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Deterioration of Vestibular Motion Perception: A Risk Factor for Postural Instability and Falls in Elderly With Type 2 Diabetes

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ABSTRACT

Aims: To assess whether impaired vestibular perception of self-motion is a risk factor for unsteadiness and falls in elderly patients with type 2 diabetes (T2D).

Materials and methods: 113 participants (65–75 years old) with T2D underwent tests of roll and pitch discrimination, postural stability (Berg Balance Scale, Modified Romberg Test, and quantitative posturography), clinical examination and blood chemistry analyses. Falls 1-year after enrolment were self-reported. We performed cluster analysis based on the values of the vestibular motion thresholds, and logistic stepwise regression to compare the clinical-biochemical parameters between clusters.

Results: We identified two clusters (VC1 $n = 65$ and VC2 $n = 48$ participants). VC2 had significantly ($p < 0.001$) higher (poorer) thresholds than VC1: mean pitch threshold 1.62°/s (95% CI 1.48–1.78) in VC2 and 0.91°/s (95% CI 0.84–0.98) in VC1, mean roll threshold 1.34°/s (95% CI 1.21–1.48) in VC2 and 0.69°/s (95% CI 0.64–0.74) in VC1. Diabetes duration was significantly ($p = 0.024$) longer in VC2 (11.96 years, 95% CI 9.23–14.68) than in VC1 (8.37 years, 95% CI 6.85–9.88). Glycaemic control was significantly ($p = 0.014$) poorer in VC2 (mean HbA1c 6.74%, 95% CI 6.47–7.06) than in VC1 (mean HbA1c 6.34%, 95% CI 6.16–6.53). VC2 had a significantly higher incidence of postural instability than VC1, with a higher risk of failing the Modified Romberg Test C4 (RR = 1.57, $\chi^2 = 5.33$, $p = 0.021$), reporting falls during follow-up (RR = 11.48, $\chi^2 = 9.40$, $p = 0.002$), and greater postural sway in the medio-lateral direction ($p < 0.025$).

Conclusions: Assessing vestibular motion thresholds identifies individuals with T2D at risk of postural instability due to altered motion perception and guides vestibular rehabilitation.

Barbara La Scaleia, Antonio Siena and Luca D'Onofrio have contributed equally.

Raffaella Buzzetti, Myrka Zago and Francesco Lacquaniti have jointly supervised this work.

1 | Introduction

Falls are the most common cause of injury-related morbidity and mortality in people older than 65 years [1]. Within this age group, around 25% have T2D, and those with diabetes experience a rate of falls 59% higher than that of non-diabetic older adults [2]. Falls are particularly dangerous in T2D, since this disease involves an increased risk of bone fragility [3] and fractures (e.g., the relative risk for hip fractures is about 1.4) [4].

Susceptibility to falls results from multiple interacting factors causing postural imbalance: diminished sensory acuity, reduced efficacy of neuromuscular responses, deconditioning due to inactivity, polypharmacy, and environmental hazards. The ability to identify specific risk factors for each individual is critical to tailor preventive or rehabilitative interventions [5].

Anchoring one's body to the direction of gravity is key to maintaining balance and preventing falls. Estimates of head and body displacement relative to gravity are normally derived by the brain from visual, somatosensory, and vestibular cues [6]. Some or all of these cues may be compromised in T2D due to retinopathy, peripheral neuropathy and vestibulopathy, which are common microvascular complications and contributors to imbalance and falls in T2D [7–9].

While the role of visual and somatosensory impairments leading to postural instability has been documented in T2D [9, 10], the vestibular contribution has been indirectly estimated with the Modified Romberg Test (MRT) of standing balance on firm and compliant surfaces [11, 12]. However, the adequacy of MRT for the identification of patients with vestibular impairments has been questioned, since the vestibular system is only one of several sensory and motor systems contributing to balance during this test [13–15].

Standard clinical vestibular testing relies on the assessment of reflexes, such as the vestibulo-ocular, vestibulo-collic, or vestibulo-spinal reflexes, which are not functionally related to the vestibular perception of body movement. A large fraction of patients with imbalance have normal results on these standard vestibular tests [14, 16]. This is because vestibular motion perception depends on sensory pathways distinct from those of the vestibular reflexes, and reflects a higher level of brain processing [17]. Therefore, although vestibular reflexes can be very useful for diagnosing semicircular canal versus otoconial end organ dysfunctions in diabetes [18, 19], tests of vestibular motion perception are more appropriate to detect vestibular problems causing imbalance [11, 19].

The vestibular thresholds of motion discrimination directly assess the vestibular perception of head and body motion [16, 20]. They correspond to the minimum amount of motion necessary to reliably recognise the direction of passive motion. They provide an accurate assay of vestibular precision in both peripheral and central vestibulopathies, since it is hard to adapt to deficits caused by threshold-level stimuli [16, 21]. Moreover, vestibular thresholds reflect neural noise within sensory processing [12, 22], and imbalance largely depends on sensory noise [23].

Here, we primarily aimed at assessing the vestibular motion thresholds in elderly people with T2D without overt vestibular symptoms. Secondarily, we aimed at correlating the vestibular thresholds with tests of balance, falls history, clinical, biochemical and pharmacotherapy parameters. We expected that the vestibular thresholds are sensitive predictors of imbalance in T2D. Moreover, significant associations between vestibular thresholds and clinical-biochemical parameters may uncover risk factors for developing self-motion misperception that impacts on imbalance.

