Diabetes mellitus (DM) is a chronic metabolic disease characterized by insulin insufficiency causing chronic degenerative complications involving almost every organ of the human body (American Diabetes Association, 2012). In patients with DM, peripheral neuropathy and retinopathy are well-established pathologies that induce balance impairment and falls (Simoneau et al., 1992, 1994; Schwartz et al., 2008). However, in recent studies, vestibular dysfunction has been demonstrated in patients with diabetes mellitus (DM). Although the exact mechanism and most involved region of the vestibular system have not yet been fully clarified, vestibular dysfunction has been demonstrated in patients with diabetes mellitus (DM). Vestibular evoked myogenic potential (VEMP) is a short latency electromyographic response to sound or vibration stimuli that may reflect otolith organ or related reflex functions. Since its first description in 1992, VEMP has become a significant part of the vestibular test battery as an objective measurement tool. In diabetic patients, VEMP responses have been studied in order to determine any otolith organ or related reflex dysfunctions. Here, we review the literature with regard to VEMP findings representing any peripheral vestibular end-organ dysfunction in patients with DM. Distinctive vestibular end-organ impairments seem to be demonstrated in patients with DM either with or without DNP via objective vestibular testing tools including VEMP recordings according to relevant studies. However, further studies with larger sample sizes are required to reveal the more definitive findings of VEMP recordings regarding the vestibular pathologies in patients with DM.

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vibration stimuli that is considered to demonstrate ipsilateral saccular and inferior vestibular nerve functions (cervical VEMP), as well as contralateral utricular and superior vestibular nerve functions (ocular VEMP) (Rosengren and Kingma, 2013; Colebatch et al., 2016). Since its first description by Colebatch and Halmagyi in 1992, VEMP has become a significant part of the vestibular test battery as an objective measurement tool. Although VEMP testing is mainly used for assessing otolith functions in clinical settings, it has also been used to evaluate the effects of sound stimuli on vestibular reflexes and otolithic projections to various muscular groups and the brain (Rosengren and Colebatch, 2018).

During VEMP testing, surface electrodes are placed on the patient's skin for recording myogenic potentials in response to sound or vibration to provide quick, safe and reliable otolithic function measurement (Fig. 1). Cervical VEMP (cVEMP) measures the inhibitory myogenic potentials of the ipsilateral tensed sternocleidomastoid muscle (sacculo-collic reflex) and is considered to evaluate saccular vestibular signals conducted via the vestibulospinal tract (Rosengren et al., 2010; Rosengren and Kingma, 2013; Rosengren and Colebatch, 2018). Ocular VEMP (oVEMP) obtains the excitatory contralateral inferior oblique muscle potentials (utriculo-ocular reflex) and is considered to measure vestibular functions from the utricle to the oculomotor nucleus, including the superior vestibular nerve and the contralateral medial longitudinal fasciculus (Rosengren et al., 2010; Rosengren and Kingma, 2013; Rosengren and Colebatch, 2018; Bayram et al., 2018).

The normal electromyographic responses of cVEMP recordings display a biphasic waveform with an initial positivity (p13) and subsequent negativity (n23), whereas normal oVEMP waves are represented by an initial negativity (n10) and subsequent positivity (p15) (Rosengren and Colebatch, 2018) (Fig. 2). Latency and threshold of the peaks and peak-to-peak amplitudes are calculated for both reflexes. The threshold value describes the minimum sound stimulus required to elicit a biphasic VEMP waveform. Since VEMP amplitudes are significantly influenced by the force of muscular contraction or stimulus intensity, the amplitude asymmetry ratio (AR) is usually used as the main measurement of interest for amplitude values. The AR value is calculated by the Jongkees formula: (larger-smaller)/(larger + smaller) × 100 (Colebatch et al., 2016).

VEMP responses have been shown to be influenced by pathological or physiological conditions. Conductive hearing loss may cause the absence of VEMP responses due to the low access of sound intensity at the oval window (Han et al., 2016) whereas VEMP responses are not influenced by sensorineural hearing (Murofushi, 2014). In people older than 60 years, VEMP responses usually show attenuation (Fife et al., 2017). Stimulus characteristics such as intensity, frequency, shape, duration and rise time can significantly affect the normal range of VEMP parameters, hence establishing their own normative data is recommended for the clinics.

