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Samaa Mohammed Elbalkeimy
Neurology and Psychiatry Department, Faculty of Medicine, Tanta University, Egypt

Mahmoud Ebrahim Elhassanien
Neurology and Psychiatry Department, Faculty of Medicine, Tanta University, Egypt

Hanan Ahmed Nagy Mohamed Saleh
Neurology and Psychiatry Department, Faculty of Medicine, Tanta University, Egypt

Azza Abbas Ghali
Neurology and Psychiatry Department, Faculty of Medicine, Tanta University, Egypt

Corresponding Author:
Samaa Mohammed Elbalkeimy
Neurology and Psychiatry Department, Faculty of Medicine, Tanta University, Egypt

Assessment of the relation between clinical severity of multiple sclerosis and cerebral perfusion

Samaa Mohammed Elbalkeimy, Mahmoud Ebrahim Elhassanien, Hanan Ahmed Nagy Mohamed Saleh and Azza Abbas Ghali

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Abstract
Background: Multiple sclerosis (MS) is a chronic inflammatory disease that is degenerative and demyelinating affected central nervous system. Magnetic resonance (MR) remains primary method for monitoring clinical evolution and therapeutic response of these cases. The study aimed to evaluate relation between cerebral perfusion and clinical severity of MS.
Methods: This cross sectional study was done on 50 cases at MS Unit at Department of Neuro Psychiatry, Centre of Psychiatry, Neurology and Neuro Surgery, Tanta University Hospitals, Egypt. All cases were subjected to full neurological examination and multiple sclerosis special tests including assessment of enhanced disability status scale (EDSS), 9-hole peg test.
Results: The mean transit time (MTT) and EDSS exhibited a significant positive correlation (r=0.667, P <0.001) in both normal appearing grey matter (NAGM) and normal appearing white matter (NAWM) (r=0.670, P<0.001). Conversely, the cerebral blood flow (CBF) and cerebral blood volume (CBV) of NAGM (r=-0.760, P<0.001) and NAWM (r=-0.781, P<0.001) exhibited a significant negative correlation (r=-0.808, P<0.001) and NAWM (r=-0.849, P<0.001).
Conclusion: We found a negative correlation among disability parameters (EDSS, 25 Foot walk, 9 Peg hole) and CBF in various GM amd WM regions, confirming that physical disability severity is related to brain hypoperfusion. Particularly, brain hypoperfusion and prolonged transit time were associated with an increase in EDSS, 25-foot walk, and 9-peg hole in numerous GM and WM.

Keywords: Assessment, relation, clinical severity, multiple sclerosis, cerebral perfusion

Introduction
Multiple sclerosis (MS) is a chronic disorder that is result of demyelinating, a degenerative and inflammatory disease that affects central nervous system (CNS) [1]. An incomplete understanding of specific pathogenesis of MS persists. According to classic theory of pathogenesis of MS, T cells are mediators of disease, which is an autoimmune disorder of CNS. Nevertheless, pathophysiological observations number are not easily accounted for in autoimmune mechanisms terms. Initially, The progressive (neurodegenerative) aspect of the disease persists despite the fact that intensive immunosuppressive interventions effectively curtail inflammatory disease activity [2]. The second discovery is that specific demyelinating lesions develop without a prior inflammatory reaction, as revealed by pathologic investigations. Third, the presence of diffuse cerebral white matter hypoperfusion in MS cases is difficult to explain through autoimmune phenomena [3].
In the past few years, there have been significant advancements in MS diagnosis and treatment. MR remains the primary method for monitoring clinical evolution and therapeutic response of these cases. On the other hand, relation between clinical features, particularly cognitive disability, and lesion volume in conventional MR sequences is low [4, 5].
Relapses are clinically indicative of inflammation, which conceptually drives the progression of disability, and neurodegeneration, which is observed as a continuous loss of function. Process heterogeneity is extremely prevalent [6]. Affecting brain perfusion are both mechanisms that are believed to be involved. The rise in cerebral blood flow (CBF) and cerebral blood volume (CBV) implicates an association between lesion pathogenesis in white matter and subtle inflammation in normal-appearing white matter (NAWM) [7]. Lesions were more frequently situated in low-perfusion regions in cases with a more neurodegenerative disease.

