetic patients: in the beginning of the disease insulin resistance promotes endothelial dysfunction (23), later on oxidative stress, carbonyl stress, and advanced glycation endproducts may combine to exaggerate structural changes in collagen and elastin structure and function and result in loss of vascular elasticity (4). Increased aldosteron secretion leads to an activation of TGF-β, which induces the growth of the extracellular matrix of endothelial cells and an accumulation of fibrinogen in the vessel wall (23, 24). Both mechanisms contribute to endothelial dysfunction. Genetic polymorphisms of the renin-angiotensin-aldosteron system (RAAS) seem to enhance this process (25).

Several drug classes interfere with these pathomechanisms and constitute lower PP: nitrates, NO-donors, drugs inhibiting the RAAS (ACE-inhibitors, AT1 receptor antagonists) (25). In diabetic patients altered BP regulation is often associated with albuminuria. Therefore, ACE inhibitors or/and antagonists of the AT1 receptors should be used as first line treatment in arterial hypertension or increased PP to profit from their additional beneficial effect on the local renal RAAS and their nephroprotective effect.

Our data are based on daytime office blood pressure readings only, which is a disadvantage of this study. This investigation is based on the 'crude' cohort of diabetic children, we did not exclude prehypertension or white coat hypertension at this stage. Twenty-four hours blood pressure profile could help to further differentiate our cohort and to find a possible circadian regulation of PP (8).

However, our aim was to describe PP regulation in a large cohort of type 1 diabetic children and to find out if there are differences compared with the reference cohorts. These data are not collected within study protocols but reflect real life conditions of approximately 90% of the children and adolescents with type 1 diabetes in Germany and Austria over the last 15 years.

To our best knowledge this is the first investigation to compare PP regulation in diabetic and non-diabetic children on a nearly nationwide scale and to prove significant alterations associated with diabetes.

Conclusion

PP regulation is significantly impaired in diabetic children and an independent marker for diabetic macroangiopathy. Measurements of PP are simple, cheap, and universally available and should therefore be used for risk stratification of cardiovascular disease (26), particularly in diabetic patients.

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Conflict of interest

The authors declare that they have no conflicts of interest relevant to this article.

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Thickness of the Supraspinatus and Biceps Tendons in Diabetic Patients

The effect of diabetes on tendons is not well known. There are some studies that analyze the impact of diabetes on tendon structures. It has been shown that chronic hyperglycemia causes some structural changes in tendon collagen (1,2). To the best of our knowledge, there is no published study on biceps and supraspinatus tendons. To observe the effect of diabetes on tendons, we studied the biceps and supraspinatus tendons because they can be easily measured by the ultrasonography (USG) technique. We measured both of these tendons using high resolution USG in 150 diabetic patients (50 type 1 and 100 type 2 diabetic patients, 75 men and 75 women, mean age 50.17 ± 15 years [±SD]) and 94 control outpatients (47 men and 47 women, mean age 47.53 ± 14 years) recruited from our clinic population.

All studies were performed and interpreted by a single radiologist using and Aloka SSD 620 ultrasound machine (Tokyo) with 7.5 MHz linear probe. The shoulder was examined by standard techniques (3). Maximal supraspinatus tendon thickness was measured on a longitudinal view, just in front of the lateral part of the humeral head (4). The long head of the biceps tendon was viewed in the bicipital groove, and its transverse thickness was measured (5).

Specifically, in diabetic patients, the thickness of the right biceps (RB) tendon was equal to 4 ± 1.05 mm, whereas it was 2.95 ± 0.38 mm in the control group ($P < 0.0001$). For the left biceps (LB) tendon, the thickness was 4.04 ± 1.02 mm in diabetic patients and 2.97 ± 0.26 mm in the control group ($P < 0.0001$). Similarly, the tendon thickness of the right supraspinatus (RS) and left supraspinatus (LS) was 6.60 ± 1.25 and 6.58 ± 1.18 mm in diabetic patients and 4.91 ± 0.41 and 4.96 ± 0.39 mm in the control group, respectively ($P < 0.0001$). The results of a logistic regression analysis indicated that the relative risk of a tendon increase in diabetic patients, as compared with the control group, was equal to 16.14 for the RB tendon, 60.66 for the LB tendon, 22.75 for the RS tendon, and 24.28 for the LS tendon.

Our results clearly indicated that there was a positive correlation between age and all four of the shoulder tendon thicknesses, i.e., $P < 0.05$ for RB and RS and $P < 0.001$ for LB and LS. On the other hand, we did not observe such a statistical relationship in the control group. Furthermore, there was only a positive correlation between the duration of diabetes and the thickness of both RS and LS, i.e., $P < 0.05$.

