The Feasibility and Efficacy of Employing Micro-Tremor and Skin Temperature to Alert for Nocturnal Hypoglycaemia in Adults with Type 1 Diabetes

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Introduction

- For people with diabetes, hypoglycaemia is considered the single greatest barrier to achieving and maintaining glycaemia within target.[1]
- During continuous glucose monitoring (CGM), unrecognised hypoglycaemia has been detected in 63% of people with type 1 diabetes, with 74% of these unrecognised hypoglycaemic events occurring during the night.[2]
- The impact of nocturnal hypoglycaemia on skin temperature remains to be defined.
- Micro-tremor, involving involuntary resting rhythmic movements of an extremity, is characterised by increased power in a specific frequency band.
- Our preliminary data suggest that micro-tremor, typically centred near 19 Hz and not visible to the naked eye, may be increased when glucose levels are in the hypoglycaemic range.
- Micro-tremor may provide an additional signal warning of nocturnal hypoglycaemia.

Aims

(1) To determine if there is a relationship between upper limb micro-tremor and/or skin temperature, and nocturnal hypoglycaemia, in adults with type 1 diabetes studied at home.
(2) To explore the feasibility of a device incorporating an algorithm utilising micro-tremor as an input to provide a signal warning of nocturnal hypoglycaemia.

Methodology

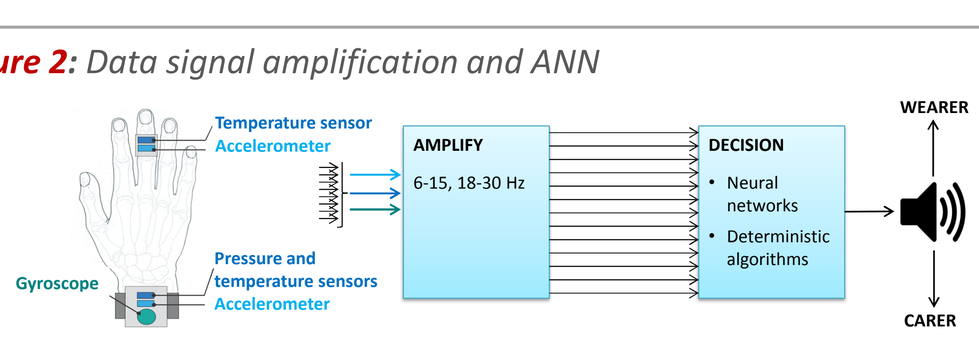
INVESTIGATIONAL DEVICE:

- The prototype device (Fig. 1) records accelerometer, temperature and gyroscope measurements from sensors located on the wearer's wrist, and records accelerometer and temperature data from a sensor located on the wearer's middle finger.

Figure 1: *The non-invasive wrist- and finger-worn investigational device*

- Each sensor provides 100 samples per second from three perpendicular axes. Accelerometer and gyroscope data are amplified and transmitted to an artificial neural network (ANN) which assesses the data to determine the likelihood of hypoglycaemia (Fig. 2).

Figure 2: *Data signal amplification and ANN*



REFERENCE GLUCOSE: CGM (Dexcom G4), calibrated in real-time using a blood glucose meter (Freestyle Optium Neo, Abbott Diabetes Care).

PARTICIPANT ELIGIBILITY: Adults with type 1 diabetes, able to use CGM, with HbA1c <9% (<75 mmol/mol) were eligible.

STUDY PROTOCOL: Participants wore the investigational device and masked CGM concurrently overnight at home for 14 nights on the non-dominant hand. Investigational device data was uploaded daily. The CGM sensor was changed after 7 days. Usual diet, insulin regimen and activities were maintained.

- Participants were requested to perform blood glucose calibrations four times per day including pre-bed.
- Data from a randomly-selected 75% subset of the nights were used to train the ANN (teach the ANN to recognise hypoglycaemia from micro-tremor); the remaining 25% of nights were used to evaluate ANN performance following training.
- For the final 30 participants, the algorithm was exposed to the accelerometer and gyroscope data with and without training.
- Study participants and investigators were masked to all investigational device information during the study.