However, In MS, there appears to be a systemic decrease in CBF [8]. However, the perfusion of grey matter is inextricably linked to neuronal activity, and the loss of regional grey matter has been acknowledged as a significant predictor of disability in MS [9]. Additionally, CBF modifications in grey matter may serve as more precise indicators of disability than those in white matter [10].

This suggests that CBF is restricted in NAWM of cases; clinically isolated syndromes (CIS), primary progressive MS, suggestive of MS, and relapsing-remitting multiple sclerosis (RRMS) were present. This means that underlying mechanism is unknown and that condition is not dependent on MS course. Early stages of disease may exhibit it. Cerebral perfusion findings are assumed to be result of axonal degeneration, mitochondrial failure, and vascular dysfunction [11, 12].

The study aimed to evaluate correlation among clinical severity of MS and cerebral perfusion.

Patients and Methods

This cross sectional study was involved ***50*** cases at the MS Unit at Department of NeuroPsychiatry, Centre Of Psychiatry, Neurology and NeuroSurgery, Tanta University Hospitals, Egypt from January 2024 to June 2024. The study was performed after approval from thet institutional ethics committee (approval number). Research was carried out in accordance with the Declaration of Helsinki.

Inclusion criteria were cases over age of 18 who have been diagnosed with MS in accordance with Mc Donald criteria of 2017, including primary or secondary progressive and relapsing remitting [13].

Exclusion criteria were presence of other myelin oligodendrocyte glycoprotein associated disease and systemic lupus erythematosus, demylinatig or autoimmune disorder as neuromyelitis optica (NMO), presence of any other neurodegenerative disorder such as dementia, presence of significant systemic disease also disabling heart failure, liver disease, pulmonary disease, kidney disease, and active malignancies, corticosteroid treatment during last month, pregnant females and patients known to had a psychotic disorder. All patients in this investigation were exposed to full history taking including age and gender, present history including duration of disease, age at MS onset, phenotype at disease onset, phenotype at time of interview, family history of MS, number of relapses timing of last clinical or radiological relapse, duration of disease and treatment history, and full neurological examination.

Multiple sclerosis special tests

Assessment of expanded disability status scale (EDSS): EDSS is an assessment scale that is administered by clinicians. It serves to assess therapeutic interventions efficacy and to describe disease progression in cases had MS. In 1954, Kurtzke developed it, and it was further developed in 1983 to include eight functional systems (FS) [14]. Brain Stem (BS), Sensory (S), Visual (V), Cerebral or Mental (Cb), Bladder-Bowel (BB), Pyramidal (P), Cerebellar (Cll), and Other (O) are the eight functional systems included. Results were subsequently analyzed using an ordinal rating system that ranged from 0 (normal neurological status) to 10 (death due to MS) in 0.5-point increments (when EDSS 1 was achieved). The EDSS lower scale values quantify impairments, while the upper scale range (> EDSS 6) evaluates the handicaps of MS patients, as determined by a neurological examination [15].

Timed 25 foot walk test (T25FW): According to evidence available regarding the "reliability, responsiveness, validity, and clinical meaningfulness of scores in MS," The T25FW is the "most accurately characterized objective measure of walking disability and is useful for a broad spectrum of walking disabilities." Also, it is simple to administer and can be used on a variety of patients [16].

9-hole peg test (NHPT): For manual dexterity, NHPT is widely acknowledged as the gold standard metric. An official publication of American Society for Occupational Therapy, Kellor *et al*. [17] initially introduced it as a measure of dexterity.

