Improved Time in Range Over 1 Year Is Associated With Reduced Albuminuria in Individuals With Sensor-Augmented Insulin Pump–Treated Type 1 Diabetes

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OBJECTIVE

To investigate the association between treatment-induced change in continuous glucose monitoring (CGM) time in range (TIR) and albuminuria in persons with type 1 diabetes (T1D) treated with sensor-augmented insulin pumps (SAP).

RESEARCH DESIGN AND METHODS

Twenty-six out of 55 participants with albuminuria and multiple daily injection therapy (25% females; median 51 [interquartile range 46–63] years of age; glycated hemoglobin A_{1c} (HbA_{1c}) 75 [68–88] mmol/mol [9.0% (8.4–10.4%)]; and urinary albumin-to-creatinine ratio (UACR) 89 [37–250] mg/g) were in a randomized controlled trial assigned to SAP therapy for 1 year. Anthropometrics, CGM data, and blood and urine samples were collected every 3 months.

RESULTS

Mean change (95% CI) in percentage of TIR (%TIR) was 13.2% (6.2; 20.2), in HbA_{1c} was −14.4 (−17.4; −10.5) mmol/mol (−1.3% [−1.6; −1.0]), and in UACR was −15% (−38; 17) (all $P < 0.05$). UACR decreased by 19% (10; 28) per 10% increase in %TIR ($P = 0.04$), 18% (1; 30) per 10 mmol/mol decrease in HbA_{1c} ($P = 0.07$), and 31% per 10-mmHg decrease in mean arterial pressure ($P < 0.001$).

CONCLUSIONS

In this longitudinal study, treatment-induced increase in %TIR was significantly associated with decrease in albuminuria in T1D.

Glycated hemoglobin A_{1c} (HbA_{1c}) is the gold standard for assessment of glucose control in people with type 1 diabetes (T1D) (1). HbA_{1c} has in several studies been shown to be a strong predictor for chronic diabetes complications but has limitations in predicting hypoglycemia risk and describing the day-to-day glucose excursions (2). Furthermore, the relationship between HbA_{1c} and mean glucose concentration varies among individuals (3).

Recently, the use of continuous glucose monitoring (CGM) has provided new measures for assessing glucose control beyond HbA_{1c} and even in real time (4). Consensus guidelines recommend keeping CGM values >70% of time in range (TIR) of 3.9–10 mmol/L because they correspond to an HbA_{1c} level <53 mmol/mol (7%) (5). However, the evidence for the relationship between CGM-derived TIR and chronic diabetes complications is limited.

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The aim of this study was to compare the changes in albuminuria over a year with the changes in TIR in people with T1D.

RESEARCH DESIGN AND METHODS

Design

Study design, participants, and procedures are described in detail elsewhere (6). In brief, a randomized, controlled, open-labeled parallel trial was conducted on 60 participants with T1D, with a history of albuminuria, and on stable renin-angiotensin-aldosterone system (RAAS) inhibition. They were randomly assigned to sensor-augmented insulin pump (SAP) or multiple daily injection (MDI) and followed for 1 year with in-clinic visits after 0, 3, 6, 9, and 12 months. The study was conducted between February 2012 and December 2014, approved by the regional ethics committee (H-3-2011-122), and registered at ClinicalTrials.gov (NCT01454700).

Participants

Adults with T1D, aged 18–75 years, HbA_{1c} $\geq$58 mmol/mol ($\geq$7.5%), estimated glomerular filtration rate $\geq$45 mL/min/1.73 m^2, treated with RAAS inhibition, and a urinary albumin-to-creatinine ratio (UACR) $\geq$30 mg/g at screening were included. A total of 273 individuals were invited to participate, 84 were screened, 63 were enrolled, and 55 completed the study, with 26 assigned to SAP and 29 to MDI.

Procedures

All participants were monitored with a blinded CGM (iPro2; Medtronic) for 6 days at baseline and for the MDI group also at the study end. All were encouraged to measure four blood glucoses daily. All were trained in carbohydrate counting and diabetes self-care.

Participants assigned to SAP wore an insulin pump (MiniMed Paradigm; Medtronic) and a real-time CGM (Enlite; Medtronic). The insulin pump was set to suspend insulin at a sensor glucose level of 3.0 mmol/L.

Study Visits

At every visit, BMI and mean arterial pressure (MAP) were calculated, and blood and urine samples were collected. For the SAP group, the CGM and insulin pump data were also uploaded (CareLink Pro; Medtronic). No adjustments for CGM malfunctions, errors, or data loss were performed.

