Journal of Neurology Research Reviews & Reports

Research Article



Effectiveness of Virtual Reality Game-Based Balance Training on Balance and Quality of Life in Patients with Parkinson's Disease: An Experimental Study

Rajesh S Vasava^{1*} and Maheshkumar Baladaniya²

¹Physiotherapist CIMS Hospital Ahmedabad, India

²Physical Therapist Neighborhood Physical therapy PC, Brooklyn, NY, USA

ABSTRACT

This study investigates the effects of a novel ap- proach to balance training on individuals with Parkinson's disease. A total of 30 patients were enrolled and divided into two groups: one received virtual reality (VR) game-based balance exercises in addition to conventional therapy, while the other underwent conventional therapy alone. The assessment of balance and quality of life utilized the Berg Balance Scale, Time Up and Go Test, and the Parkinson Disease Questionnaire 39. The results revealed statistically significant improvements in static and dynamic balance, as well as quality of life, in the group that received VR-based training. Specifically, the group with combined therapy exhibited more substantial improvements in balance and quality of life compared to the conventional therapy group. The findings highlight the potential of VR technology as an effective tool for enhancing rehabilitation outcomes and quality of life in Parkinson's disease patients.

*Corresponding author

Rajesh S Vasava, Physiotherapist CIMS Hospital Ahmedabad, India.

Received: June 06, 2022; Accepted: June 13, 2022; Published: June 20, 2022

Keywords: Parkinson's Disease, Virtual Reality (VR), Game-Based Exercises, Comparative Therapy, Rehabilitation Therapy

Introduction

Parkinson's disease (PD) is the most prevalent chronic progressive neuro degenerative disorder characterized by issues related to balance and movement [1, 2]. First described as "The Shaking Palsy" by James Parkinson in 1817, this condition is primarily attributed to a deficiency of dopamine resulting from the degeneration of the substantianigra pars compact, impacting the normal function of the cerebral basal ganglia [3-5]. Although the etiology of Parkinson's disease remains largely idiopathic, it may be influenced by various factors, including genetic predisposition, oxidative stress, and environmental influences [6, 7].

Individuals with Parkinson's disease commonly present with a spectrum of motor and non-motor dysfunctions, including gait and balance difficulties, rigidity, intentional and resting tremors, and slowness of movement, along with sensory, speech, cognitive, and autonomic dysfunctions [8]. This disease can result in physical lethargy, a loss of independence, and a substantial impact on both balance and overall quality of life.



Figure 1: Dopaminergic Insufficiencies in PD

In the elderly population, age-related degeneration can lead to vestibular dysfunctions, affecting the central nervous system's capacity to process vestibular and proprioceptive signals, thereby influencing balance and postural adaptive reflexes and potentially leading to postural instability [6]. All three systems - the somatosensory system, audiovisual system, and vestibular system play pivotal roles in posture control and balance. The degeneration of the substantial nigra exacerbates these issues, leading to balance and postural control impairments and diminishing the quality of life [9].

Some studies suggest that the prevalence of Parkinson's disease in India is relatively low. The World Health Orga- nization (WHO) Questionnaire, with modifications, or the NIMHANS Questionnaire, have been utilized to assess preva- lence. Population-based prevalence rates for Parkinson's dis- ease vary, ranging from 6 to 53 cases per 100,000 individ- uals. Interestingly, some studies indicate a threefold higher prevalence rate in rural areas compared to urban areas - 41 in rural and 14 in urban areas per 100,000 individuals. Moreover, as age advances, the likelihood of developing Parkinson's disease increases, with a prevalence rate of 247 per 100,000 individuals among those over 60 years of age, while the 50-60 age group represents an average prevalence [10, 11].

Virtual reality (VR) training is emerging as an advanced therapeutic intervention in the field of rehabilitation, offering distinct advantages over standard physical rehabilitation. VR technologies encompass complex motion cameras equipped with kinetic sensors, cost-effective joysticks, and various immersionbased systems. Essentially, VR creates a computer- based multisensory environment, enabling user interaction and providing immediate audio-visual sensory feedback, all in a safe and engaging manner [10]. VR finds its application in physiotherapy and rehabilitation, sparking heightened interest with minimal rehabilitation difficulties and enhanced patient safety. By altering neural organization and promoting neural plasticity in patients with neural degeneration, VR stands as an advanced rehabilitation technology. It offers vestibular rehabilitation, aiding patients in improving balance, functional capacity, self-confidence, and ultimately, their quality of life. It also contributes to a reduction in the risk of falls and enhances cognitive functions and the capacity of patients to learn, retain, and transfer activities, as observed following VR- based training [8, 9-13]. The complexity, cost, and immersion levels of VR technologies vary significantly, ranging from simple joysticks (e.g., Wii remote) to more intricate motion cameras (e.g., Kinect sensor) [14].

