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LETTER TO THE EDITOR

Pressure pain sensitivity: A new stress measure in children and adolescents with type 1 diabetes?

Annemarie Cecilie Grauslund, Emilie Bundgaard Lindkvist, Steffen Ullitz Thorsen, Søren Ballegaard, Jens Faber, Jannet Svensson, Anna Korsgaard Berg

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Annemarie Cecilie Grauslund, Steffen Ullitz Thorsen, Jannet Svensson, Anna Korsgaard Berg, Department of Pediatrics, Herlev and Gentofte Hospital, Herlev 2730, Denmark

Emilie Bundgaard Lindkvist, Jannet Svensson, Anna Korsgaard Berg, Copenhagen University Hospital, Steno Diabetes Center Copenhagen, Herlev 2730, Denmark

Steffen Ullitz Thorsen, Department of Clinical Immunology, Rigshospitalet, University of Copenhagen, Copenhagen 2100, Denmark

Søren Ballegaard, Jens Faber, Department of Endocrinology, Herlev and Gentofte Hospital, Herlev 2730, Denmark

Jannet Svensson, Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen 2200, Denmark

Corresponding author: Anna Korsgaard Berg, MD, PhD, Copenhagen University Hospital, Steno Diabetes Center Copenhagen, Borgmester Ib Juuls Vej 83, Herlev 2730, Denmark. anna.korsgaard.berg@regionh.dk

Abstract

Type 1 diabetes (T1D) is associated with general- and diabetes-specific stress which has multiple adverse effects. Hence measuring stress is of great importance. An algometer measuring pressure pain sensitivity (PPS) has been shown to correlate to certain stress measures in adults. However, it has never been investigated in children and adolescents. The aim of our study was to examine associations between PPS and glycated hemoglobin (HbA1c), salivary cortisol and two questionnaires as well as to identify whether the algometer can be used as a clinical tool among children and adolescents with T1D. Eighty-three participants aged 6-18 years and diagnosed with T1D were included in this study with data from two study visits. Salivary cortisol, PPS and questionnaires were collected, measured, and answered on site. HbA1c was collected from medical files. We found correlations between PPS and HbA1c (rho = 0.35, P = 0.046), cortisol (rho = -0.25, P = 0.02) and Perceived Stress Scale (rho = -0.44, P = 0.02) in different subgroups based on age. Males scored higher in PPS than females (P < 0.001). We found PPS to be correlated to HbA1c but otherwise inconsistent in results. High PPS values indicated either measurement difficulties or hypersensibility towards pain.

Key Words: Stress; Children and adolescents; Type 1 diabetes; Autonomic dysfunction

Core Tip: The aim of present study was to examine whether pressure pain sensitivity (PPS) in children and adolescents associates with other stress measures and determine if it can be used as a clinical tool in this population. Our study revealed some unexpected discrepancies examining PPS in a pediatric population with type 1 diabetes, highlighting the need for more research to validate if PPS is a clinically useful measure in children.

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TO THE EDITOR

Type 1 diabetes (T1D) is associated to general- and diabetes-specific stress, which is linked to high glycated hemoglobin (HbA1c)[1], increased morbidity and mortality, and decreased quality of life[2]. In adults, Ballegaard *et al*[3,4] found pressure pain sensitivity (PPS) measured with an algometer to be correlated with established stress measures, thereby introducing an objective, non-invasive method of measuring stress. The aim of this study was to examine how PPS in children and adolescents associates with other stress measures and whether it can be used as a clinical tool in this population.

Data were collected as part of a prospective study of dermatological complications to diabetes devices. The present study included individuals with T1D between the ages of 6-18 years, and two study visits for each participant were selected based on available data. Exclusion criterium was participant or caregiver not being able to speak or read Danish.

PPS was measured using the algometer with two to three consecutive measurements on the index finger and tibia for method introduction before placement on the sternum. Increasing pressure was put on the skin for three seconds and participants were asked to say "stop" just before or *as* the pressure turned into pain or discomfort. The measurement was also stopped when a noxious withdrawal reflex (NWR) was observed, or if there was an activation of an alarm at maximum pressure (= 30 on PPS scale). PPS-score ranges from 30-100 with values ≥ 60 being the cut-off point for high level of stress in adults, based on receiver operating characteristic curves[4,5]. Salivary cortisol was analyzed with radioimmunoassay and HbA1c collected from medical files. Perceived Stress Scale (PSS) and World Health Organization-5 Well-Being Index (WHO-5), two questionnaires regarding stress and well-being, were completed during visits. PSS was answered by participants from age 10 years and WHO-5 from age 6 years. Examinations were conducted between April 1, 2020 and April 9, 2021. The study was approved by the Danish Data Protection Agency (P-2020-2) and the Regional Committee in Health Research Ethics (H-18059790) and followed Danish legislation regarding consent. Statistical analyses were made using the statistical software package R, version 4.2.2. Spearman's rank correlation was used for correlation analyses. Sex differences were analyzed using Mann-Whitney *U* test. The study population was analyzed as a whole and divided in two age groups (6-12 years, 13-18 years). A P value of < 0.05 was considered statistically significant.