2 | Materials and Methods

2.1 | Study Population and Design

We consecutively enroled community-dwelling individuals, 65–75 years old, with a diagnosis of T2D based on the criteria of the American Diabetes Association [24], referring to the outpatient clinic of the Diabetology Unit of AOU (Azienda Ospedaliera Universitaria) Policlinico Umberto I, Sapienza University of Rome. The age range of 65–75 years was chosen to include a representative sample of the elderly population with T2D, while maintaining a relatively narrow range to reduce the impact of age-related factors, such as variations in vestibular thresholds [25]. We excluded patients who could not stand unassisted, weighed more than 120 kg, had a waist circumference that could not accommodate the safety belts of the vestibular chair (approximately 150 cm), had foot ulcers or amputations, heart failure (NYHA 2–4), active cancer or a diagnosis of cancer within 5 years from enrolment, prior stroke, blindness, severe neuropathy (Neuropathy Disability Score NDS > 9), a history of severe hypoglycemia, dizziness, vertigo, spontaneous or positionally induced nystagmus, or vestibular migraine. Patients with a history of head-and-neck injury, limited neck mobility, history of head and neck surgery, central nervous system disorders, dementia, external or middle ear diseases, or those with a history of usage of ototoxic drugs were also excluded from the study.

We computed the sample size required to identify a significant difference of vestibular thresholds between subjects who passed condition four of MRT (MRT C4) versus those who failed it, since the outcome of this postural test is customarily attributed to a vestibular contribution [11, 12]. To this end, we used the effect size of published data from elderly without diabetes who performed roll tests and MRT similar to ours [26]. To our knowledge, there are no comparable data available for people with diabetes. Power analysis with power = 0.8, alpha = 0.05 and effect size = 0.59 (Cohen's d) yielded a sample size of 94 individuals, assuming that 50% of them failed MRT C4, a percentage roughly similar to that of previous reports [11, 25, 26]. We recruited about 20% more individuals to account for possible dropouts. The final sample included 113 individuals (28 females; 85 males; 68.8 ± 3.3 years, mean ± SD). We did not intentionally recruit a cohort with an uneven sex balance, but men volunteered more often to participate. Table 1 reports summary statistics for the study population. All participants gave written informed consent to procedures approved by the Institutional Review Board of Santa Lucia Foundation (protocol *n*. CE/PROG.756) and the

TABLE 1 | Participants' data, mean (or median) values and 95% confidence intervals for continuous variables.

Variable	Value
Age, yrs	69 [67–70]
Sex, M/F number	85/28
BMI, Kg/m^2	28.1 [27.4–29.0]
Active smokers, %	13.3
Duration of diabetes, yrs	8 [6–10]
HbA_{1C}, %	6.50 [6.35–6.67]
mmol/mol	48 [46–49]
eGFR, mL/min	85.1 [81.0–89.3]
Microalbuminuria, %	8.8
Retinopathy, %	13.3
Hypertension, %	77.0
Dyslipidemia, %	85.8
ECG pathological, %	14.2
CAN, %	22.5
Neuropathy (NDS):	
None ($\leq$ 2), %	71.7
Mild (3–5); %	22.1
Moderate (6–8), %	6.2
Severe ($\geq$ 9), %	0
Treatment of diabetes:	
Diet alone, %	2.7
Metformin, %	92.9
SGLT2i, %	26.6
GLP-1RA, %	40.7
DPP4, %	7.1
Rapid insulin, %	5.3
Basal insulin, %	23.0
Fallers in 1-year followup, %	9.5

Ethical Committee of AOU Policlinico Umberto 1 (prot. 111/20, *n*. 5635), in conformity with the Declaration of Helsinki (World Medical Association) regarding the use of human participants in research. All participants underwent detailed clinical examination and blood chemistry analyses at AOU Policlinico Umberto I, Sapienza University. They performed the vestibular and postural tests at IRCCS Santa Lucia Foundation, Neurorehabilitation Hospital, Rome (Italy).

Vestibular motion discrimination of earth-horizontal roll rotation (i.e., about the naso-occipital axis) and pitch rotation (i.e., about the interaural axis) was assessed in all study participants (n = 113). Roll and pitch thresholds assess canal-otolith integration relevant to motions in the medio-lateral and antero-posterior directions, respectively [27], that is, the cardinal directions for postural stability [28]. Balance was assessed with the Berg Balance Scale (BBS, [29]) and the Modified Romberg test (MRT, 11–12) involving quantitative posturography. One participant opted not to perform BBS for undisclosed reasons. Additionally, a malfunction of the computer timer used to monitor the test (see below) affected another participant's results. As a result, the BBS test was completed by a total of 111 participants. All vestibular and postural tests were performed on the same day, allowing sufficient time to rest between each test (typically 10–15 min).

Participants were asked to report the occurrence of accidental falls in the year following the tests. Eighteen participants did not return the report, leaving a total of 95 participants with a record of falls.

As a reference for vestibular thresholds, we considered published data in healthy adults (n = 105) aged between 18 and 80 years who performed tests of roll tilt identical to ours [25].

2.2 | Clinical and Laboratory Tests

The following demographic, anthropometric and medical history data were collected: age, sex, weight, height, BMI, smoking status, diabetes onset and duration, comorbidities, and pharmacological treatments. Biochemistry data were obtained from electronic medical records: glycaemic control (HbA1c, fasting blood glucose), lipid profile (total cholesterol, HDL- and LDL-cholesterol, triglycerides), and renal function (estimated glomerular filtration rate [eGFR], urine creatinine and albumin). Peripheral diabetic neuropathy was assessed by means of questionnaires and tests from the Neuropathy Disability Score (NDS). NDS collects data on the vibration perception with a 128 Hz tuning fork, thermal perception with a metallic rod, pin-prick sensation, and Achilles tendon reflexes, obtaining a stratification of diabetic neuropathy: none ($\leq$ 2), mild (3–5), moderate (6–8), severe ($\geq$ 9). Cardiovascular Autonomic Neuropathy (CAN) was assessed by means of cardiovascular autonomic reflex tests (CARTs), including heart rate variations during deep breathing, lying-to-standing and Valsalva manoeuvre. Early or established CAN is defined as one or two altered CARTs, respectively [30]. Resting ECG was routinely performed. Diabetic retinopathy was diagnosed by an ophthalmologist on the basis of fundus photographs. Chronic kidney disease was assessed by albumin-to-creatinine ratio (ACR), and defined as present when ACR was $>$ 30 mg/g. A history of macrovascular complications was assessed by retrieving data from clinical charts about records of coronary artery disease, cerebrovascular disease, or carotid artery stenosis.