In contrast, several studies suggest that conventional physiotherapy interventions have a positive impact on gait, balance, and quality of life in patients with Parkinson's disease. These interventions enhance postural control, balance, confidence levels, and overall quality of life, with exercises like balance training, muscle strengthening, and gait training proving to be effective [15, 16].

This study assesses balance and quality of life using the Berg Balance Scale, Time Up and Go test, and the Parkin- son Disease Questionnaire 39. The Berg Balance Scale, composed of 14 items, is summed to yield a total score between 0 and 56, with higher scores indicating better balance [17]. The Time Up and Go test is a quick and simple assessment that measures a patient's ability to stand up, walk for three meters, turn, walk back, and sit down, with lower scores indicating better conditions and scores increasing as conditions become more challenging [18]. The Parkinson Disease Questionnaire 39 is a widely used rating scale, assessing various components related to functioning, disability, health, activities, participation, and environmental factors, thereby providing insights into the quality of life of patients [19].

The primary objective of this study is to investigate the ef- fects of virtual reality game-based exercise training, combined with conventional training, on balance and quality of life in patients with Parkinson's disease.

Methodology

After obtaining ethical clearance based on predefined inclu- sion criteria, we enrolled a total of 30 patients from various rehabilitation centers in Ahmedabad. These patients were then provided with an explanation of the study's purpose and procedures. Those willing to participate in the study were requested to sign a consent form.



Figure 2: Virtual Reality set-up



Figure 3: Virtual Reality Training Protocol

Patient selection was conducted using a purposive sampling method. Data collection involved recording detailed infor- mation about the Parkinson's patients, including their demo- graphic particulars, the duration of symptom occurrences, and the chief complaints of the patients. Pre- and post-outcome measures were also documented. Following this, patients were briefed about the testing process and the measurement of pre- data and post-data. To ensure randomization, the subjects were divided into two groups, namely Group A and Group B. The interventions administered to each group were as follows:

• **Group A:** VR exercises combined with conventional therapy (total duration: 60 minutes)

• Group B: Conventional therapy alone (total duration: 30 minutes)

The VR training consisted of the following games:

- 100-meter running
- VR skateboarding
- Football
- An interface featuring three game modes, involving color matching, a bakery activity, and a memory number exer- cise
- Long jump, with each game lasting for a two-minute session.

Conventional therapy included interventions focused on static and dynamic posture maintenance tasks.

In both groups, we assessed balance using the Berg Balance Scale and the Time Up and Go Test, while the quality of life was evaluated using the Parkinson Disease Questionnaire.

| Table I: | Conventional | Training | Protocol for | -3weeks |
|----------|--------------|----------|--------------|---------|
| | | | | |

| Supporting Surface | Solid without task | | | |
|--|--|--|--|--|
| Static 15 minutes (3 minutes of each exercise and 1 minute of rest in between) | Stance width from wide to narrow base of support • Shoulder width • Partial tandem • Tandem • 1 leg standing | | | |

Table II: Conventional Training Protocol for Balance For1-3weeks

| Supporting Surface | Solid without task |
|---|--|
| Dynamic weight shift 15 minutes (3 minutes of each exercise and 1 minute of rest in between) | Step size: small to big Choice stepping Rope crossing (forward–backward) Rope crossing (right-left) |

Data Analysis

A. Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 21.0 for windows was used for statistical analysis. Microsoft excel was used to create graphs and tables. BBS, TUG, and PDQ- 39 were assessed in Parkinson's disease patients. The pre and post value were collected from both the group before and after an intervention.

All the measuring variables of the pre-treatment mean values in both groups showed non- significant differences, these finding demonstrated the homogeneity between both groups before starting the study and reflecting the validity of the sample collection and subjects were randomly distributed in bothgroups.

