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Reproducibility of vibration perception threshold values in children and adolescents with type 1 diabetes mellitus and associated factors

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ABSTRACT

Aims: To define the reproducibility of vibration perception thresholds (VPTs) and the possible associated factors, as an early index of peripheral diabetic neuropathy (PDN) in type 1 diabetes mellitus (T1DM) children and adolescents.

Methods: A single examiner studied 118 T1DM subjects (aged 13.5 ± 3.4 years) and 79 controls (aged 12.0 ± 3.07 years). Glycaemic control was assessed with HbA1c levels. VPT was measured twice on upper and lower limbs, using a Biothesiometer. Concordance between the two VPT measurements was evaluated using the Cohen's Weighted Kappa statistic (Kappa = 0.41–0.60 → moderate concordance, Kappa = 0.61–0.80 → substantial concordance).

Results: T1DM children had significantly higher VPTs than controls at all sites ($p = 0.001$), but with lower Kappa values (0.64–0.70). VPT values increased in parallel with HbA1c (*a.* < 8%, *b.* 8–9.5%, *c.* > 9.5%) and T1DM duration (*a.* < 5 years, *b.*5.1–10, *c.* > 10 years). However, Kappa values were lower in the groups with the poorest control (HbA1c > 9.5%) (Kappa = 0.54–0.76) or the longest T1DM duration (>10 years) (Kappa = 0.49–0.71). Although VPTs increased with stature and male gender, no effect on VPT reproducibility was observed. However, obesity was associated with lower VPT values and poorer concordance.

Conclusions: These findings suggest that the reproducibility of VPTs is lower in the high-risk patients for early subclinical PDN development, who need a regular follow-up.

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1. Introduction

Peripheral diabetic neuropathy (PDN) is recognized as a major complication of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), resulting in significant morbidity and mortality. Considerable amount of resources are consumed for the treatment of neuropathy, which is usually ineffective, when clinical manifestations of the neural damage are already present.

Although clinical complications are uncommon in children with T1DM, there is evidence that the pathogenesis of PDN may develop early in childhood and adolescence [1–4]. Abnormalities indicative of early diabetic neuropathy have been described even in recently diagnosed patients, with a diabetes duration of less than one year [5]. Interestingly, near-normalization of blood glucose levels has been shown to reverse the early signs of PDN [6,7]. Conclusively there is a need for screening programs targeted at the early identification of neural deficits in children and adolescents with T1DM.

The estimation of motor and sensory velocities in nerve conduction studies (NCS) is considered as the gold standard method for the early detection of peripheral neuropathy. NCS is a sensitive, accurate, reproducible, and independent of the patient's cooperation electrophysiological method, and is strongly correlated with underlying structural nerve deficits [8–10]. On the other hand NCS is not suitable for use as a screening tool since it is invasive and difficult in conducting [11]. However the thermal [12] and vibration perception thresholds (VPT) have been routinely used as two of the first quantitative sensory tests to determine small and large fiber deficits respectively, in adult patients with diabetes [13]. In particular the estimation of VPT includes repetitive mechanical indentation of the skin, delivered at prescribed frequency and amplitude through automated instruments and is considered a sensitive and reproducible test for afferent systems served by peripheral myelinated fibers of large caliber [14]. There are different commercially available devices for measuring VPT, such as the Biothesiometer, the Neurothesiometer, the Vibration II, the Vibrameter and the CASE IV System. Among them, the Biothesiometer, which is quick, portable and relatively inexpensive, could be suitable as a screening tool in pediatric populations. However the main disadvantage of the Biothesiometer is the "off scale" measurements experienced in adult patients with long diabetes duration, who might suffer from severe neuropathy [15]. In these patients loss of sensation can progress far beyond the maximum VPT value of the Biothesiometer. This is not the case in children and adolescents, in whom PDN is usually asymptomatic or rarely presenting with mild clinical symptoms.

In previous studies the reproducibility of the Biothesiometer has been examined in adults, with excellent reliability in the majority of the subjects [15,16], however no similar reports exist in pediatric populations.

The aim of our study was to evaluate the reproducibility of the estimation of VPT, as a screening tool in pediatric populations using the Biothesiometer, as well as the factors affecting it.

2. Methods

VPTs were measured by a single examiner in a total of 118 children and adolescents with T1DM and 79 non-diabetic children (control group). The T1DM group consisted of 60 girls and 58 boys, with a mean ± SD age of 13.5 ± 3.4 years (range: 8–20 years) and a diabetes duration of 5.7 ± 3.5years (2–16 years). No subject had a recent history of febrile illness at the time of the examination. Among them, (18/118) 15.3% patients with coexisting autoimmune thyroiditis were euthyroid. None of the patients received other medications, apart from insulin or levothyroxine (11% of the patients), or suffered from diseases affecting the central or peripheral nervous system. Only three patients (2.5%) had symptoms of neuropathy, described as numbness in the lower limbs. The control group consisted of 79 age- and sex-matched healthy children and adolescents (48 girls and 31 boys), with a mean ± SD age of 12.0 ± 3.07 years (range: 8–19 years). The control subjects received no medication affecting their reaction time, had no recent injury on upper or lower limbs and had a negative family history concerning neuropathies. Informed consent was obtained from the child or the adolescent and the accompanying parent and the study was approved by the Hospital Ethical Committee.

At the day of each data collection a clinical evaluation of study participants was conducted, including assessment of their pubertal status and growth and thyroid gland palpation. Neurologic examination, including muscle tone, muscle strength and tendon reflexes, was also carried out in all subjects.

Glycosylated hemoglobin A1c (HbA1c) was measured as an index of metabolic control on a DCA 2000 analyzer. The normal range for HbA1c in our Laboratory was 25–46 mmol/mol (4.4–6.4%). At the same time, glucose levels were measured with a single portable glucose meter. In case of blood glycose levels <70 mg/dl, hypoglycaemia was managed accordingly and subsequently the patients continued with the VPT testing. The measurement of VPTs was carried out in a quiet room with a constant temperature. The examiner was not fully blinded; he knew if the subject was a patient or a control, but he was not aware of the detailed history of the patient (duration of diabetes or metabolic control). VPTs were measured twice successively during the same visit in upper and lower limbs in both T1DM and control groups, using a Biothesiometer (Bio-Medical Instrument Co., Newbury, OH, USA). The subjects were placed at ease in a supine or a prone position, depending on the examined site, on an examination bench. To avoid transfer of vibrations through the examination bench to the body, the Biothesiometer was placed on a separate table, which had no contact to the bench. The same apparatus was used throughout the whole study and all threshold determinations were carried out by a single examiner.

The instrument was applied to the skin with a pressure equal to its own weight (440 g). Care was taken to apply the stimulator at the same point on each subject. Four sites, relevant for examination of polyneuropathy, were selected for threshold determinations of vibration sensation; the pulp of the thumb and index finger, the malleolus and the pulp of the big toe. All measurements were taken on both sites of the body.

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