Results

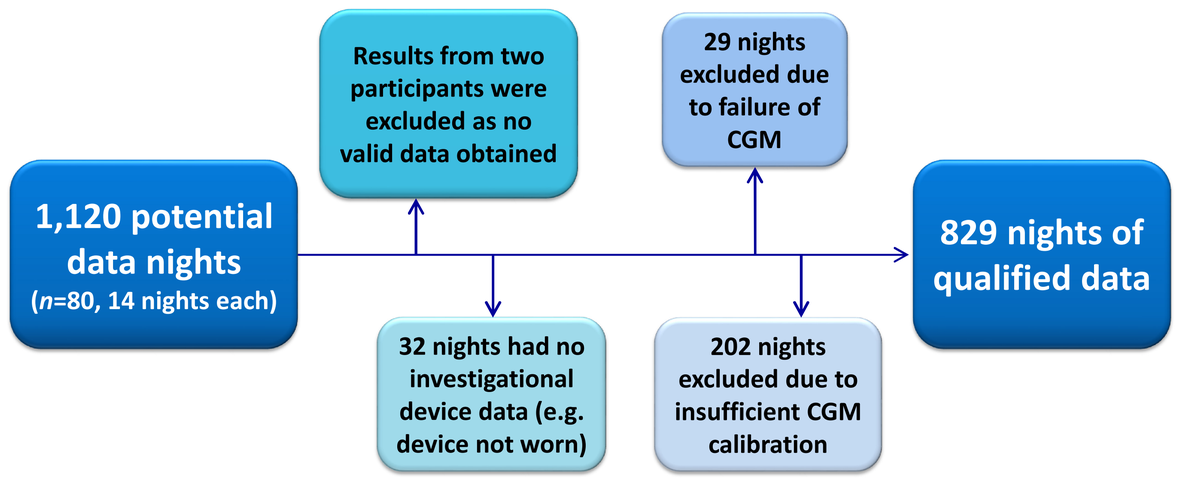
Table 1: *Participant baseline clinical characteristics (n = 80)*

Sex (female)	42 (53%)
Age (years)	45 ± 15
Diabetes duration (years)	24 ± 12
Insulin delivery via pump	43 (54%)
HbA1c (% | mmol/mol)	7.8 ± 0.9 | 62 ± 10
BMI (kg/m²)	27.8 ± 0.5
Impaired awareness of hypoglycaemia (Gold score >4)	17 (21%)

Mean ± SD for continuous variables, counts (%) for categorical variables

Results (cont.)

Figure 3: *Eligible study nights flow diagram*



- Amplitude of micro-tremor at 19 Hz and 5 Hz frequencies were fundamental to nocturnal hypoglycaemia recognition.
- Other frequencies also provided input to the ANN.
- Skin temperature did not correlate with nocturnal hypoglycaemia.

Table 2: *Device specificity, and device sensitivity by hypoglycaemia glucose nadir when trained on all participants: (**A**) all assessable nights; (**B**) novel nights (i.e. with training nights excluded).*

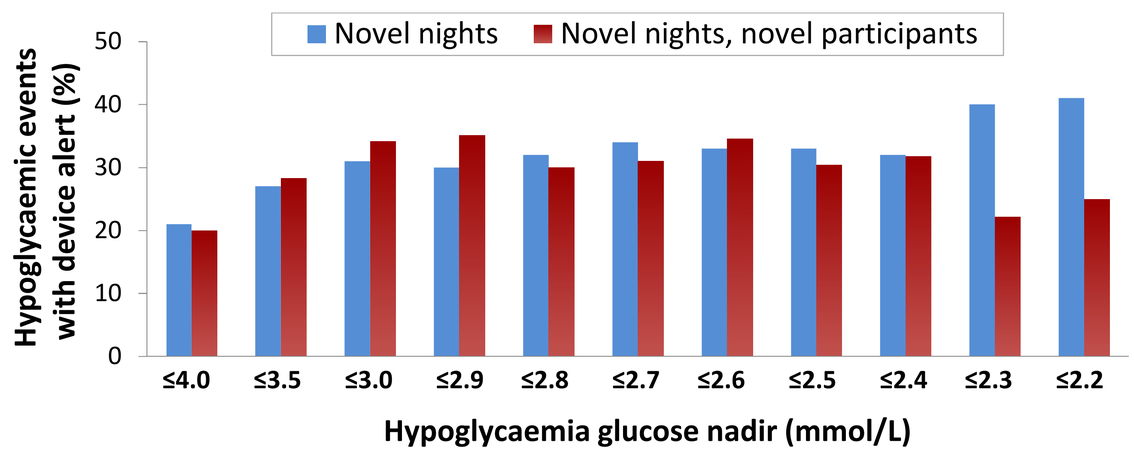
(A)