Table III: Conventional Training Protocol for Balance For4-6 Weeks

| Supporting Surface | Solid surface Holding a volley- ball with arm extended |
|---|--|
| Static posture15 minutes (3 min- utes of each exercise and 1 minute of rest in between) | Stance width from wide to narrow base of support Shoulder width Partial tandem Tandem 1 leg standing |

Table IV: Conventional Training Protocol For 4-6 Weeks

| Supporting Surface | Solid surface Holding a volley- |
|--|--|
| Dynamic weight shift 15 min (3 minute so feach exercise and 1 minute of rest in between) | Step size: small to big Choice stepping Rope cross- ing(forward-backward) Rope crossing(right-left) |



Figure 4: Static Balance Conventional Training - 1



Figure 5: Static Balance Conventional Training - 2

Statistical analysis of Intra group for PDQ-39 & BBS were done by using Wilcox on sign rank test and for TUG, Paired T-test was used. And for the Statistical analysis of Inter group for PDQ-39 & BBS were done by using Mann-Whitney U test and for TUG, Unpaired T-test was used.

Table V shows Group an Intra-group analysis & Table VI

| Table V: Group an Intra-Group Analysis | | | | |
|--|-----------------------------|-------------------|------------------------|----------|
| Outcome | Mean | | T-Value or Z-Value | P-Value |
| PDQ-39 | Pre = 76.2667 | Post = 65.86667 | Z value = 3.418817 | 0.000629 |
| BBS | $\frac{\text{Pre}}{38.8} =$ | Post = 50.2666666 | Z value = 73.413281 | 0.000642 |
| TUG | Pre = 12.85 | Post = 9.4647 | T value = 10.900218 | 0.000000 |



Figure 6: Dynamic Balance Conventional Training - 1





T-Value Outcome Mean **P-Value** or Z-Value PDQ-39 Pre = Post = Z value = 0.000554 78.5333 3.453327 73.6 BBS Pre = Post = Z value = 0.000590 43.333333 39.6 3.436294 TUG Pre = Post = 0.000000 T value = 12.68 11.035 8.989520 INTRA GROUP ANALYSIS - PDQ-39 78.53 80 76.26 75 70 65.86 65 60 55 PRE POST Group -A Group -B

Table VI: Group B Intra-Group Analysis

Figure 8: Intra Group Analysis of PDQ-39



Figure 9: Intra Group Analysis of BBS



Figure 10: Intra Group Analysis of TUG

Table VII: Intra-Group Analysis

| Outcome | Mean | | T-Value or Z-Value | PDQ-39 |
|---------|---------------------------|-------------------------|-------------------------|----------|
| PDQ-39 | Group- A = 65.86667 | Group-B = 73.6 | Z value = 4.120101 | 0.000005 |
| BBS | Group- A = 50.2666666 | Group-B = 743.333333 | Z value = 3.601327 | 0.000140 |
| TUG | Group-A = 43.3333333 | Group- B= 311.035 | T value = - 3.121288 | 0.004152 |



Figure 11: Intra Group Analysis of PDQ-39



Figure 12: Intra Group Analysis of BBS

shows Group B Intra-group analysis. The analysis concludes that there is a statistically significant difference in PDQ-39, BBS & TUG in Quality of life and Balance in Experimental Group.

Graphs 8, 9, 10 show mean value of Pre & Post values of PDQ-39, BBS, TUG of Group - 1 and Group - B. For PDQ- 39 and TUG mean value decreases after 6 weeks, whereas for BBS it increases after 6 weeks.

This analysis concludes that there is statistically significant difference in both the groups. Group A shows more statically difference than group b So, that improvement in Quality of life and balance is significantly more in Group A than in Group B.



Figure 13: Intra Group Analysis of TUG

This analysis concludes that there is statistically significant difference in both the groups. Group A shows more statically difference than group b So, that improvement in Quality of life and balance is significantly more in Group A thanin Group B.