2.3 | Vestibular and Postural Tests

Setup, protocols and data analyses are summarised herein. Full details are provided in the online Supporting Information S1.

To assess vestibular motion thresholds, participants sat in an upright position, securely held in place in a chair mounted on top of a motion platform. To minimise non-vestibular motion cues, participants kept their eyes closed in the light-tight room, wore noise-cancelling headphones to mask auditory cues, and placed their feet on a foam pad to reduce plantar cues about body displacement. Platform motion was controlled at 1 KHz,

while the position and orientation of the platform and the participant's head were monitored at 200 Hz. Participants entered the responses via a gamepad.

Stimuli were 5-s-duration single cycles of 0.2 Hz sinusoidal angular acceleration applied about the naso-occipital axis for roll (right-ear-down or left-ear-down) and about the interaural axis for pitch (nose-up or nose-down). In each trial, the magnitude of the stimuli was adjusted based on a 3Down-1Up adaptive staircase. Motion thresholds are reported using the peak velocity of the smallest stimulus that was reliably perceived by each participant in a given condition.

Participants performed two separate sessions for roll and pitch in counterbalanced order, interspersed with the balance tests.

The MRT involved four conditions (C1–C4), scored on a pass/fail basis. To pass C1, participants had to stand on the force plate for 30 s with eyes open. To pass C2, they had to stand on the force plate for 30 s with eyes closed (thus removing visual cues). To pass C3, they had to stand on a medium-density foam pad (reducing somatosensory cues from the feet) placed on top of the force plate with eyes open for 30 s. To pass C4, they had to stand on the foam with eyes closed (reducing both visual and somatosensory cues) for 30 s. Participants failed if, before the end of the trial, they opened their eyes or arms or moved their feet to maintain stability, or the experimenter had to intervene to prevent a fall. Participants performed three trials for each condition for quantitative posturography, but each condition was scored after the first two trials. In each trial, ground reaction forces were recorded at 100 Hz.

The BBS involved 14 conditions [29]: (1) sitting to standing, (2) standing unsupported, (3) sitting unsupported, (4) standing to sit, (5) transfers, (6) standing unsupported with eyes closed, (7) standing unsupported with feet together, (8) reaching forward with outstretched arms while standing, (9) pick up an object from the floor from a standing position, (10) turning to look behind over the left and right shoulders while standing, (11) turn 360°, (12) place each foot alternately on step or stool while standing unsupported, (13) standing unsupported with one foot in front, (14) standing on one leg. For most items, the subject was asked to maintain a given position for a specific time (different for each item, see [29]), monitored by a computer timer. Each condition was scored 0 to 4 from the lowest to highest level of function. Points were progressively deducted if participants failed to meet the time or distance requirements, needed cueing/supervision, touched an external support or received assistance from the examiner.

The maximum score for BBS is 56 (14 items $\times$ 4). A score $\leq$ 50 served as an evidence-based functional measure to assess if the individual risk of future falls is higher than the probability of falls of age-matched community-dwelling persons [31].

2.4 | Data Analysis

Data analyses were performed using MATLAB 2023a (The MathWorks, MA, USA) and R 4.3.2.

2.4.1 | Vestibular Thresholds

We fit a Gaussian cumulative distribution psychometric function [32] to the responses with a maximum likelihood estimate via a Generalised Linear Model and a probit link function [20, 23]. The threshold parameter corresponded to the standard deviation of the distribution [20, 23]. Thresholds were log-transformed to obtain a lognormal distribution [20, 23, 28].

We used the k-means clustering (*kmeans* function of MATLAB Statistics and Machine Learning Toolbox R2023a) of the z-scores of the log-transformed thresholds in both roll and pitch sessions of each participant, randomly initialising the cluster centroid positions (2000 replications to minimise the possibility of misleading local minima). This algorithm partitions the observations into k clusters in which each observation belongs to the cluster with the nearest mean (cluster centroid). For a given initial set of clusters, the algorithm allocates the remaining data to the nearest clusters, and then repeatedly changes the membership until the error function does not change significantly or the membership no longer changes [33].

The k-means algorithm is efficient in clustering large data sets, since its computational complexity is linearly proportional to the size of the data sets, it often terminates at a local optimum, the clusters have convex shapes, and it works on numerical data, but its performance is dependent on the initialisation of the centres [33]. For this last reason, we randomly initialised the cluster centroid positions 2000 times (see above).

In k-means, the number of clusters must be supplied as a parameter. We used the silhouette method [34] to determine the optimal number of clusters to be input to k-means. Notice that the combination of k-means with silhouettes is the preferred method in publications that applied cluster analysis to identify homogeneous groups of people with diabetes [35]. The silhouette S_i for the ith point is defined as

$$S_i = \frac{(b_i - a_i)}{\max(a_i, b_i)}$$

where a_i is the average distance from the ith point to the other points in the same cluster as i, and b_i is the minimum average distance from the ith point to points in a different cluster, computed over all clusters. Silhouette scores can range from -1 to $+1$. A high silhouette score indicates that the item is well-matched to its cluster, and poorly matched to neighbouring clusters. However, the silhouette scores are affected by the dimensionality of the data: as dimensionality increases, distances tend to become more uniform, often resulting in lower silhouette scores [33, 34].

