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Published in:
Diabetes Research and Clinical Practice

DOI:
10.1016/j.diabres.2013.01.026

2013

Impaired vibrotactile sense at low frequencies in fingers in autoantibody positive and negative diabetes

Brief report

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Abstract

Vibration thresholds in index and little finger pulps in subjects with autoantibody [GADA, IA-2A and/or ICA] positive and negative diabetes 20 years after diagnosis were higher than in age-matched controls at low frequencies (8 and 16 Hz), irrespective of HbA1c values, indicating selective impairment of Meissner´s corpuscles and/or their innervating axons.

Key words: Diabetes, Autoantibody, Vibrotactile sense, Meissner´s corpuscles, Finger pulps

Neuropathy develops earlier in type 1 [1] than in type 2 diabetic rats [2], but data in humans are conflicting. Disturbed vibrotactile sense depends on definition and type of subjects as well as upon evaluated extremity [3-6]. Autoimmune activity [presence of islet antibodies: glutamic acid decarboxylase antibodies (GADA), islet cell antibodies (ICA) and IA-2A antibodies] in type 1 diabetes predicts beta-cell failure, whereas beta-cell damage is less pronounced in autoantibody negative type 2 diabetes [7], but its potential long term influence on vibrotactile sense, presently examined in subjects with autoantibody positive and negative diabetes, is unknown.

Materials and methods

Consecutive adult subjects with diabetes diagnosed 1985–1987 (age >15 years; n=233) were followed up. After 20 years 50/118 survivors [7] were examined with respect to vibrotactile sense, length, weight, blood pressure, blood samples, type of diabetes treatment and complications. Subjects were regarded as islet autoantibody positive if they had one or more types of antibodies (GADA, IA-2A and ICA) at onset. Vibrotactile thresholds in index and little finger pulps, reflecting median and ulnar nerve function, respectively, at different frequencies (8, 16, 32, 64, 125, 250 and 500 Hz) were measured by tactilometer [3,4]. Sensibility index was calculated (normal index=1.0; abnormal<0.8 [8]). The study was ethically approved (LU 327/2006).

Results

All presented comparisons of autoantibody positive (n=15) and autoantibody negative (n=35) diabetic patients were done 20 years after diagnosis of diabetes if not otherwise stated (Table 1). HbA1c values decreased during follow up (onset, 3, 5 and 20 years after diagnosis) in autoantibody positive ($p=0.026$), but not in autoantibody negative patients (Fig. 1).

Two different control groups [3,4] were included since thresholds increase with age. Essentially no differences between subjects with autoantibody positive and negative diabetes were detected. Subjects with autoantibody positive and negative diabetes showed significantly higher vibration thresholds, mainly at lower frequencies (8 and 16 Hz), in the index and little fingers bilaterally. Vibration thresholds were significantly increased in single finger pulps, particularly in subjects with autoantibody positive diabetes (for example 32, 64, 250 and 500 Hz), compared to age-matched control subjects.

A lower sensibility index in both index and little fingers bilaterally was observed in patients with autoantibody positive diabetes compared to age-matched controls. No differences in sensibility index were observed between patients with autoantibody positive and negative diabetes or between patients with autoantibody negative diabetes and their age-matched controls.

The proportion of patients with pathological sensibility index (i.e. <0.8) in at least one or four fingers was not significantly different between autoantibody negative and positive diabetes. Neither did prevalence of pathological sensibility index among diabetic patients differ from prevalence among healthy controls.

Vibration thresholds did not differ between subjects with HbA1c values > or < 63 mmol/mol (7.9 % DCCT) at onset, at follow up 20 years after diagnosis, or expressed as mean value of HbA1c values over 20 years in the two autoantibody tested groups.

HbA1c values did not correlate with vibration thresholds or with sensibility index (SI) in any of the investigated fingers. Neither BMI nor laboratory results correlated with vibrotactile sense. However, age correlated with vibration thresholds, but not with SI, in all fingers at higher frequencies [i.e. 125, 250 and 500 Hz (Spearman´s correlation; rho-values 0.36 – 0.50; $p \leq 0.01$)].