Discussion

This study aimed to assess the effects of virtual reality game-based balance exercises in combination with conven- tional balance training on balance and quality of life in Parkin- son's disease patients. A total of 30 patients were selected based on specific criteria and divided into two groups: Group A and Group B. Group A received virtual reality balance training in addition to conventional balance training for 5 days a week over a period of 6 weeks, while Group B underwent conventional training only, also for 5 days a week over 6 weeks. Both groups received a 30-minute conventional training program, with Group A receiving an additional virtual reality training component. The assessment of balance and quality of life was conducted using three outcome measures, focusing on static and dynamic balance, which was evaluated using the Berg Balance Scale and the Time Up and Go Test, and the quality of life was assessed using the Parkinson Disease Questionnaire.

The study's primary objective was to determine the effects of virtual reality balance exercises on both static and dy- namic balance when compared to conventional physiotherapy exercises. The results of the study indicated a statistically significant improvement in Group A compared to Group B. Specifically, Group A exhibited more substantial improve- ments in static balance, dynamic balance, and quality of life. In Group A, the mean value of the Berg Balance Scale improved from 33.2 to 53.4, while in Group B, it improved from 31.03 to 40. Similarly, Group A saw a reduction in the mean value of the Time Up and Go Test from 10.4 to 12.68, whereas in Group B, it decreased from 11.03 to 12.68. The mean value of the Parkinson Disease Questionnaire 39 also decreased from 60.8 to 73.6 in Group A, and from 70.6 to 78.53 in Group B.

The results of this study underscore the statistically sig- nificant improvement in both balance and quality of life in Group A when compared to Group B. This indicates that the combination of conventional therapy with virtual reality game- based training has a more pronounced effect on balance and quality of life than conventional training alone.

Virtual reality balance training emerged as an effective tool for improving balance and quality of life in Parkinson's disease patients, suggesting that virtual reality could play a significant role in the rehabilitation of patients with balance and quality of life impairments. Gaming-based virtual reality, offering immediate audio and visual feedback, enhances motivation and encourages a higher number of repetitions. Virtual reality-based training provides optokinetic stimulation, promotes smooth pursuit movements, and helps train the ankle and hip strategies through strength training, ultimately resulting in improved balance and quality of life in patients with Parkinson's disease. The enhancement in the patient's condition can be attributed to the stimulation of neural plasticity.

Previous studies have also supported the positive impact of virtual reality training. It has been noted that individuals with Parkinson's disease often exhibit reduced stepping responses, increasing the risk of falls. Virtual reality training has been found to improve these stepping responses and reduce the risk of falls in these patients. Virtual reality serves as an advanced rehabilitation tool that stimulates movement through computer-based virtual environments. When incorporated into conventional training, it encourages patients and has been shown to alleviate both motor and non-motor symptoms in Parkinson's disease patients.

In summary, this study indicates that virtual reality-based balance training can significantly enhance both balance and the quality of life in Parkinson's disease patients. The incorpo- ration of

virtual reality into rehabilitation programs holds great promise for improving the well-being and functional abilities of individuals with Parkinson's disease.

Conclusion

This study underscores the potential of virtual reality (VR) gamebased balance training as a valuable intervention for individuals living with Parkinson's disease. The combination of VR exercises with conventional therapy resulted in signifi- can't improvements in static and dynamic balance and quality of life. The benefits of VR technology, such as immedi- ate feedback and enhanced motivation, were evident in the improved outcomes of the group that received VR training. Additionally, the stimulation of neural plasticity through VR exercises played a crucial role in enhancing balance and overall well-being in these patients. The study findings align with previous research demonstrating the positive impact of VR-based training on individuals with Parkinson's disease [20-41].

The results emphasize the potential of VR as an advanced tool in rehabilitation, capable of addressing both motor and non-motor symptoms in this population. The integration of VR technology into conventional therapy programs holds promise for enhancing the functional abilities and overall quality of life of individuals with Parkinson's disease. In conclusion, this research supports the incorporation of VR-based balance training as a significant advancement in the rehabilitation of Parkinson's disease patients, with the potential for widespread adoption in clinical practice to improve the well-being of individuals facing balance and quality of life challenges.