2.4.2 | Postural Sway

We quantitatively analysed only the passed trials, since only these had the fixed required number of time samples. We computed the root-mean-square displacements of the Centre of Pressure (CoP) in the medio-lateral (rmsDistML) and antero-posterior (rmsDistAP) directions, and log-transformed them to obtain normal distributions.

2.4.3 | Clinical-Biochemical Parameters

We applied cluster analysis on the *z*-scores of age, transformed BMI, diabetes duration, transformed HbA1c, eGFR as continuous variables, sex, smoking status, CAN, microalbuminuria, retinopathy, hypertension, neuropathy, dyslipidemia, and pathological ECG as binary variables. HbA1c was normalised using the box-cox transformation $(HbA1c^{\lambda} - 1)/\lambda$, with ($\lambda = -2.1189$). BMI was normalised by taking its inverse (1/BMI). Neuropathy was assessed by NDS. Since the vast majority of the participants had NDS scores ≤ 2 (corresponding to no evidence of neuropathy, see Table 1), we binarised also this variable: neuropathy absent for NDS ≤ 2, present for NDS ≥ 3.

For clustering based on clinical-biochemical parameters, we used the K-prototypes method [36] that combines k-means (for numerical data) and k-modes (for categorical data). Simply, the k-modes algorithm uses a matching dissimilarity measure to deal with categorical objects, replaces the means of clusters with modes, and uses a frequency-based method to update modes in the clustering process to minimise the clustering cost function [36]. K-prototypes are widely used, including studies on TD2 clinical clusters. We implemented K-prototypes in R (package clustMixType Version 0.3–14) using 2000 randomly chosen initial cluster prototypes (see above for k-means).

2.5 | Statistical Methods

We verified the normality of the distribution of data with the Kolmogorov-Smirnov test, and the homoscedasticity in different samples with the Bartlett test [37]. When the data were not normally distributed, we used non-parametric statistics (Wilcoxon rank sum test). Descriptive statistics include mean values, SD, and 95% Confidence Interval (95% CI).

To check for a correlation between the vestibular thresholds in roll and those in pitch, we carried out a linear regression (MATLAB function *fitlm* with option RobustOpts = on, using the *bisquare* weight function) between the log-transformed threshold values. We used multiple logistic regressions to model the relationships between the vestibular clusters and the demographic, clinical and biochemical parameters. Logistic regression was used because of the binary nature of the vestibular clusters (since they were determined to be two a posteriori, see *Results*). The basic model included the same variables as for cluster analysis of the clinical-biochemical parameters. To assess the potential role of anti-diabetes treatments, we added the following binary treatments to the basic model: metformin, SGLT2i, GLP-1RA, DPP4i, and Basal-Insulin. Stepwise regression analysis was performed by means of the MATLAB function *stepwiseglm*, which uses a mixed forward and backward stepwise procedure. The models with the lowest Akaike Information Criterion (AIC) score were retained. The sensitivity and specificity of vestibular clustering for predicting falls in the 1-year follow-up were computed from the percentages of fallers and non-fallers [31] in the two clusters with high and low thresholds.

We also statistically compared the demographic, clinical and biochemical parameters between the two clusters of vestibular parameters. $p < 0.05$ was considered statistically significant.

3 | Results

3.1 | Vestibular Thresholds

We did not find any significant difference between the vestibular thresholds (in both roll and pitch sessions) of males and those of females (*t*-test, $p > 0.174$). Pitch thresholds (mean 1.163 deg/s, 95% CI [1.075–1.259], $n = 113$) were significantly higher (poorer) than roll thresholds (mean 0.914 deg/s, 95% CI [0.840–0.995], $n = 113$) (paired *t*-test, $p < 0.001$, Figure S1A). Linear regression between the log-transformed vestibular thresholds in roll and pitch confirmed that the latter were significantly higher than the former (intercept 0.205, $p < 0.001$), and also showed a positive linear correlation between the two thresholds (slope 0.599, $p < 0.001$, Figure S1B).

3.1.1 | Cluster Analysis

We used cluster analysis to group participants with similar vestibular thresholds, considering both roll and pitch sessions. The optimal clustering solutions were determined by using a combination of k-means and silhouette algorithms (see *Methods*).

In this manner, we partitioned the results of the thresholds in two groups with 65 (VC1) and 48 (VC2) participants (silhouette score = 0.591, Figure S1B). Vestibular thresholds were significantly higher (poorer) in VC2 than in VC1 for both roll and pitch (*t*-test, $p < 0.001$, Table 2, Figure 1A,B). When we compared the roll thresholds with the reference values reported by [25] for their subgroup of healthy participants aged between 60 and 80 years, we found that the VC1 thresholds did not differ significantly (*t*-test, $p = 0.68$) from these values, while the VC2 thresholds were significantly higher (*t*-test, $p < 0.001$).

3.2 | Balance

Few participants (9/95, 9.5% of the sample) reported the occurrence of falls in the year following the vestibular tests (one participant reported three falls, two participants reported two falls, the others one fall). The performance with the Berg Balance Scale (BBS) also was generally good. Out of a maximum score of 56, the average BBS score was 53.9 ± 2.32 (mean $\pm$ SD, $n = 111$). Only 8 individuals (7%) had a BBS score ≤ 50 (see *Methods*). No participant failed the conditions C1, C2, or C3 of the Modified Romberg Test (MRT). However, 48% of the participants (54 out of 113) failed MRT C4, demonstrating postural instability under the demanding conditions of standing on a foam pad with eyes closed.

TABLE 2 | Comparison of vestibular thresholds, demographic, clinical and laboratory continuous data between the 2 clusters of participants, VC1 (lower vestibular thresholds) and VC2 (higher vestibular thresholds).