Statistics

In this subanalysis, only the CGM data for the SAP group were included for analysis. Consensus guidelines for reporting CGM data were followed (5,7). Percentage of TIR (%TIR 3.9–10.0 mmol/L), time above range level 1 (%TAR_1 >10.0 mmol/L), time above range level 2 (%TAR_2 >13.9 mmol/L), time below range level 1 (%TBR_1 <3.9 mmol/L), time below range level 2 (%TBR_2 <3.0 mmol/L), and the glucose management indicator (GMI) (8) were calculated. Glycemic variability was expressed as coefficient of variation (%CV).

A linear mixed model with a participant-specific random intercept was used to analyze the effect of changes in %TIR, %CV, and GMI on the changes in UACR, adjusting for changes in MAP, HbA_{1c}, and BMI. UACR was skewedly distributed and logarithmically transformed before analysis. Normally distributed data were presented as mean (95% CI). Nonnormally distributed data were presented as median and interquartile range. All statistical analyses were performed with SAS 9.4 M5 (SAS Institute Inc.).

RESULTS

Twenty-six participants were assigned to the SAP group. They included 25% women and had a median (interquartile range) age of 51 (46–63) years, diabetes duration of 32 (23–43) years, BMI of 27.5 (23.5–31.1) kg/m^2, HbA_{1c} of 75 (68–88) mmol/mol (9.0% [8.4–10.4%]), and UACR of 89 (37–250) mg/g. All participants were on RAAS inhibition treatment at baseline.

HbA_{1c} and UACR improved significantly from baseline to study end. There were no changes in MAP, BMI, or in the treatment with RAAS or any other antihypertensive drugs (6).

Participants used the CGM, on average, for 68% (61–78%) of the total follow-up time (Table 1). There was a significant improvement in CGM-derived TIR, average glucose level, glycemic variability, and GMI from baseline to study end (all $P < 0.01$) (Table 1).

The changes in UACR from baseline to study end were inversely correlated with the changes in %TIR ($R = -0.03$; $P = 0.04$) (Supplementary Fig. 1). However, no significant difference was observed in UACR changes when stratifying the %TIR changes into quartiles ($P = 0.5$) (Supplementary Table 1).

The UACR decreased, with 19% (10–28%) per 10% increase in %TIR ($P = 0.038$) and with 22% (11–33%) per 10-mmHg decrease in MAP ($P < 0.001$) (Supplementary Fig. 2). In the adjusted model only, changes in UACR were also significantly related to the changes in average glucose level and GMI (both $P = 0.03$). No relationships were seen in the adjusted model between the changes in UACR and HbA_{1c} ($P = 0.071$), %CV ($P = 0.59$), and BMI ($P = 0.83$) (Supplementary Table 2).

CONCLUSIONS

In this 1-year longitudinal study, treatment-induced increase in CGM-derived TIR was significantly associated with reduced albuminuria in individuals with SAP-treated T1D and albuminuria. This was independent of changes in blood pressure, HbA_{1c}, and BMI. Furthermore, the glycemic variability did not have any significant impact on albumin excretion. This is the first study to demonstrate a prospective association of changes in CGM-derived %TIR and GMI with improvements in albuminuria.

Former studies have confirmed the relationship between HbA_{1c} and %TIR, but less evidence exists on the link between %TIR and chronic diabetes complications. The available studies are limited to individuals with type 2 diabetes and retinopathy (9), observation of seven-point finger prick measurements (10), and/or retrospective data with 3 days' consecutive CGM data (11), in contrast to the recommendation that CGM data from at least 10–14 days are needed (5). The strength of this study is that CGM data were collected for 1 year and were analyzed every 3 months in relation to corresponding levels of HbA_{1c}, UACR, and MAP.

In our original published study (6), changes in albuminuria were only significantly lower for the SAP group compared with the MDI group when accounting for changes in HbA_{1c}. This extended analysis shows that the reduction in albuminuria is better explained by the changes in %TIR and GMI. In contrast, the improvements in glycemic variability for the SAP group could not explain the changes in albuminuria. Thus, we can speculate that albuminuria may be determined by the overall glucose load rather than by the glucose fluctuations. However, more studies are needed to confirm these findings.

The study has limitations. First, the MDI group was not included in the main analysis because they only wore blinded CGMs for 6 days at baseline and at study end. According to consensus guidelines