References

- Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. Journal of Neurology, Neurosurgery; Psychiatry 79: 368-376.
- Dickson DW (2012) Parkinson's Disease and Parkinsonism: Neuropathology. Cold Spring Harbor Perspectives in Medicine 2: a009258.
- 3. Parkinson J (2002) An Essay on the Shaking Palsy. J Neuropsychiatry Clin- Neurosci 2002 14: 223-236.
- 4. Stoessl AJ, Lehericy S, Strafella AP (2014) Imaging insights into basal ganglia function, Parkinson's disease and dystonia. The Lancet 384: 532-544.
- 5. Galvan A, Wichmann T (2008) Pathophysiology of Parkinsonism. Clinical Neurophysiology 119: 1459-1474.
- 6. Lees A (2017) An essay on the shaking palsy. Brain 140: 843-848.
- Wu T, Wang J, Wang C, Hallett M, Zang Y, Wu X, et al. (2012) Basal ganglia circuits changes in Parkinson's disease patients. Neuroscience Letters 524: 55-59.
- El-Kholy WA-H, Taha HM, Hamada SM, Sayed MA-F (2015) Effect of different modes of therapy on vestibular and balance dysfunction in Parkinson's disease. Egyptian Journal of Ear, Nose, Throat and Allied Sciences 16: 123-131.
- Konczak J, Sciutti A, Avanzino L, Squeri V, Gori M, et al. (2012) Parkinson's disease accelerates age-related decline in haptic perception by altering somatosensory integration. Brain 135: 3371-3379.
- Takamatsu Y, Fujita M, Ho GJ, Wada R, Sugama S, et al. (2018) Motor and Nonmotor Symptoms of Parkinson's Disease: Antagonistic Pleiotropy Phenomena Derived from alpha - Synuclein Evolvability textquestiondown Parkinson's Disease. 22: 5789424.
- Gokcal E, Gur VE, Selvitop R, BabacanYildiz G, Asil T (2017) Motor and NonMotor Symptoms in Parkinson's

Disease: Effects on Quality of Life. Arch Neuropsychiatr 54: 143-148.

- 12. Opara JA, Brola W, Leonardi M, Błaszczyk B (2012) Quality of life in Parkinson's Disease. J Med Life 5: 375-381
- 13. Smith PF (2018) Vestibular Functions and Parkinson's Disease. Front Neurol 9: 1085.
- 14. Dibble LE, Addison O, Papa E (2009) The Effects of Exercise on Balance in Persons with Parkinson's Disease: A Systematic Review Across the Disability Spectrum: Journal of Neurologic Physical Therapy 33: 14-26.
- 15. Gourie-Devi M (2014) Epidemiology of neurological disorders in India: Re- view of background, prevalence and incidence of epilepsy, stroke, Parkinson's disease and tremors. Neurol India 62: 588-598.
- Keshner EA, Patrice Tamar Weiss, Dorit Geifman, Daphne Raban (2004) Tracking the evolution of virtual reality applications to rehabilitation as a field of study. J NeuroEngineering Rehabil 76.
- Yang W-C, Wang H-K, Wu R-M, Lo C-S, Lin K-H (2016) Home-based virtual reality balance training and conventional balance training in Parkinson's disease: A randomized controlled trial. Journal of the Formosan Medical Association 115: 734-743.
- Liao Y-Y, Yang Y-R, Cheng S-J, Wu Y-R, Fuh J-L, et al. (2015) Virtual Reality–Based Training to Improve Obstacle-Crossing Performance and Dynamic Balance in Patients With Parkinson's Disease. Neurorehabil Neural Repair 29: 658-667.
- Severiano MIR, Zeigelboim BS, Teive HAG, Santos GJB, Fonseca VR (2018) Effect of virtual reality in Parkinson's disease: a prospective observational study. Arq Neuro-Psiquiatr 76: 78-84.
- Bala A, Gupta B (2013) Parkinsons disease in India: An analysis of publica- tions output during 2002- 2011. Int J NutrPharmacolNeurol Dis 3: 254-262.
- 21. Tan LCS, Venketasubramanian N, Hong CY, Sahadevan S, Chin JJ, et al. (2004) Prevalence of Parkinson disease in Singapore: Chinese vs Malays vs Indians. Neurology. 2004 Jun 8.
- 22. Lange BS, Requejo P, Flynn SM, Rizzo AA, Valero-Cuevas FJ, Baker L, et al. (2004) The Potential of Virtual Reality and Gaming to Assist Successful Aging with Disability. Physical Medicine and Rehabilitation Clinics of North America 62: 1999-2004.
- 23. Huang D, Mao Y, Chen P, Li L () Virtual reality training improves balance function. Neural Regen Res. 2014.
- 24. Levin MF (2011) Can virtual reality offer enriched environments for rehabili- tation? Expert Review of Neurotherapeutics 11: 153-155.
- 25. Lei C, Sunzi K, Dai F, Liu X, Wang Y, et al. (2019) Effects of virtual reality rehabilitation training on gait and balance in patients with Parkinson's disease: A systematic review. Cikajlo I, editor. PLoS ONE 14: e0224819.
- 26. Dibble LE, Addison O, Papa E (2009) The Effects of Exercise on Balance in Persons with Parkinson's Disease: A Systematic Review Across the Disability Spectrum: Journal of Neurologic Physical Therapy 33:14-26.
- 27. El-Kholy WA-H, Taha HM, Hamada SM, Sayed MA-F (2015) Effect of different modes of therapy on vestibular and balance dysfunction in Parkinson's disease. Egyptian Journal of Ear, Nose, Throat and Allied Sciences 16: 123-131.
- 28. Downs S, Marquez J, Chiarelli P (2013) The Berg Balance Scale has high intra- and inter-rater reliability but absolute reliability varies across the scale: a systematic review. Journal