	Vestibular Clusters			
	VC2 $n = 48$	**VC1 $n = 65$**	***p***	**Test**
Roll threshold [deg/s]	**1.34 [1.21–1.48]**	**0.69 [0.64–0.74]**	**< 0.001*** **	**TT2**
Pitch threshold [deg/s]	**1.62 [1.48–1.78]**	**0.91 [0.84–0.98]**	**< 0.001*** **	**TT2**
Age (years)	70 [68–71]	67 [67–69]	0.109	W
BMI (Kg/m^2)	27.6 [28.7–26.6]	28.6 [29.8–27.4]	0.223	TT2
Fasting blood glucose (mg/dL)	*131.88 [121.62–142.13]*	*120.48 [113.75–127.2]*	*0.055*	*TT2*
Total cholesterol (mg/dL)	158.98 [145.32–172.64]	160.63 [151.42–169.84]	0.835	TT2
HDL cholesterol (mg/dL)	45.5 [41–49]	48 [45–51]	0.476	W
LDL cholesterol (mg/dL)	88.04 [76.82–99.26]	86.26 [78.51–94.01]	0.788	TT2
Triglyceride (mg/dL)	115.56 [100.27–130.85]	131.03 [117.07–144.99]	0.141	TT2
Creatinine (mg/dL)	0.9 [0.8–0.98]	0.9 [0.84–0.97]	0.956	W
Diabetes duration (years)	**11.96 [9.23–14.68]**	**8.37 [6.85–9.88]**	**0.024*** **	**TT2**
HbA1c (%) **(mmol/mol)**	**6.74 [6.47–7.06]** **50 [47–54]**	**6.34 [6.16–6.53]** **46 [44–48]**	**0.014*** **	**TT2**
eGFR (mL/min/1.73 m^2)	85.42 [78.77–92.06]	84.94 [79.40–90.40]	0.911	TT2

Note: For each parameter, the mean [95% CI] or median [95% CI] value is reported for normally or not-normally distributed data, respectively. Bold parameters are statistically significant. Italic parameters are borderline significant.
Abbreviations: TT2: Two-sample *t*-test; W: Wilcoxon rank sum test.

3.3 | Relationship Between Vestibular Clusters and Balance

The cluster of participants with higher (poorer) vestibular thresholds (VC2) had a greater postural instability than the cluster with lower vestibular thresholds (VC1) (Figure 1). In particular, VC2 had a higher risk of failing MRT C4 (Figure 1C) (risk ratio RR = 1.57; 95% CI [1.07–2.30]; $\chi^2 = 5.33$; $p = 0.021$), of scoring ≤ 50 at BBS (RR = 3.94; 95% CI [0.83–18.66]; $\chi^2 = 3.54$; $p = 0.06$, borderline significant), and of reporting falls during the 1-year follow-up (Figure 1D) (RR = 11.48; 95% CI [1.50–88.19]; $\chi^2 = 9.40$; $p = 0.002$). In particular, the sensitivity of vestibular clustering for the risk of falls was 88.9% (95% CI [51.75–99.72]), while the specificity was 63.95% (95% CI [52.88–74.03]). Furthermore, postural sway measured as root-mean-square displacement of the centre of pressure in the medio-lateral direction (rmsDistML) was significantly greater in VC2 than in VC1 in MRT C2 (Figure 1E) and C3 (Figure 1F) (*t*-test, all $p < 0.025$), but not in MRT C1 (*t*-test, $p = 0.113$). Postural sway in the antero-posterior direction (rmsDistAP) in VC2 was not significantly different from that in VC1 (C1 $p = 0.386$, C2 $p = 0.113$, C3 $p = 0.913$).

When we analysed roll and pitch thresholds separately rather than aggregating them for clustering, we found a trend similar to that reported above for the vestibular clusters. However, the trend was statistically weaker. Thus, the coefficients of linear regression between either roll or pitch and rmsDistML were positive, indicating that the higher (worse) the threshold, the greater was the postural sway in the medio-lateral direction, but not statistically significant in C1 (all $p > 0.115$) and C2 ($p = 0.461$ for roll, $p = 0.070$ for pitch borderline significant). In C3, the same regression was statistically significant for pitch ($p = 0.015$) but not for roll ($p = 0.085$ borderline significant). Finally, as in the case of the vestibular clusters, neither roll nor pitch was statistically correlated with rmsDistAP (all $p > 0.440$).

For comparison purposes, we also analysed the balance data as a function of the presence or absence of neuropathy. We clustered the participants into two groups (see *Methods* and Table 1): (1) those without neuropathy (NDS ≤ 2, $n = 81$), and (2) those with mild (NDS 3-5, $n = 25$) or moderate neuropathy (NDS 6-8, $n = 7$), since there were no participants with severe neuropathy (NDS ≥ 9). We found that the cluster of participants with neuropathy had a significantly higher risk of failing MRT C4 (risk ratio RR = 1.49; 95% CI [1.03–2.16]; $\chi^2 = 3.87$; $p = 0.049$), but not of scoring ≤ 50 at BBS (RR = 2.58; 95% CI [0.69–9.68]; $\chi^2 = 2.09$; $p = 0.149$), and of reporting falls during the 1-year follow-up (RR = 1.196; 95% CI [0.322–4.451]; $\chi^2 = 0.07$; $p = 0.789$). Furthermore, postural sway parameters (rmsDistML and rmsDistAP) were not significantly different between these two clusters in MRT C1-C2-C3 (*t*-test, all $p > 0.103$).