Discussion

The findings that vibrotactile sense was disturbed particularly at low (8 and 16 Hz) frequencies indicate that mainly Meissner´s corpuscles, and/or their innervating axons, are affected in both autoantibody positive and negative diabetes, while the Pacinian corpuscles, responsible for vibrotactile sense approximately at 80 Hz and higher, or their innervating axons, were less affected [3,9]. The two groups of subjects had similar duration of diabetes. It would have been valuable to have data on vibrotactile sense at diagnosis, but the present technique was not developed at that time.

As beta-cell function is dependent on the presence of autoantibodies [10], a division of our patients based upon autoimmune activity seems to be more relevant than a division based upon clinical characteristics only, when pathophysiological mechanisms are considered. Presence of ICA autoantibodies at diagnosis of clinical type 2 diabetes is a marker of a more favorable cardiovascular risk profile five years after diagnosis [11]. There is an association between carotid atherosclerosis and cardiovascular autonomic neuropathy in type 2 diabetes [12]. However, the relevance of autoantibodies for complications in type 1 diabetes is different. In subjects with type 1 diabetes, high levels of GAD65 antibodies are related to increased severity of complications (retinopathy and nephropathy). Presence of such antibodies is suggested as predictors for progression of type 1 diabetes or complications [13].

Presence of autoantibodies against GADA at onset of type 1 diabetes also increases the risk for development of diabetic retinopathy [14], and recently reported anti-endothelial and anti-neuronal effects of autoantibodies from subjects with diabetes with particularly painful neuropathy [15] are also relevant for our findings. These relationships between autoantibodies and complications (microangiopathy and neuropathy) in type 1 diabetes render our present division in autoantibody positive and negative diabetes appropriate. However, as neuropathy is present also in autoantibody negative diabetes, other pathophysiological mechanisms must also be involved.

The higher proportion of signs of neuropathy in our older control subjects may partly depend on their higher age. In spite of our autoantibody negative patients being significantly older than autoantibody positive patients, few or no differences were found between the groups. A substantial proportion of those with good glycaemic control [HbA1c < 63 mmol/mol (7.9 % DCCT)] had peripheral neuropathy. Interestingly, vibration thresholds did not differ between diabetic patients with HbA1c values above or below this level at any time, indicating a complex pattern of risk factors for development of neuropathy and that HbA1c alone is not a risk factor for neuropathy [4,16].

Conflict of interest

The authors declare that they have no conflict of interest, but TS is shareholder of VibroSense Dynamics AB, Malmö, Sweden; producer of VibroSense Meter and Tactilometer.

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Table 1. Characteristics and vibration thresholds of autoantibody positive (AB+) and negative (AB-) patients with diabetes compared with control subjects from two previous studies [3,4] [#, §]. Values are from present follow up if not otherwise stated.

Autoantibodies at onset	**Positive (AB+) (n=15)**	**Negative (AB-) (n=35)**	**Control AB+ (n=25)**	**Control AB- (n=28)**	**Kruskal-Wallis**	**P-value control vs AB+**	**P-value control vs AB-**	**P-value AB+ vs AB-**
Age (years)	51 [18]	69 [16]	52 [12.3]	74 [2]	**<0.0001**	0.45	**0.02**	**0.001**
Gender (F/M)	7/8	12/23	12/13	0/28	**0.0004**	0.52	**0.001**	0.51
BMI	23.4 [5.2]	26.9 [7.3]	NA	27.2 [4.3]	**0.04**	NA	0.49	**0.046**
C-peptide (nmol/l)	0.03 [0]	0.7 [0.6]	NA	1.54 [0.8]	**<0.0001**	NA	**<0.0001**	**<0.0001**
HbA1c at onset (%)	11.1 [2.3]	8.5 [3.9]	NA	NA	-	NA	NA	**0.02**

HbA1c at onset (mmol/mol)	97 [25]	69 [42]	NA	NA	-	NA	NA	**0.02**
HbA1c [&] (%)	8.3 [2.4]	7.8 [2.0]	5.3 [0.6]	5.5 [0.5]	**<0.0001**	**<0.0001**	**<0.0001**	0.1
HbA1c [&] (mmol/mol)	67 [26]	61 [21]	34.3 [6.5]	36.4 [5.2]	**<0.0001**	**<0.0001**	**<0.0001**	0.1
HbA1c [€] (%)	9.6 [2.4]	8.1 [2.2]	NA	NA	-	NA	NA	**0.02**
HbA1c [€] (mmol/mol)	82 [27]	64 [24]	NA	NA	-	NA	NA	**0.02**
HDL (mmol/l)	1.3 [0.5]	1.1 [0.4]	NA	1.2 [0.4]	**0.02**	NA	0.17	**0.01**
LDL (mmol/l)	3.0 [0.6]	2.3 [1.4]	NA	3.0 [1.4]	**0.002**	NA	**0.001**	**0.01**
LDL/HDL ratio	2.2 [1.2]	1.9 [1.4]	NA	2.4 [1.4]	0.08	NA	**0.03**	0.58