GROUP	SPECIFICITY	SENSITIVITY BY GLUCOSE NADIR (mmol/L)									
		≤ 2.2	≤ 2.3	≤ 2.4	≤ 2.5	≤ 2.6	≤ 2.7	≤ 2.8	≤ 2.9	≤ 3.0	≤ 3.5	≤ 4.0
All	90% (541/604)	69% (24/35)	67% (29/43)	64% (35/55)	63% (38/60)	64% (43/67)	64% (48/75)	64% (51/80)	62% (57/92)	59% (58/98)	48% (68/143)	39% (77/199)
GOLD SCORE ≤4.0	91% (429/473)	65% (15/23)	63% (19/30)	61% (23/38)	60% (25/42)	60% (28/47)	60% (33/55)	62% (36/58)	59% (40/68)	58% (41/71)	47% (50/106)	38% (57/150)
GOLD SCORE >4.0	85% (112/131)	75% (9/12)	77% (10/13)	71% (12/17)	72% (13/18)	75% (15/20)	75% (15/20)	68% (15/22)	71% (17/24)	63% (17/27)	49% (18/37)	41% (20/49)

(B)

GROUP	SPECIFICITY	SENSITIVITY BY GLUCOSE NADIR (mmol/L)									
		≤ 2.2	≤ 2.3	≤ 2.4	≤ 2.5	≤ 2.6	≤ 2.7	≤ 2.8	≤ 2.9	≤ 3.0	≤ 3.5	≤ 4.0
All	78% (119/153)	41% (7/17)	40% (8/20)	32% (8/25)	33% (9/27)	33% (9/27)	34% (10/29)	32% (10/31)	30% (10/33)	31% (11/35)	27% (12/44)	21% (12/56)
GOLD SCORE ≤4.0	81% (96/119)	38% (5/13)	38% (6/16)	32% (6/19)	33% (7/21)	33% (7/21)	35% (8/23)	35% (8/23)	32% (8/25)	35% (9/26)	29% (10/34)	24% (10/41)
GOLD SCORE >4.0	68% (23/34)	50% (2/4)	50% (2/4)	33% (2/6)	33% (2/6)	33% (2/6)	33% (2/6)	25% (2/8)	25% (2/8)	22% (2/9)	20% (2/10)	13% (2/15)

Figure 4: *Device alert sensitivity by hypoglycaemia glucose nadir during untrained nights on non-novel and novel participants.*



Conclusions

- Changes in micro-tremor amplitude relate to the severity of nocturnal hypoglycaemia.
- Substantial inter-individual variation in micro-tremor responses suggest that training of an ANN is important for hypoglycaemia recognition.
- Skin temperature was not useful for nocturnal hypoglycaemia detection.
- At present, device sensitivity and specificity are not adequate for utility as a stand-alone hypoglycaemia detection device. Further refinement of the device is currently underway.
- This technology may provide for an additional (orthogonal) signal to CGM for nocturnal hypoglycaemia detection as part of a future closed-loop system.

References and Acknowledgements

[1] Frier BM. Diabetes Metab Res Rev. 2008; 24(2):87-92
[2] Chico A, *et al*. Diabetes Care. 2003; 26(4):1153-7

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