3.4 | Relationship Between Vestibular Clusters and Clinical-Biochemical Data

Cluster VC2 had significantly higher levels of HbA1c (Figure 1G) (*t*-test, $p = 0.014$) and longer diabetes duration (Figure 1H) (*t*-test, $p = 0.024$) than cluster VC1. Mean HbA1c was 6.34% (95% CI [6.16–6.53]) (46 mmol/mol (95% CI [44–48])) and 6.74% (95% CI [6.47–7.06]) (50 mmol/mol (95% CI [47–54])) in VC1 and VC2, respectively (Table 2). The mean diabetes duration was 8.37 years (95% CI [6.85–9.88]) and 11.96 years (95% CI [9.23–14.68]) in VC1 and VC2, respectively. Participants on antihypertensive drugs, Basal-Insulin or GLP-1RA, more frequently belonged to VC2 (see Table 3).

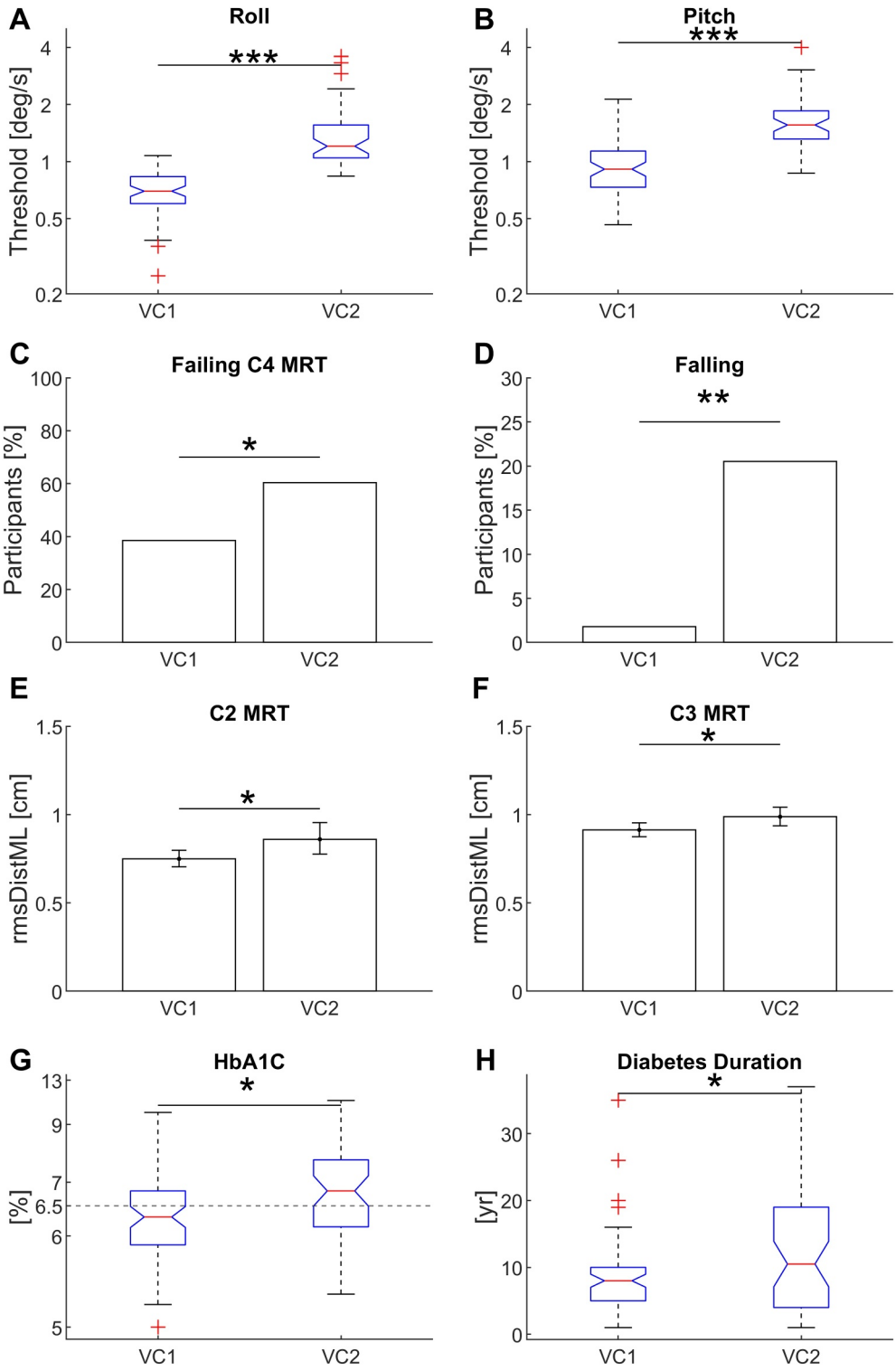

FIGURE 1 | Comparison of different parameters between the two clusters, VC1 and VC2. Top to bottom, roll (A) and pitch (B) thresholds (log-scale), percentage of participants who failed condition C4 of Modified Romberg Test (C) and those who fell in 1-year follow-up (D), root-mean-square distance of the centre of pressure in the medio-lateral direction in condition 2 (E) and 3 (F) of the Modified Romberg Test, HbA1c (G) and diabetes duration (H). Box-and-whisker plots indicate the median and the 25th and 75th quartiles, and the whiskers show the 5th and 95th percentile. + markers denote outliers. The number of participants was 65 and 48 for VC1 and VC2, respectively, for all parameters except for the percentage of participants reporting falls, where the number of participants was 56 and 39 for VC1 and VC2, respectively. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

Stepwise regression analysis showed that the chance of belonging to VC2 significantly depended on increasing age, HbA1c, and presence of hypertension (all $p < 0.027$) (Table S1). Adding pharmacological treatments on top of the basic model showed a significant effect of Basal-Insulin only ($p = 0.008$).

TABLE 3 | Comparison of demographic, clinical, and laboratory binary data between VC1 and VC2. For each parameter, the risk ratio [95% CI] is reported.