There are some similar studies on patients with amiloidosis (4). They found thickening of the rotator cuff due to the deposition of a β_2-microglobulin amiloidosis of the patients on chronic hemodialysis. In our study, none of the patients had a terminal kidney disease or had undergone hemodialysis treatment.

In summary, we observed an increase in biceps and supraspinatus tendon thickness in diabetic patients that was aggravated with aging in diabetic patients, although such a relationship did not exist for the control group. Our study is an important step in the direction of explaining this newly recognized complication of diabetes by using a noninvasive and relatively inexpensive USG technique, even though we need further studies to support our claim.

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Impaired Cerebrovascular Reactivity in Type 1 Diabetic Children

The risk of vascular disease is not distributed equally among type 1 diabetic patients. Subgroups exist with a relatively low risk versus a high risk of vascular disease (1). Screening for diabetic retinopathy and nephropathy is the most widely used parameter to obtain additional information on the vascular state in patients with diabetes. However, in children, both vascular screening parameters have shown certain limitations (2). The Doppler method has been demonstrated to detect diabetic vasculopathy at a very early stage of endothelial dysfunction. We investigated the neurovascular coupling mechanism that adapts cerebral blood flow to cortical activity and performed a functional transcranial Doppler test using a visual stimulus.

The aim of our present investigation was to describe endothelial function in healthy children and patients suffering from type 1 diabetes for less and greater than 5 years without any apparent diabetic complications, such as microalbuminuria or retinopathy. All children had a normal 24-h ambulatory arterial blood pressure recording and a normal lipid status. We evaluated evoked blood flow ve-

Table 1—*Descriptive and Doppler data*

	Control subjects	Diabetes duration <5 years	Diabetes duration >5 years	*P*
Descriptive data				
Volunteers (*n*)	29	29	53	
Girl/boy ratio (*n*)	14/13	15/14	25/28	
Age (years)	13.3 ± 2.7	13 ± 2	14.8 ± 2.5	NS*
BMI (kg/m^2)	19.5 ± 2.4	19.4 ± 2.8	22.4 ± 3.7	NS*
Diabetes duration (years)	—	2.9 ± 1.5	8.4 ± 2.3	<0.001†
Fasting glucose level (mmol/l)	—	9.8 ± 1.2	10.4 ± 1.5	NS†
Last HbA_{1c} (%)	—	8 ± 2	8.4 ± 1.7	NS†
Long-term (>2 years) HbA_{1c} (%)	—	7.9 ± 1.1	7.5 ± 1	NS†
Albumin/creatinin ratio	—	11 ± 11	8.6 ± 6.6	NS‡
24-h RR recording above reference (%)	—	13 ± 17	14 ± 20	NS‡
Cholesterol (mmol/l)	4.14 ± .6	4.7 ± 0.9	4.3 ± 0.7	NS*
Triglyceride (mmol/l)	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3	NS*
HDL cholesterol (mmol/l)	—	1.8 ± 0.4	1.7 ± 0.3	NS†
LDL cholesterol (mmol/l)	—	2.4 ± 0.5	2.2 ± 0.7	NS†
LDL/HDL ratio	—	1.3	1.3	—
Insulin dose (IE/kg)	—	1 ± 0.25	1 ± 0.2	NS†
Doppler data				
Resting blood flow velocity (cm/s)	60 ± 10	65 ± 14	58 ± 12	NS*
Time delay (s)	1.7 ± 1	1.8 ± 1	1.5 ± 1.1	NS*
Rate time (s)	3 ± 1.8	3.2 ± 1.6	3 ± 1.8	NS*
Gain, difference to baseline (%)	15.2 ± 4	18.3 ± 7.5	17.5 ± 5.5	NS*
Attenuation	0.38 ± 0.13	0.47 ± 0.14	0.48 ± 0.16	<0.025*
Natural frequency (1/s)	0.22 ± 0.06	0.21 ± 0.05	0.21 ± 0.05	NS*

Data are means ± SD unless otherwise indicated. Statistical methods: *ANOVA, †*t* test, ‡Wilcoxon's rank sum test.

locity changes in the posterior cerebral artery according to a control system approach, specifying a five-parameter model (3). The parameters specifying the entire time course of the blood flow regulation were time delay, rate time, attenuation, gain, and natural frequency. The time delay is the time span between change in test conditions (signalized by a tone) and the evoked flow response. The rate time specifies the initial up-stroke in flow velocity, whereas the attenuation parameter describes the damping of the system before the stable new blood flow level is reached, as indicated by the gain parameter. The natural frequency describes the oscillation of the system as if it were undampened. The results of descriptive as well as Doppler data are shown in Table 1 together with statistical results.

