THE PREVALENCE OF AUTONOMIC AND PERIPHERAL NEUROPATHY IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETIC MELLITUS (T1D) AND ITS ASSOCIATION WITH THE HOMOZYGOUS STATUS OF *Z-2/Z-2* POLYMORPHISM OF THE ALDOSE REDUCTASE GENE (*AKR1B1*) IN THE POLYOL PATHWAY.

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Introduction: Diabetic neuropathy (DN) significantly reduces patients' quality of life and increases cardiovascular death risk. However, it is the least recognized complication of diabetes. Z-2/Z-2 polymorphism of the aldose reductase (*AKP1B1*) gene increases the expression of the relative enzyme and is likely to contribute to DN expression.

Purpose: To study the prevalence of DN in T1D children and adolescents and its associations with the homozygous state of Z-2 / Z-2 polymorphism of the *AKR1B1* gene.

Methods: We evaluated 106 T1D children and adolescents (mean±SD age:13.5±3.46 years, T1D duration: 5.3±3.4 years) and 100 healthy controls (age:11.9±2.7 years). Pupillary dilation (PD) in darkness was assessed as an index of diabetes autonomic neuropathy (DAN), using a Polaroid Pupillometer. Abnormal cut-off values (<5%) were calculated from control values distribution. Nerve conduction studies (NCS) were performed with a standard technique using surface electrodes. The polymorphisms of *AKR1B1* gene were evaluated using microsatellite sequence Z.

Results: PD impairment was more frequent in the T1D group compared to controls (31.6% vs 3.3%,p<0.001, Table 1.). PD was associated with age (rho=0.16, p=0.038), HbA1c (rho=0.23, p=0.048) and T1D duration (rho=0.20, p=0.022). There was a strong correlation between PD and NCS in T1D patients (rho=0.34, p=0.008). In T1D patients, Abnormal NCS was neither associated with age (rho=0.01, p=0.91), nor with HbA1c (rho=0.14, p=0.27), or disease duration (rho= -0.2, p=0.12).

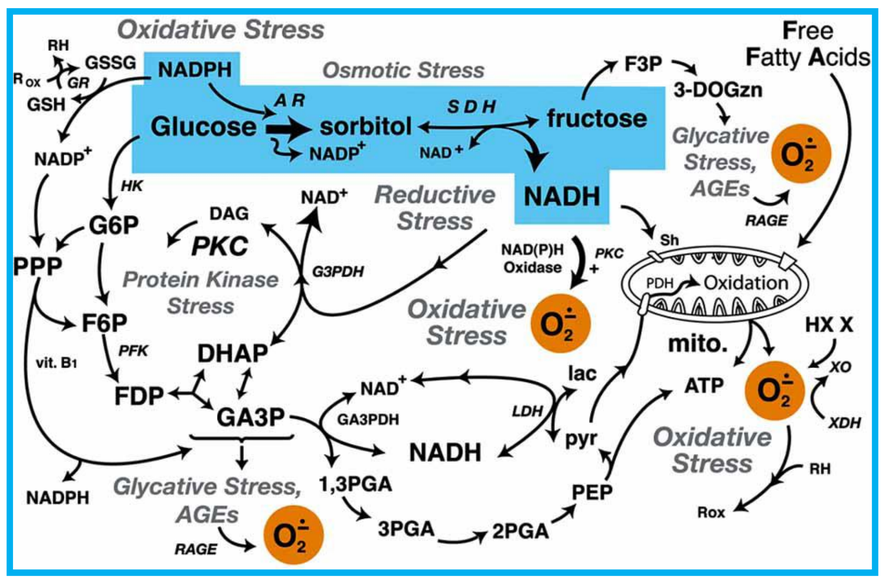

Figure 1. the metabolic pathway of polyols

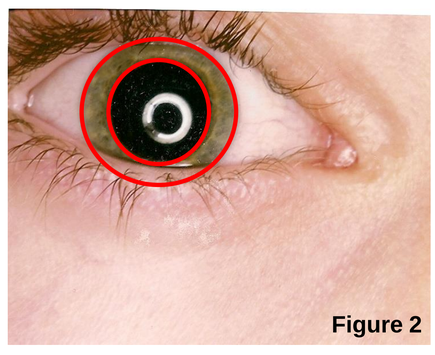

Figure 2

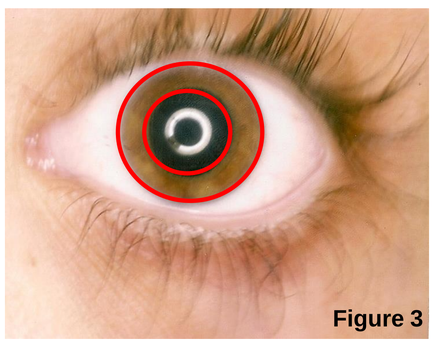

Figure 3

Figure 2 & 3. Normal (Fig. 2) and abnormal (Fig. 3) pupillary dilatation in darkness.

Table 1. Impaired Pupillary Dilation in patients and controls

Pupillary Dilation			
population	Normal	Abnormal	total
patients (n) proportion%	65 61.32%	41 38.68%	106 100%
controls(n) proportion%	97 96.04%	4 3.96%	101 100%
total	162 78.26%	45 21.74%	207 100%
Fischer's exact test, p<0.001			

Table 2. Proportion of the homozygous polymorphism of *AKR1B1* gene in relation with NCS

Peripheral neuropathy			
Polymorphism	no	yes	total
heterozygous/ without	34 (66.67%)	17 (33.33%)	51 100%
homozygous	1 (16.67%)	5 (83.33%)	6 100%
total	35 61,40%	22 38,6%	57 100%
Fischer's exact test, p=0.027			

Table 3. Proportion of the homozygous polymorphism of *AKR1B1* gene in relation with PD

Autonomic neuropathy			
Polymorphism	no	yes	total
heterozygous/ without	61 (67.78%)	29 (32.22%)	90 100%
homozygous	6 (37.5%)	10 (62.5%)	16 100%
total	65 63.21%	39 36.79%	106 100%
Fischer's exact test, p=0.023			

Patients homozygous for Z-2 polymorphism of the *AKR1B1* gene had higher prevalence of NCS abnormality (83.33% vs 33.33%,p=0.027, Table 2.) and also of PD abnormality (62.5% vs 37.5%, p=0.023, Table 3.). In a probabilistic view homozygous patients had a 10-fold higher probability for NCS abnormality (OR=9.99, Z=2.03, p=0.042), 3.5-fold higher probability for PD abnormality (OR=3.5, Z=2.23, p=0.026), 5-fold higher probability for both conditions (NCS+PD abnormality) (OR=5.11, Z=2.22,p=0.027) and 3-fold higher probability for either condition (NCS or PD abnormality) (OR=3.15, Z=1.98, p=0.048) compared with heterozygous and patients without the aforementioned polymorphism.

Conclusions: Impaired indices of peripheral and autonomic DN were present in a significant proportion of young T1D patients, although asymptomatic. Indices of DAN were associated with age, diabetes duration and glycemic control, while NCS were not. PD and NCS abnormalities were strongly related to the homozygosity of Z-2/Z-2 polymorphism of *AKR1B1* gene in the polyol pathway.

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