Table 1—Overview of the study outcomes at each visit

	Month						
	0	3	6	9	12	$Change_{end-baseline}$	*P* value
Days from baseline	0± 0	103 ± 25	193 ± 27	289 ± 28	392 ± 33		
HbA_{1c}, mmol/mol	76.0 ± 12.5	69.8 ± 11.7	64.0 ± 11.4	62.6 ± 13.5	61.8 ± 11.4	−14.4 (−17.4; −10.5)	<0.0001
HbA_{1c}, %	9.1 ± 1.1	8.5 ± 1.1	8.0 ± 1.0	7.9 ± 1.2	7.8 ± 1.04	−1.3 (−1.6; −0.96)	
UACR*, mg/g	95.8 ± 3.7	93.5 ± 3.5	70.1 ± 4.4	65.6 ± 4.0	76.3 ± 3.8	−15 (−38; 17)	0.049
MAP†, mmHg	98.9 ± 9.7	96.2 ± 14.0	94.3 ± 11.9	96.6 ± 9.8	97.9 ± 12.4	−1.9 (−6.3; 2.5)	0.90
BMI, kg/m^2	27.5 ± 5.1	27.6 ± 5.5	27.7 ± 5.1	27.5 ± 5.2	27.4 ± 5.6	0.3 (−0.2; 0.7)	0.18
CGM uploads, *N*	26	24	24	25	22		
CGM readings, %	81 ± 31	63 ± 30	55 ± 20	61 ± 32	78 ± 51		
CGM readings, h	116 ± 45	961 ± 462	1,717 ± 623	1,403 ± 732	1,938 ± 1,267		
$\%TAR_2$	18 ± 13	15 ± 12	11.4 ± 8.7	11.5 ± 10	9.0 ± 7.7	−7.0 (−10.9; −3.3)	0.002
$\%TAR_1$	42.3 ± 16.9	49.7 ± 19.4	42.5 ± 17.2	38.8 ± 18.2	32.3 ± 14.4	−7.4 (−12.9; −1.9)	<0.0001
%TIR	46.9 ± 20.1	47.1 ± 19.0	53.5 ± 20.0	57.9 ± 19.9	64.3 ± 13.4	13.2 (6.2; 20.2)	0.0003
$\%TBR_1$	10.7 ± 12.5	3.2 ± 9.8	4.0 ± 11.4	3.3 ± 5.1	3.4 ± 2.6	−6.3 (−11.1; −1.6)	0.008
$\%TBR_2$	3.3 ± 3.8	0.2 ± 0.3	0.3 ± 0.3	0.4 ± 0.4	0.6 ± 0.7	−2.7 (−3.8; −1.9)	<0.0001
$Mean_{SG}$, mmol/L	9.6 ± 1.8	10.3 ± 1.6	9.7 ± 1.4	9.4 ± 1.6	8.9 ± 1.3	−0.5 (−1.02; −0.03)	0.0001
SD_{SG}, mmol/L	4.0 ± 1.0	3.2 ± 0.5	3.1± 0.4	3.2 ± 0.5	3.2 ± 0.6	−0.7 (−1.0; −0.4)	<0.0001
CV_{SG}, %	41.9 ± 8.4	31.1 ± 3.9	32.4 ± 3.7	34.2 ± 3.6	36.3 ± 4.6	−5.6 (−8.1; −3.1)	<0.0001
GMI_{SG}, mmol/mol	58.0 ± 8.2	61.2 ± 7.6	58.2 ± 6.5	57.0 ± 7.3	54.4 ± 6.0	−2.5 (−4.8; −0.1)	0.0001

The top portion shows mean ± SD of HbA_{1c}, UACR, MAP, and BMI for each visit. The bottom portion shows the data for CGM (Enlite; Medtronic) as the number of participants with successful uploads; the percentage of CGM use for each observation period; percentage of %TIR (3.9–10.0 mmol/L), $\%TAR_1$ (>10.0 mmol/L), $\%TAR_2$ (>13.9 mmol/L), and $\%TBR_1$ (<3.9 mmol/L) as well as time in clinical hypoglycemia range ($\%TBR_2$: <3.0 mmol/L); and sensor glucose–calculated mean ($Mean_{SG}$), SD (SD_{SG}), CV (CV_{SG}), and GMI (GMI_{SG}). Changes from baseline to study end are presented as mean (95% CI). *Three samples of morning spot urine were collected to quantify UACR by enzyme immunoassay. Presented UACR values are geometric means ± the antilogarithmic of the SD and changes in percentage. †Three blood pressures per visit were measured, and the last two systolic (SBP) and diastolic blood pressures (DBP) were averaged to calculate MAP: MAP = 1/3(SBP − DBP) + DBP. *P* values were calculated using a linear mixed model with participant-specific intercept as a random effect and time from baseline as a fixed effect.

for CGM use recommending >70% of possible CGM readings over a 2-week period, the MDI group had insufficient CGM data to assess the glucose control (7,12). However, when including the MDI group in the analysis, the relationships between %TIR and UACR almost reached statistical significance ($P = 0.052$) (Supplementary Table 3). Lastly, the study was neither designed nor powered to demonstrate whether %TIR or any other CGM-derived metrics were better correlated to changes in albuminuria than HbA_{1c} alone.

Nonetheless, we conclude that increased %TIR is significantly associated with improved excretion of albumin in the urine in individuals with T1D and that %TIR complements HbA_{1c} with real-time evaluations of the glucose control in relation to effect on albuminuria.

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