This study comprised 83 participants, 51% male, mean (± SD) age was 12.6 (± 2.9) years and median (Q1-Q3) T1D duration was 0.8 years (0.01; 3.4). Forty-one percent were diagnosed with T1D within three months prior to their first study visit. Tables 1 and 2 show correlation analyses at the first visit (Table 1) and in between visits (Table 2) for the whole population as well as when stratified into age groups. Unexpectedly, negative correlations were found between PPS and cortisol in the total population (rho = -0.25, P = 0.02), in the 13 to 18-year-olds (rho = -0.35, P = 0.045), and between PPS and PSS in the 6 to 12-year-olds (rho = -0.44, P = 0.02). A positive correlation between PPS and HbA1c was present in the 13 to 18-year-olds (rho = 0.35, P = 0.046) and this finding persisted when comparing differences in PPS and HbA1c between the two visits (rho = 0.45, P = 0.048). Males scored higher than females in PPS in the total population (median difference = 17.5, P < 0.001), this being driven by the younger age group (P < 0.001) since no sex difference was present among 13 to 18-year-olds. No sex differences were found among the other variables. The PPS measurements were strongly and internally correlated when measured on the index finger, the tibia, and the sternum (all r > 0.5, all P < 0.001).

To summarize, we found a positive correlation between PPS and HbA1c in the old age group and unexpectedly negative correlations at the first visit between PPS and cortisol and PPS and PSS, the latter being present in the young age group. The negative and missing correlations contrast the findings of Ballegaard *et al*[3] who in adults found significant correlations between PPS and physiological markers of stress (heart rate, blood pressure, pressure rate product), regulation of glucose metabolism in adults with type 2 diabetes[5-7], survival in persons with ischemic heart disease[8] and questionnaires regarding mental and physical health[4]. Interestingly, we found that the younger males scored higher than the younger females but no differences among the older participants. Conversely Ballegaard *et al*[3] found the opposite correlation in adults which is more in line with the general assumption that females score higher in stress than males[9]. When using the algometer, a sex specific scale is activated. Hence our opposing findings may be explained by an irrelevance of different scales for sex in younger children. Despite the set-up with measuring on finger and tibia first

Table 1 Pressure pain sensitivity and correlations to stress measures during the first study visit

	Age: 6-12 yr; (M = 24, F = 25)		Age: 13-18 yr; (M = 18, F = 16)		Total population; (M = 42, F = 41)	
	Median (Q1; Q3), *N* (missing)	Rho (*P* value)	Median (Q1; Q3), *N* (missing)	Rho (*P* value)	Median (Q1; Q3), *N* (missing)	Rho (*P* value)
Pressure pain sensitivity[1]	85 (68; 99), 0		76 (66; 91), 0		81 (66; 96), 0	
Perceived stress scale[2]	12 (8; 16), 23	-0.44 (0.02)[3]	16 (10; 18), 9	0.16 (0.45)	15 (9; 18), 32	-0.18 (0.20)
WHO-5	72 (64; 84), 7	0.29 (0.06)	62 (46; 76), 4	-0.21 (0.26)	68 (59; 80), 11	0.14 (0.23)
Salivary cortisol (nmol/L)	6.8 (5.8; 8.5), 0	-0.13 (0.38)	9.4 (5.6; 15.3), 0	-0.35 (0.045)[3]	7.4 (5.7; 10.4), 0	-0.25 (0.02)[3]
HbA1c (mmol/mol)	63 (53; 8), 0	-0.27 (0.06)	67 (59; 72), 1	0.35 (0.046)[3]	66 (53; 80), 1	-0.07 (0.51)

[1]Pressure pain sensitivity score is an average of two to three measurements at the sternum. Third measurement was performed if a difference > 10 was present between the two first measurements. Distribution of cause of termination: First measurement: 18 with noxious withdrawal reflex, 65 said "stop"; second measurement: 15 with NWR, 66 said "stop", 1 alarm; third measurement: 4 with NWR, 2 said "stop".
[2]Answered by children above age 10 yr.
[3]Indicates a significant correlation (Spearman; $P < 0.05$).
M: Male; F: Female; Q1; Q3: First and third quartile; HbA1c: Glycated hemoglobin; WHO-5: World Health Organization-5 Well-Being Index.