2. Role of VEMP testing in the diagnosis of common vestibular diseases

Abnormal cVEMP or oVEMP findings including latency, amplitude and threshold may be a sign of pathological conditions along the vestibulo-collic or vestibulo-ocular reflex pathways. Unilateral absence of both cVEMP and oVEMP responses may indicate a lesion localized at the vestibular end organs, otolith projections and nerve root entry, whereas central disorders or demyelinating pathologies of the vestibular nerve may present with delayed latencies of both reflexes (Colebatch et al., 2016). Nowadays, VEMP testing constitutes an important part of the vestibular test battery and provides either diagnostic or assistive contributions in the clinical evaluation of common vestibular diseases such as superior canal dehiscence syndrome (SCDS), Ménière's disease (MD) and vestibular neuritis (VN) (Murofushi, 2016).

SCDS was first described by Minor et al., in 1998 and the disease is characterized by a defect nearly always located in the bone overlying the superior semicircular canal (SCC). In the diagnosis of SCDS, recognition of the defect with temporal bone computed tomography scans is essential. Nevertheless, VEMP findings can also provide significant data regarding diagnosis and defect functionality. Significantly lower cVEMP thresholds were demonstrated in patients with SCDS (Welgampola et al., 2008; Niesten et al., 2013). Corrected cVEMP amplitude values have 100% sensitivity and 93% specificity in SCDS diagnosis (Fife et al., 2017). In oVEMP testing, higher amplitudes with pathologically lower thresholds for air-conducted sound stimuli were demonstrated in patients with SCDS (Minor et al., 1998; Rosengren et al., 2008; Fife et al., 2017). In the diagnosis of SCDS, the sensitivity and specificity of oVEMP thresholds were 77% and 93%, respectively, while the sensitivity and specificity range of oVEMP amplitudes were 77%–100% and 98%–100%, respectively (Fife et al., 2017). Welgampola et al. (2008) reported that successful canal plugging resulted in normalization of reflex thresholds, therefore VEMP testing may also be useful in monitoring the effectiveness of plugging surgery in SCDS. However,
VEMP recordings are particularly amenable for unilateral SCDS by means of interaural comparison rather than bilateral vestibulopathy.

Although MD is usually diagnosed by clinical criteria, laboratory tests such as caloric test are also performed to support the diagnosis in some cases (Erwin, 2004), de Waele et al. (1999). Published the first report of cVEMP in MD with the absence of cVEMP responses in 54% of patients’ affected ears. Reduction of ipsilateral cVEMP amplitudes has been reported in different studies with a prevalence of around 50% in MD (Huang et al., 2011; Taylor et al., 2011), while oVEMP abnormalities were demonstrated with a prevalence of 45–54% (Taylor et al., 2011; Murofushi et al., 2011; Winters et al., 2011). VEMP testing enables demonstration of a vestibular loss in MD but there is not sufficient evidence regarding the usefulness of VEMP in diagnosing MD. However, it can be used for monitoring the status of vestibular dysfunction during the disease process (Fife et al., 2017).

Vestibular neuritis is an acute vestibular pathology that is mostly diagnosed by the typical clinical signs of acute unilateral loss of vestibular function (Jeong et al., 2013). VEMP testing is suggested to indicate the pattern of vestibular nerve involvement in VN whether the disease affects the superior, inferior division of the nerve or pan-neuritis (Colebatch et al., 2016). However, sufficient data does not exist in the literature concerning VEMP abnormalities related to common vestibular diseases such as in the literature, hence VEMP testing may not be useful in the diagnosis of these pathological conditions (Fife et al., 2017). However, specific VEMP abnormalities related to common vestibular diseases are a significant research interest among clinicians and promise to contribute data to the diagnosis.

3. Diabetes mellitus and vestibular dysfunction

Although the exact mechanism has not yet been fully clarified, vestibular dysfunction has been demonstrated in diabetic patients (Agrawal et al., 2009; Agrawal et al., 2010; Ward et al., 2015). The ratio of vestibular dysfunction was shown 70% higher among diabetic patients than healthy people (Agrawal et al., 2009). The falling risk is significantly increased in DM and diabetic neuropathy (DNP) (Agrawal et al., 2010). Besides the role of DNP, peripheral vestibular end-organ pathologies may also promote balance impairments in these patients. Agrawal et al. (2010) reported that vestibular dysfunction may independently induce balance disorders even after adjusting for DNP in patients with DM. Moreover, vestibular dysfunction may occur without prominent vestibular symptoms in patients with DM, as was recently introduced to the literature as ‘subclinical vestibular neuropathy’ (Konukseven et al., 2015). In this scenario, it is suggested that vestibular pathology can be determined via objective vestibular diagnostic testing tools although patients with DM were free of vestibular symptoms.