		Vestibular clusters				
		VC2 $n = 48$	**VC1 $n = 65$**	**Risk ratio**	**χ^2**	***p***
Sex (female)	YES	11	17	0.90 [0.54–1.52]	0.155	0.694
	NO	37	48			
Smoking status (current smoker)	YES	6	9	0.93 [0.48–1.81]	0.043	0.835
	NO	42	56			
CAN (pathological)	YES	12	13	1.18 [0.73–1.9]	0.423	0.515
	NO	35	51			
Previous cardiovascular event	YES	7	6	1.31 [0.75–2.29]	0.777	0.378
	NO	41	59			
ECG (pathological)	*YES*	*10*	*6*	*1.60 [1.01–2.51]*	*3.058*	*0.08*
	NO	*38*	*59*			
Retinopathy	YES	9	6	1.51 [0.93–2.434]	2.173	0.14
	NO	39	59			
Microalbuminuria	YES	5	5	1.20 [0.62–2.32]	0.254	0.614
	NO	43	60			
Hypertension	*YES*	*41*	*46*	*1.75 [0.90–3.43]*	*3.344*	*0.068*
	NO	*7*	*19*			
Dyslipidemia	YES	43	54	1.42 [0.66–3.03]	0.962	0.328
	NO	5	11			
Thyroiditis	YES	6	7	1.10 [0.59–2.07]	0.081	0.776
	NO	42	58			
Neuropathy (NDS $\geq$ 3)	YES	13	19	0.94 [0.58–1.53]	0.063	0.802
	NO	35	46			
Antihypertensive drugs	**YES**	**40**	**41**	**1.98 [1.04–3.74]**	**5.581**	**0.018***
	NO	**8**	**24**			
Omega3	YES	5	6	1.08 [0.54–2.14]	0.044	0.834
	NO	43	59			
Fibrate	YES	8	6	1.41 [0.85–2.36]	1.406	0.236
	NO	40	59			
Ezetimibe	YES	11	10	1.30 [0.81–2.10]	1.035	0.309
	NO	37	55			
Statin	YES	36	47	1.08 [0.66–1.79]	0.103	0.749
	NO	12	18			
Rapid-insulin	YES	4	2	1.62 [0.88–2.98]	1.517	0.218
	NO	44	63			
Basal-insulin	**YES**	**20**	**6**	**2.39 [1.65–3.46]**	**16.398**	**< 0.001*****
	NO	**28**	**59**			
DPP4i	YES	2	6	0.57 [0.17–1.93]	1.076	0.3
	NO	46	59			
GLP-1RA	**YES**	**25**	**21**	**1.58 [1.04–2.42]**	**4.474**	**0.034***
	NO	**23**	**44**			
SGLT2i	YES	13	17	1.03 [0.64–1.66]	0.012	0.912
	NO	35	48			
Metformin	YES	45	60	1.14 [0.46–2.87]	0.087	0.768
	NO	3	5			

Note: Bold parameters are statistically significant. Italic parameters are borderline significant.

3.5 | Cluster Analysis on Clinical-Biochemical Data

We next asked whether the participants could also be clustered based on the clinical-biochemical data, and whether such clustering predicted the vestibular thresholds. Here, we used K-prototypes to account for both numerical and categorical data (see *Methods*). With this method, we found 2 clusters with 80 (CC1) and 33 (CC2) participants (silhouette score = 0.244). Notice that the silhouette score for this clustering is smaller than that obtained for clustering participants based on vestibular thresholds (see above). This difference is likely due to the higher dimensionality of the clinical-biochemical dataset (14 variables) than that of vestibular thresholds (2 variables).

Cluster CC2 had significantly higher HbA1c, fasting blood glucose, longer diabetes duration, lower BMI, and presence of pathological ECG (all $p < 0.05$). Participants on Basal-Insulin, GLP-1RA, or SGLT2i more frequently belonged to CC2. Critically, vestibular thresholds were significantly higher in CC2 than in CC1 for both roll and pitch (t-test, $p < 0.007$, Figure S2), thus corroborating the previous results.

4 | Discussion

The participants of this study were clustered in two groups based on the values of the vestibular thresholds of motion discrimination. One group (VC1, 58% of the participants) had thresholds overlapping those of reference data from healthy elderly [25]. In comparison, the second group (VC2, 42% of the participants) had significantly higher thresholds as well as higher incidence of postural instability assessed from the Berg Balance Scale, Modified Romberg Test, posturography, and incidence of falls. Moreover, increased vestibular thresholds in the second group were associated with longer diabetes duration, poorer glycaemic control (higher HbA1c), and hypertension. The results were qualitatively confirmed by clustering the participants based on the clinical-biochemical data.

Our findings are relevant vis-à-vis of the growing focus on early detection of increased risk of postural instability and falls in the elderly, a risk that is considerably higher in people with diabetes [2]. The correct identification of specific risk factors for each individual is crucial to design specific interventions [5]. We showed that one risk factor is represented by the impaired vestibular perception of self-motion. The sensitivity of our vestibular tests for risk of falls in a 1-year follow-up was high (about 89%) compared with current predictive measures [31]. However, the specificity was not as high (about 64%). Both parameters of predictive accuracy (sensitivity and specificity) should be interpreted with caution, since the outcome measure to be predicted was limited (only nine participants reported falls during the 1-year follow-up).