Table 2 Within-variable differences between the two study visits and the correlations between changes in Pressure pain sensitivity and changes in Perceived stress scale, World Health Organization-5 Well-Being Index, salivary cortisol and glycated hemoglobin respectively

	Age: 6-12 yr; (M = 24, F = 25)		Age: 13-18 yr; (M = 18, F = 16)		Total population; (M = 42, F = 41)	
	Median (Q1; Q3), *N* (missing)	Rho (*P* value)	Median (Q1; Q3), *N* (missing)	Rho (*P* value)	Median (Q1; Q3), *N* (missing)	Rho (*P* value)
Pressure pain sensitivity[1]	4.5 (0; 13), 0		3 (-2.9; 8.4), 0		3.5 (-0.8; 11.2), 0	
Perceived stress scale[2]	-2 (-7; 0), 24	-0.08 (0.70)	1.5 (-2.3; 4.3), 10	0.06 (0.77)	-1 (-5; 3), 34	-0.04 (0.80)
WHO-5	4 (-8; 12), 8	-0.08 (0.63)	0 (-12; 8), 5	0.34 (0.068)	0 (-8; 11), 13	0.10 (0.43)
Salivary cortisol (nmol/L)	-0.07 (-0.38; 1.3)	-0.14 (0.33)	-0.2 (-3.1; 5.4), 0	0.25 (0.16)	-0.07 (-3.5; 0.75), 0	0.02 (0.87)
HbA1c (mmol/mol)[3]	0 (-5.5; 2.5), 4	0.05 (0.82)	0 (-5; 2.3), 2	0.45 (0.048)[4]	0 (-5; 2.5), 6	0.19 (0.22)

[1]Pressure pain sensitivity score is an average of two to three measurements at the sternum. Third measurement was performed if a difference > 10 was present between the two first measurements. Distribution of cause of termination: First measurement: 18 with noxious withdrawal reflex, 65 said "stop"; second measurement: 15 with NWR, 66 said "stop", 1 alarm; third measurement: 4 with NWR, 2 said "stop".
[2]Answered by children above age 10 yr.
[3]Participants newly diagnosed with Type 1 Diabetes (duration < 3 months) were excluded from analyses ($n = 49$ participants remained, $n = 27$ aged 6-12 yr, $n = 22$ aged 13-18 yr).
[4]Indicates a significant correlation (Spearman; $P < 0.05$).
M: Male; F: Female; Q1; Q3: First and third quartile; HbA1c: Glycated hemoglobin; WHO-5: World Health Organization-5 Well-Being Index.

and then sternum, a high percentage of participants said stop right away even at repeated visits. The *a priori* fear of being hurt and/or problems with understanding the instruction may be more prominent in younger children. A possible scenario could also be that participants wished to appear strong and therefore waited too long before saying stop. The population's high PPS levels can be interpreted as either an expression of a psychological response, measurement difficulties or a general centrally induced hypersensibility caused by autonomic imbalance due to T1D[7]. PPS was significantly lower in participants with NWR compared to participants saying "stop" but too few measurements terminated because of NWR were available to enable subgroup analyses. The study was running during the COVID-19 pandemic which might have influenced stress and well-being. Cortisol levels were not adjusted to potentially influencing factors such as exercise and food intake. The study had minimal selection bias since participants enrolled in a study regarding skin problems. Furthermore, the variation in age allowed subgroup analyses.

In conclusion, there was a moderate to strong internal correlation between PPS measured on the three locations, however, the correlations of PPS to other indicators of stress such as cortisol and PSS was unexpectedly negative. PPS-values were generally high compared to adults reflecting either measurement difficulties or hypersensibility towards pain and the use of sex-specific scale was less relevant in the youngest age group. Our study revealed some unexpected

discrepancies examining PPS in a pediatric population with T1D highlighting the need for more research to validate if PPS is a clinically useful measure in children.

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FOOTNOTES

Author contributions: Grauslund AC, Ballegaard S, Faber J, Thorsen SU, Svensson J and Berg AK designed the research; Grauslund AC, Svensson J and Berg AK did the clinical visits and investigations; Grauslund AC and Berg AK analyzed the data; Grauslund AC prepared the first original draft; Ballegaard S validated the technique for measurement of PPS; Lindkvist EB helped with analytical tools; Svensson J, Thorsen SU and Berg AK supervised the first author; Lindkvist EB, Ballegaard S, Faber J, Thorsen SU, Svensson J and Berg AK reviewed and edited the manuscript. All authors have read and approved the final manuscript.

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Country/Territory of origin: Denmark

ORCID number: Annemarie Cecilie Grauslund 0000-0001-5148-9756; Emilie Bundgaard Lindkvist 0000-0001-5044-2569; Steffen Ullitz Thorsen 0000-0003-4783-2931; Søren Ballegaard 0000-0002-4253-6909; Jens Faber 0000-0003-3525-3772; Jannet Svensson 0000-0002-9365-0728; Anna Korsgaard Berg 0000-0002-1260-0615.

Corresponding Author's Membership in Professional Societies: International Society of Pediatric and Adolescent Diabetes.

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