A number of morphological studies demonstrated vestibular end-organ disease in experimental diabetic animals (Myers and Ross, 1987; Myers, 1998). In experimentally-induced DM, type 1 hair cell loss in the saccule (Myers and Ross, 1987) and vestibulo-cochlear nerve myelin degeneration (Myers, 1998) have been shown due to hyperglycemia-induced metabolic stress. As a consequence of metabolic stress, extracellular matrix overproduction and accumulation of lysosomes and lipid droplets were observed in the utricle and saccule (Myers and Ross, 1987). Due to excessive accumulation of extracellular matrix, the diffusion of oxygen and waste products was impaired and the presence of hair cell degeneration mostly occurs in the saccule. Also, vestibulocochlear nerve damage was demonstrated, including disruption of the myelin sheath lamellae and myelin sheath thinning in diabetic rats (Myers, 1998).

Recent developments in the field of the vestibular test battery have enabled investigators to evaluate each vestibular end organ separately (Curthoys, 2012), and the studies demonstrated that each vestibular end-organ function can be affected in DM (Kamali et al., 2013; Ward et al., 2015; Konukseven et al., 2015). In the study of Ward et al. (2015), the authors determined the relative sparing of posterior SCC in diabetic patients. Kocdor et al. (2016) found a neuroepithelial pathology in the saccules of diabetic patients, manifested as a lower density of type I vestibular hair cells and concluded that selective and deleterious effects on human vestibular sensory epithelia may be present in DM. Jauregui-Renaud et al. (2017) demonstrated utricular dysfunction via decreased response to utricular stimulation by unilateral centrifugation in patients with type 2 DM. These findings promoted studies investigating VEMP findings to reflect any otoith organ or related reflex dysfunction in DM.

4. Diabetes mellitus and VEMP

In 2001, Perez et al. (2001) evaluated vestibular evoked potentials in experimentally-induced DM type 2 DM and showed significantly prolonged first wave latency with decreased amplitude in diabetic animals. According to these findings, the authors stated that vestibular impairment of the inner ear has been unveiled by using an objective test in DM. However, since 2001, the number of studies regarding VEMP responses in DM is still limited in the literature. In these studies, VEMP testing was mostly performed to evaluate peripheral vestibular end organ pathologies and also to demonstrate the effect of DNP on vestibular function in patients with DM. The prevalence of DNP is about 8% in newly diagnosed disease, while the ratio of DNP is greater than 50% in DM. A single report of cVEMP in DM with the absence of cVEMP responses was demonstrated. However, cVEMP amplitudes has been reported in different studies with a prevalence of 45–54% (Taylor et al., 2011; Murofushi et al., 2011; Winters et al., 2011). VEMP testing enables demonstration of a vestibular loss in DM but there is not sufficient evidence regarding the usefulness of VEMP in diagnosing MD. However, it can be used for monitoring the status of vestibular dysfunction during the disease process (Fife et al., 2017).

Fig. 2. Examples of normal cVEMP (a) and oVEMP (b) traces (Neuro-Audio Version, 2010; Neurosoft, Ivanovo, Russia).
A summary of published articles investigating the association of diabetes mellitus and vestibular evoked myogenic potentials.

Table 1

| Author            | Year Published | Study Type     | Sample (n)                      | Test   | Findings                                      |
|-------------------|----------------|----------------|--------------------------------|--------|-----------------------------------------------|
| Peres et al.      | 2001           | Experimental   | 14 sand rat                    | VsEPs  | Prolonged first wave latency decreased amplitude |
| Bektaş et al.     | 2008           | Clinical       | 25 NIDDM + PNP, 13 NIDDM, 21 controls | cVEMP  | No difference                                 |
| Kamali et al.     | 2013           | Clinical       | 14 type 1 DM + PNP, 10 type 1 DM, 24 controls | cVEMP  | Prolonged latency in type 1 DM + PNP          |
| Ward et al.       | 2015           | Clinical       | 25 type II DM, 25 controls     | cVEMP  | Decreased cVEMP peak-to-peak amplitude and oVEMP n1 amplitude |
| Konukseven et al. | 2015           | Clinical       | 30 type II DM, 30 prediabetes, 31 controls | oVEMP  | Prolonged VEMP latencies in type II DM        |
| Kalkan et al.     | 2018           | Clinical       | 33 type II DM + PNP, 33 type II DM, 35 controls | oVEMP  | Lower peak-to-peak VEMP amplitudes in the DM + DPN and DM groups |

cVEMP: cervical vestibular evoked myogenic potentials, DM: diabetes mellitus, NIDDM: non-insulin-dependent diabetes mellitus, PNP: polyneuropathy, oVEMP: ocular vestibular evoked myogenic potentials, VsEPs: vestibular evoked potentials.
sample sizes are required to reveal the more definitive findings of VEMP recordings regarding the vestibular pathologies in patients with DM.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joto.2019.05.001.

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