With regards to postural stability, the group of participants with higher vestibular thresholds had a significantly higher risk of failing MRT C4 (standing on foam with eyes closed, which may rely on vestibular cues primarily, [11–12]) as well as significantly increased variability of postural sway in the mediolateral direction in MRT C2 (eyes closed on firm surface) and MRT C3 (eyes open on foam), but not in MRT C1 (eyes open on firm surface). Pitch thresholds were more consistently related to postural sway than roll thresholds when they were considered separately. During quiet stance, the mediolateral direction is the axis of greater potential instability due to the short basis of support, and excessive sway along this axis can predict future falls in the elderly [38]. Moreover, it has been argued that, even in healthy young adults, higher vestibular motion thresholds resulting from temporal integration of noisy canal and otolithic cues may represent a critical element contributing to variability in mediolateral postural sway when visual and kinaesthetic cues are unreliable or unavailable, as it happens in MRT C2, C3 and C4 but not in MRT C1 [39].

Vestibulopathy is a known metabolic and microvascular complication of T2D, its prevalence increasing with age, disease duration, HbA1c levels, systemic arterial pressure, and comorbidities [11, 40]. Vestibulopathy can lead to overt symptoms, such as nausea, dizziness, vertigo, nystagmus, spatial disorientation, blurred vision, or stumbling, but it can also be subclinical, as in our participants. In particular, since the vestibular system encodes self-motion information [41], its dysfunction can cause abnormal perception of head motion. In turn, misperception of self-motion can cause postural instability [28].

A variety of postural tests, such as the Berg Balance Scale, Romberg test, or quantitative posturography, can diagnose postural instability, but they cannot unambiguously reveal its sensory origin [42]. On the other hand, routine clinical vestibular tests typically rely on the assessment of reflexes [18, 19], which do not assess vestibular perception [16].

Here, we applied well-established quantitative methods to measure the vestibular discrimination of motion direction along the roll and pitch directions [20, 25]. Roll and pitch tilts target canal-otolith integration within the brain, which plays a critical role in postural stability [28]. Indeed, these vestibular motion thresholds are typically elevated in peripheral and central vestibulopathies that determine vestibular hypofunction [16, 21, 22, 43], and their increase is often associated with postural instability [28, 39].

Vestibular neurons at different stages of the central pathways of the brain are tuned to natural head motion stimuli [44]. Sensed head motion is processed by central vestibulo-motor pathways [41, 44]. Degradation of vestibular inputs can lead to increased sway, imbalance, and higher risk of falls [45], consistent with the present results.

Our findings indicate that longer diabetes duration, poorer glycaemic control (evidenced by increased HbA1c and fasting blood glucose levels), hypertension, and basal-insulin use are risk factors for developing impaired vestibular motion perception. The underlying pathophysiological mechanisms remain unknown. However, one likely mechanism is the oxidative stress in diabetes. High glucose levels can stimulate free radical production [46], leading to oxidative stress in several organs, including the vestibular apparatus. Vestibular neurons are particularly vulnerable to the action of free radicals because of their high metabolic demands [25]. In fact, primary vestibular

afferents and central vestibular neurons in primates have high discharge rates of action potentials even at rest [25]. This high electrical activity involves heavy metabolic loads, with extensive oxidative ATP production by the mitochondria that can contribute to oxidative stress and free radicals [25].

As mentioned above, we found that increased vestibular thresholds were associated with longer diabetes duration, poorer glycaemic control, and hypertension. These risk factors for developing a vestibulopathy in diabetes have already been noticed in previous studies [11, 40, 47]. We also found that participants treated with basal insulin had a higher probability of increased vestibular thresholds than those without such treatment. A previous review and meta-analysis showed that the risk of falls in diabetes is significantly higher in insulin-treated than non-insulin-treated patients [48].

In sum, diagnosis of impaired motion perception using the vestibular thresholds may identify a subpopulation in T2D for whom risk factor management might reduce the incidence of postural instability and falls. Our sample involved elderly outpatients with generally good glycaemic control (mean value of HbA1c = 6.5% or 48 mmol/mol over all the population). It is likely that patients with poorer glycaemic control should have worse vestibular thresholds [11]. Moreover, few participants had peripheral neuropathy or retinopathy, and reported falls in the followup.

Regarding peripheral neuropathy, 72% of our participants showed no signs of neuropathy, 28% had mild or moderate neuropathy, and none had severe neuropathy. Mild or moderate neuropathy had a modest impact on balance, significantly increasing the risk of failing MRT C4 but showing no significant effects on BBS score, postural sway, or reported falls. It is important to note that severe peripheral neuropathy is known to have major effects on balance [10, 42].

To ensure robust estimates of the vestibular thresholds comparable to published normative data, we employed a sophisticated apparatus and protocol [20]. Nonetheless, simpler and faster approaches such as those outlined in [49] could be implemented for large-scale clinical screening. Crucially, identifying a potential risk of instability and falls due to a vestibular deficit of motion perception should prompt preventive or rehabilitative interventions targeted to the specific deficit, rather than generic postural training.

Author Contributions

B.L.S. researched and analysed data, contributed to discussion, and wrote the first draft of the manuscript; A.S. researched data and contributed to discussion; L.D.O. researched data, reviewed and edited the manuscript; A.C. researched data and contributed to discussion; G.C. contributed hardware for the experiments; A.L. researched data and contributed to discussion; G.N.C. researched data and contributed to discussion; E.M. researched data, reviewed and edited the manuscript; S.Z. researched data and contributed to discussion; R.B. conceived and supervised the project, researched data, contributed to discussion, reviewed and edited the manuscript; M.Z. conceived and supervised the project, researched data, contributed to discussion, reviewed and edited the manuscript; F.L. conceived and supervised the project, researched data, contributed to discussion, and wrote the final draft of the manuscript. All authors approved the final version of the manuscript.

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Ethics Statement

The study was approved by the Institutional Review Board of Santa Lucia Foundation and the Ethical Committee of AOU Policlinico Umberto 1.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data analyzed in this study are included in the published article and its online supplementary file. Additional data are available from the corresponding authors upon reasonable request.

Peer Review

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.