Cholesterol (mmol/l)	4.6 [0.5]	4.0 [1.5]	NA	5.0 [1.1]	**0.0004**	NA	**0.0002**	0.06
Triglycerides (mmol/l)	0.8 [0.4]	1.3 [0.8]	NA	1.5 [1.1]	**0.0002**	NA	0.34	**0.001**
SBP (mm Hg)	140 [29]	150 [20]	NA	NA	-	NA	NA	**0.03**
DBP (mm Hg)	80 [4]	80 [15]	NA	NA	-	NA	NA	0.69
Hypertension	5 (33 %)	24 (69 %)	0 (0 %)	NA	**<0.0001**	**0.002**	NA	**0.02**
Angina pectoris	1 (6.7 %)	7 (20 %)	0 (0 %)	NA	**0.04**	0.19	NA	0.24
Stroke	0 (0 %)	3 (9 %)	0 (0 %)	NA	0.16	0.99	NA	0.24
	Diabetes treatment							
Diet	0 (0 %)	13 (37.1 %)	0 (0 %)	0 (0 %)		-	-	-
OHA	0 (0 %)	17 (48.6 %)	0 (0 %)	0 (0 %)		-	-	-
Insulin	15 (100 %)	5 (14.3 %)	0 (0 %)	0 (0 %)	-	**<0.0001°**	**<0.0001°**	**<0.0001°**

	Clinical diagnosis							
Clinical diagnosis (T1D/T2D)	8/7	3/32	NA	NA	-	-	-	-
	Vibration thresholds							
Pathologyζ at least one finger	5 (33 %)	17 (49 %)	4 (16 %)	9 (32 %)	-	0.35	0.18	0.32
Pathologyζ in four fingers	1 (6.7 %)	7 (20 %)	0 (0 %)	4 (14 %)	-	0.19	0.55	0.24
Right index finger	**Positive (AB+)**	**Negative (AB-)**	**Control AB+**	**Control AB-**	**Kruskal-Wallis**	**P-value control vs AB+**	**P-value control vs AB-**	**P-value AB+ vs AB-**
8 Hz	107 [6.0]	111 [7.0]	105 [3.0]	108 [12.6]	**0.0003**	0.19	0.07	**0.03**
16 Hz	115 [5.3]	117 [10.0]	112 [2.5]	114 [10.8]	**0.001**	**0.001**	0.05	0.51

32.5 Hz	118 [4.0]	118 [6.0]	115 [5.3]	121 [10.4]	0.312	0.10	0.40	0.72
64 Hz	110 [7.5]	114 [9.0]	113 [9.0]	116 [7.6]	**0.03**	0.24	0.07	0.18
125 Hz	110 [7.3]	117 [16.0]	108 [9.3]	116 [13.0]	**0.03**	0.62	0.08	0.12
250 Hz	125 [18.0]	128 [18.0]	118 [9.3]	127 [16.9]	**0.004**	0.10	0.28	**0.03**
500 Hz	140 [17.5]	143 [19.0]	135 [12.5]	146 [20.4]	**0.001**	0.22	0.14	0.17
SI	0.9 [0.12]	0.86 [0.27]	0.99 [0.16]	0.91 [0.40]	0.22	0.05	0.93	0.73
			Right little finger					
8 Hz	107 [6.0]	111 [5.8]	104 [3.0]	107 [11.8]	**0.0003**	**0.001**	**0.046**	0.22
16 Hz	113 [5.8]	116 [9.3]	111 [5.5]	112 [8.4]	**0.006**	**0.005**	0.06	0.74
32.5 Hz	121 [6.5]	119 [7.3]	117 [8.3]	119 [10.3]	0.052	**0.009**	0.87	0.59
64 Hz	112 [6.8]	114 [14.8]	116 [6.0]	117 [14.2]	**0.03**	0.06	**0.02**	0.49
125 Hz	112 [12.5]	116 [21.8]	111 [8.5]	118 [14.5]	0.09	0.86	0.43	0.33
250 Hz	117 [17.0]	123 [24.0]	117 [11.3]	128 [19.3]	**0.003**	0.26	0.18	0.53
500 Hz	139 [18.3]	141 [26.0]	132 [13.8]	143 [20.2]	**0.002**	**0.047**	0.56	0.70
SI	0.89 [0.14]	0.91 [0.38]	0.96 [0.18]	0.92 [0.36]	0.31	**0.046**	0.92	0.62
			Left index finger					