of Physiotherapy 59: 93-99.

- 29. Silva B, Faria C, Santos M, Swarowsky A (2017) Assessing Timed Up and Go in Parkinson's disease: Reliability and validity of Timed Up and Go Assessment of biomechanical strategies. J Rehabil Med 49: 723-731.
- Nilsson MH, Westergren A, Carlsson G, Hagell P (2010) Uncovering Indi- cators of the International Classification of Functioning, Disability, and Health from the 39-Item Parkinson's Disease Questionnaire. Parkinson's Disease 984673.
- Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. Journal of Neurology, Neurosurgery; Psychiatry 79: 368-376.
- 32. Rinalduzzi S, Trompetto C, Marinelli L, Alibardi A, Missori P, et al. (2015) Balance Dysfunction in Parkinson's Disease. BioMed Research International 434683.
- 33. Ja O, W Brola, M Leonardi, B Błaszczyk (2012) Quality of life in Parkinson's Disease 5: 375-381.
- 34. Yang W-C, Wang H-K, Wu R-M, Lo C-S, Lin K-H (2016) Home-based virtual reality balance training and conventional balance training in Parkinson's disease: A randomized controlled trial. Journal of the Formosan Medical Association 115: 734-743.
- 35. van der Kolk NM, King LA (2013) Effects of exercise on mobility in people with Parkinson's disease: Exercise in Parkinson's Disease. Mov Disord 28: 1587-1596.

- 36. Mendes FA dos S, Pompeu JE, Lobo AM, da Silva KG, Oliveira T de P, et al. (2012) Motor learning, retention and transfer after virtualreality- based training in Parkinson's disease – effect of motor and cognitive demands of games: a longitudinal, controlled clinical study. Physiotherapy 98: 217-223.
- Liao Y-Y, Yang Y-R, Cheng S-J, Wu Y-R, Fuh J-L, et al. (2015) Virtual Reality–Based Training to Improve Obstacle-Crossing Performance and Dynamic Balance in Patients With Parkinson's Disease. Neurorehabil Neural Repair 29: 658-667.
- Severiano MIR, Zeigelboim BS, Teive HAG, Santos GJB, Fonseca VR (2018) Effect of virtual reality in Parkinson's disease: a prospective observational study. Arq Neuro-Psiquiatr 76: 78-84.
- 39. Nilsson MH, Westergren A, Carlsson G, Hagell P (2010) Uncovering Indi- cators of the International Classification of Functioning, Disability, and Health from the 39-Item Parkinson's Disease Questionnaire. Parkinson's Disease 984673.
- 40. Downs S, Marquez J, Chiarelli P (2013) The Berg Balance Scale has high intra- and inter-rater reliability but absolute reliability varies across the scale: a systematic review. Journal of Physiotherapy 59: 93-99.
- 41. Silva B, Faria Č, Santos M, Swarowsky A (2017) Assessing Timed Up and Go in Parkinson's disease: Reliability and validity of Timed Up and Go Assessment of biomechanical strategies. J Rehabil Med 49: 723-731.

Copyright: ©2022 Rajesh S Vasava. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.