It is still an open discussion as to what extent a diabetic state results in vascular alterations in children. The increase in the parameter attenuation in both diabetic groups is indicative of a lack of dilative agents under regulative conditions, thus increasing the vessel wall rigidity. Because the parameter gain remained unchanged, the initial functional impairment was completely compensated when stable blood flow conditions were reached. This constellation is in agreement with the understanding of endothelial dysfunction (1,2). A total of 10% of the patients with a diabetes duration <5 years and 15% of those with a duration of >5 years showed attenuation values above the upper tolerance limit of $2\sigma_{control}$ of the healthy subjects. None of the data sets fell beyond the lower limit. Because the HbA_{1c} values of the outliers were not statistically different compared with their group values, correlation of both is weak, and the evaluation of HbA_{1c} status together with endothelial function might assess the individual vascular risk more appropriately. Besides the limitation that the cerebrovasculature differs from the peripheral vasculature in many aspects, we presented a painless and easy-to-perform method that may indeed be feasible for investigating and monitoring endothelial function in children.

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COMMENTS AND RESPONSES

Subcutaneous Glucose Monitoring

Microdialysis vs. intracorporeal

This letter is in response to the study by Jungheim et al. (1) in the September issue of *Diabetes Care*. They studied a subcutaneous glucose monitoring system in 23 subjects with diabetes over a 3-day period. They report a satisfactory mean absolute difference (MAD) between sensor values and capillary blood glucose of 14.8%.

I agree with the authors that their sensor, which uses microdialysis, appears to function in a stable fashion. It is impressive that they found it necessary to calibrate the device only once during this period, at a mean time of 4.7 h after insertion. As the authors point out, this stability (if verified) probably constitutes an advantage over intracorporeally placed sensors, which tend to undergo a decline in sensitivity over time and therefore require periodic recalibration.

However, I believe that another part of this report is misleading. Their first sentence states that devices for continuous glucose monitoring should display the data in real time rather than retrospectively. I think all workers in this field and all potential users of these devices would agree. It is for precisely this reason that I think that it is invalid for the authors to subtract 31 min from the time value for each sensed glucose value. I understand their rationale: the microdialysis system creates an intrinsic lag (time for fluid transportation through the dialysis system). Nonetheless, when a patient with diabetes uses this system in real time, this lag cannot be conveniently removed by subtraction. In fact, this could be a problem in the clinical situation of rapidly declining glycemia when the patient needs to know the glucose level immediately. I believe that in the displayed figure, the time values for the sensor readings were retrospectively corrected for this 31-min delay; thus, it would appear much different without such a correction. It would be more clinically relevant to show the actual time values. Furthermore, it appears that the MAD of 14.8% was also based on time-corrected values, and I suspect that the MAD would be substantially greater without this correction. Studies performed by my colleagues and I using intracorporeal sensors have not used corrections for sensor delay (2–6).

I think readers may have taken away a misleading message from this report, i. e., that dialysis-based sensors are likely to be more stable over time than intracorporeal systems. I think a more balanced set of conclusions would be that dialysis-based sensors are likely to be more stable over time than intracorporeal systems; on the other hand, dialysis-based sensors are more likely than intracorporeal sensors to exhibit error caused by delays intrinsic to the device, and judgments of superiority of one system over the other await prospective studies where sensor accuracy is assessed in real time.

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Response to Ward

We read with interest the comments of Ward (1) on our microdialysis-based continuous glucose monitoring system. We especially appreciate that he shares our delight on the stability (i.e., lack of time-dependent signal decline) of this system, which has been verified by standardized regression analysis.

Furthermore, Ward raises the important general question of the optimal way to evaluate a continuous glucose monitoring device—an open question so far. Our suggestion is to perform an evaluation of a continuous glucose monitoring device in a stepwise approach consisting of a technical evaluation followed by a clinical evaluation.

First, there is certainly a need for an accuracy and precision analysis (2) to evaluate the technical performance of a device. Obviously, for this evaluation, glucose values generated by test and reference method are matched according to the moment at which the samples are taken and not according to the moment at which they are measured. Consequently, for the technical evaluation presented, it was not only justified but also mandatory to correct the data for the time lag between sample collection and analysis.

We agree with Ward that there is also a need for a clinical evaluation to predict the clinical efficiency of continuous glucose monitoring devices. But how should an appropriate clinical evaluation of real-time continuous glucose monitoring devices be done? Ward proposed an evaluation by performing a simple accuracy and precision analysis of the data without correcting for the time lag between sample collection and measurement display. This approach totally