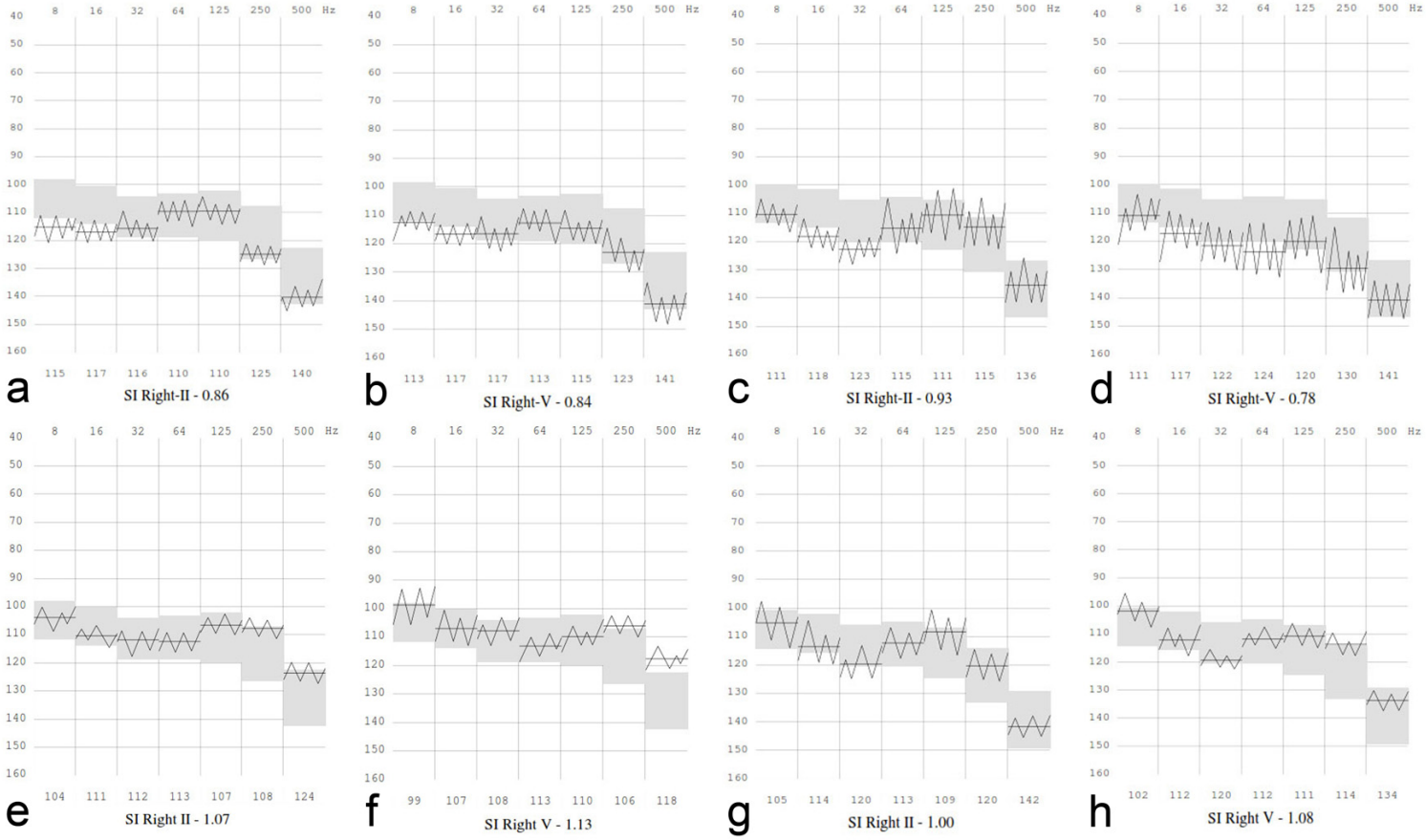
8 Hz	108 [9.3]	111 [7.5]	103 [4.5]	106 [12.0]	**<0.0001**	**0.002**	0.08	0.20
16 Hz	116 [9.3]	117 [7.5]	110 [4.3]	112 [9.7]	**<0.0001**	**0.001**	**0.01**	0.49
32.5 Hz	116 [8.0]	117 [6.8]	114 [6.3]	118 [7.4]	**0.048**	0.59	0.57	0.24
64 Hz	105 [9.0]	110 [14.5]	111 [8.3]	114 [8.6]	0.05	0.11	0.07	0.44
125 Hz	109 [11.5]	113 [18.3]	108 [9.5]	109 [13.8]	0.18	0.97	0.93	0.29
250 Hz	119 [15.0]	126 [24.3]	114 [7.5]	125 [15.0]	**0.002**	**0.04**	0.75	0.60
500 Hz	131 [11.8]	141 [24.8]	130 [12.3]	142 [13.9]	**0.002**	0.09	0.32	0.29
SI	0.94 [0.18]	0.89 [0.33]	1.05 [0.16]	0.99 [0.34]	0.09	**0.02**	0.43	0.84
			Left little finger					
8 Hz	107 [3.8]	110 [9.5]	102 [5.0]	102 [10.5]	**<0.0001**	**0.0003**	**0.002**	0.15
16 Hz	114 [4.8]	116 [8.8]	109 [4.3]	110 [7.0]	**<0.0001**	**<0.0001**	**0.01**	0.55
32.5 Hz	118 [10.0]	118 [8.8]	115 [4.0]	118 [9.3]	**0.04**	0.08	046	0.67
64 Hz	110 [9.3]	114 [14.0]	113 [5.5]	117 [11.6]	0.14	0.14	0.25	0.28
125 Hz	112 [9.8]	114 [21.0]	109 [6.0]	113 [8.7]	0.08	0.52	0.88	0.45
250 Hz	116 [17.8]	124 [28.0]	115 [5.8]	124 [12.8]	**0.03**	0.26	0.92	0.59
500 Hz	138 [21.0]	138 [21.0]	131 [12.3]	145 [14.9]	**0.01**	0.11	0.66	0.50

