Vestibular Nerve Stimulation as a Potential New Therapeutic Modality for Type 2 Diabetes Mellitus

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ABSTRACT

There is a substantial body of evidence, from disparate sources, that vestibular stimulation, particularly of the otolith organs, can modulate metabolism and thus energy homeostasis. We have previously suggested that repeated otolith stimulation could be used to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). Here we present double-blind pilot data from 30 Indian patients with T2DM who were randomized 1:1 to active and sham stimulation. All subjects received standard dietary advice. The 15 active patients used an electrical vestibular nerve stimulation device at up to 1mA, for about five hours a week over a three-month period. This technique has previously been shown to specifically activate the otolith organs. The mean HbA1c of the active group fell from 7.22% to 5.03% over the trial. Conversely, the mean HbA1c of the control group went from 7.75% to 7.36%. The marked fall in the HbA1c of the active group was greater than would be expected on the basis of weight loss alone. Given the relatively small number of participants and striking effect observed replication of these data is necessary.

MAIN TEXT

Two of us (JM & PDM) have recently reviewed the wide-ranging body of evidence that stimulation of the vestibular (balance) system can influence metabolism and body composition [1]. We pointed out that the vestibular system appears to play a key (though much underrecognized) role in metabolic homeostasis. This is reflected neuroanatomically by vestibular projections to multiple brainstem and hypothalamic nuclei involved in the central control of metabolism, including: the central melanocortin system (CMS) that is involved in appetite regulation and fixing a set-point for body fat; major parasympathetic sites; and centers that regulate brown adipose tissue (BAT) [1-3].

We suggested this is because, from a teleological perspective, these metabolic centers utilize vestibular inputs to gauge levels of physical activity [1,2]. We propose that it would be evolutionarily advantageous in “a scenario of long-term physical activity (i.e. chronic vestibular activation) [to reduce] fat storage while simultaneously increasing substrate utilization towards muscle and bone” [1]. This aligns with the observation that it is the macular (otolith) components of the vestibular system, which detect movement on the horizontal and vertical, that are most implicated in modulating metabolism [1,2]. Our review concluded by noting that vestibular stimulation offers a potential “novel therapeutic avenue for ... type 2 diabetes” [1]. A promising delivery mechanism in this regard is bipolar vestibular nerve stimulation (VeNS) using a small electrical current of about 1mA, applied non-invasively to the skin over the mastoids. This is because VeNS has been shown to specifically activate the otoliths and is thought to have a good safety profile [1,2].

SSK has previously published a case study suggesting that vestibular stimulation in the form of swinging could lead to an improvement in glycemic control in type 2 diabetes (T2DM) [4]. Together we collaborated in designing a double-blind, randomized, controlled pilot study to assess the effect of VeNS in adults with T2DM. The study recruited 30 patients and was carried out after gaining ethical approval at SSK’s institution (Indian Trial ID CTRI/2019/06/019854). All subjects were put on a daily diet of 1500kCal and randomized 1:1 to either daily usage for 1 hour of a VeNS stimulator (0.1 to 1mA, titrated in 0.1mA steps by subjects according to

comfort; 0.5Hz AC square wave with a 50% duty cycle) or, alternatively, usage of a sham device that beeped and flashed but didn't deliver an active stimulus. The active group had a mean BMI of 26.6kg/m², a mean age of 52 years and 6 of its members were female. The control group had a mean BMI of 25kg/m², a mean age of 54 years and 4 females. The subjects were weighed and had their HbA1c checked at baseline and at 3 months (See Table 1). There were no significant adverse events and no dropouts.

A marked improvement in glycaemic control was observed, with the mean HbA1c of the active group falling by 2.19%. Notably, although the weight of the active group also fell by an average of 2.4kg, the fall in HbA1c was a lot greater than would be anticipated on the basis of weight loss alone. We state this because of a systematic review looking at over 17,000 patients with T2DM concluded that HbA1c falls by about 0.1% for every 1kg reduction in weight [5]. On that basis we would have expected a fall in HbA1c of between 0.2 and 0.3%, rather than the observed almost 2.2% drop in the active group.

We have discussed elsewhere why VeNS may cause weight to fall [1,2], however clearly the reduction in the HbA1c of the active group in response to VeNS is so striking that it mandates replication to ensure its validity. Nonetheless, what might underly this striking improvement in glycemic control? As discussed above, the vestibular system inputs into various nuclei involved in metabolism, including the CMS and centers involved in the control of brown fat. This is relevant as there is evidence that activation of melanocortin-4 receptors and brown fat can both independently lead to a reduction in insulin resistance [6,7]. We have also recently suggested that AMP-activated protein kinase, which improves glycemic control, is likely to be upregulated by VeNS [8].

It should also be borne in mind that all the subjects in this study were Indian, who tend to have more visceral and abdominal fat, for any given BMI, compared to European populations [9], so it may be that this group is especially receptive to VeNS. However, in an African T2DM population rebounding regularly for 9 weeks on a minitrampoline, an activity which also activates the otoliths, caused a fall in mean HbA1c of over 1.5% [10]. Nonetheless, the

number of subjects in this pilot study was relatively small and moreover, given the dramatic result, replication is mandatory. However, if these striking improvements in glycemic control are indeed reproducible then VeNS may well constitute an important, and entirely novel, non-pharmacological treatment modality for T2DM.

TABLE 1: Change in HbA1c and Total Body Weight

Measurement	Timepoint	Active Group	Control Group
HbA1c (%) (NGSP assay) (n=15)	Baseline	7.22 +/- 1.57	7.75 +/- 1.25
	3 months	5.03 +/- 0.65	7.36 +/- 1.11
Total Body Weight (kg) (n=15)	Baseline	70.7 +/- 8.2	65.1 +/- 8.9
	3 months	68.3 +/- 9.2	65.2 +/- 9.0

Data entered as mean and SD.

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DISCLOSURES

JM and PDM are co-founders of Neurovalens, a medical device company that provided the VeNS devices used in the study. JM is CEO of Neurovalens and PDM is a non-executive director. They were involved in the design of the study but not in its execution. SSK was the PI of the study and a larger paper describing its execution and findings is in process.