SI	0.89 [0.17]	0.87 [0.35]	1.01 [0.15]	1.02 [0.25]	0.05	**0.01**	0.12	0.79

Values are median [IQR] or number (%).
Comparisons are done using the Kruskal-Wallis test with subsequent Mann-Whitney test (columns to the right; significant values in bold) or with chi-square test (° different treatments and pathology).
SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; NA, data are not available; OHA, oral hypoglycaemic agents; T1D, type 1 diabetes; T2D, type 2 diabetes; SI, sensibility index [8].
$^{\epsilon}$ mean of HbA1c values at onset, 3, 5 and 20 years.
$^{\&}$ HbA1c values at follow up 20 years after onset.
$^{\zeta}$ SI<0.8.

Figure legend

Figure 1. Tactilograms from subjects with autoantibody positive (a, b) and negative (c, d) diabetes and their age-matched controls (e, f and g, h, respectively) from the index (a, c, e, g) and the little (b, d, f, h) fingers. The vibration thresholds are graphically displayed on an inverted scale with low intensity (amplitude) at the top and high intensity at the bottom on the y-scale and the seven investigated frequencies on the x-scale.


8 16 32 64 125 250 500 Hz
40 50 60 70 80 90 100 110 120 130 140 150 160
a
115 117 116 110 110 125 140
SI Right-II - 0.86
b
113 117 117 113 115 123 141
SI Right-V - 0.84
c
111 118 123 115 111 115 136
SI Right-II - 0.93
d
111 117 122 124 120 130 141
SI Right-V - 0.78
e
104 111 112 113 107 108 124
SI Right II - 1.07
f
99 107 108 113 110 106 118
SI Right V - 1.13
g
105 114 120 113 109 120 142
SI Right II - 1.00
h
102 112 120 112 111 114 134
SI Right V - 1.08