Radiology imaging

MRI brain with MS protocol included conventional MR examination (T1WI, T2WI, and FLAIR in axial, sagittal planes), 3D T2 -FLAIR (Axial and Sagittal) and post single dose gadolinium enhanced T1 weighed images for selected cases (naive cases). A gradient-echo echo planar sequence was implemented in transverse plane to implement dynamic susceptibility contrast MRI (DSC-MRI) with subsequent parameters: In-plane voxel size is 1.8 mm, the matrix is 128, the slice thickness is 5 mm, and signal bandwidth is 1470 Hz/pixel. The field of view is 230 mm. 1000/54/30° are TR/TE/flip angles, respectively. Further post-processing was performed on DSC-MRI images by an off-line workstation. Analysis of perfusion data was conducted. By computing CBF, CBV, and MTT, absolute perfusion parameters were found. Calculated by establishing regions of interest (ROI) in periventricular NAWM and thalamus of brain. The extent of ROI was fixed, and they were positioned to prevent venous and arterial structures, also MS lesions.

Statistical analysis

An analysis was conducted using SPSS v28, (IBM Inc., Armonk, NY, USA). We used histograms and Shapiro-Wilks test to find out if data was normally distributed. Measures of quantitative parametric data were presented as means and standard deviations (SD). Statistics that are not parametric were shown using a median and an interquartile range (IQR). Numbers and percentages were used to represent qualitative variables. Two quantitative variables were estimated by Pearson correlation to see how closely they were related to one another. For statistical purposes, A two-tailed P value < 0.05 is used to determine if a result is significant.

Results

Table 1 shows that 50 cases were involved in current study; 34 (68%) females and 16 (32%) males, their mean age was 36.48± 10.06 years. Among studied patients; 8 (16%) patients had a positive family history of MS.

Regarding medical history, mean age at MS onset was 30.78± 9.09 years. Phenotype of MS at onset was PPMS in 5 (10%) patients and was RRMS in 45(90%) patients. The median the progression index was 0.73 and the median number of relapse was 3. Among the studied patients, 39 (78%) patients received highly efficacious DMT and 11 (22%) patients received platform DMT. Table 2.

Table 3 shows clinical data at interview and disability of the studied patients, where the median EDSS was 3, the mean 25-Foot walk was 8.58± 4.65 and the 9-Peg hole was 41.64±

10.56. The radiological findings of the NAGM showed the mean CBF was 52.07± 19.09, the mean CBV was 4.3± 0.71 and the mean MTT was 5.91± 2.16. The radiological findings of the NAWM showed the mean CBF was 30.69± 13.21, the mean CBV was 2.22± 0.54 and the mean MTT was 5.92± 2.16. Table 4.

There was a significant negative correlation between EDSS and 9 Peg Hole (r=0.302, P=0.033), MTT in both 25 Foot Walk (r=0.862, P0.001), NAGM (r=0.670, P0.001), and NAWM (r=0.667, P0.001), and a significant negative correlation between EDSS and CBF in both NAGM (r=-0.760, P0.001) and NAWM (r=-0.781, P0.001). Table 5; Figure 1 There was a significant negative correlation between the 25-foot walk and the 9-foot hole (r=0.580, P0.001), the MTT in both NAGM and NAWM (r=0.621, P0.001), the 25-foot walk and the CBF in both NAGM and NAWM (r=-0.759, P0.001), and the CBV in both NAGM and NAWM (r=-0.764, P0.001). Table 5; Figure 2

There was a significant positive correlation among MTT and 9 Peg hole in both NAGM (r=0.612, P<0.001) and in NAWM (r=0.609, P <0.001), and there was a significant negative correlation among 9 Peg hole and CBF in both NAGM (r=-0.669, P<0.001) and in NAWM (r=-0.680, P<0.001), and CBV in both NAGM (r=-0.677, P<0.001) and in NAWM (r=-0.675, P<0.001). Table 5; Figure 3.

Table 1: Baseline charcterestics of the studied patients

		Total (n=50)
Age (years)		36.48± 10.06
Sex	Male	16 (32%)
	Female	34 (68%)
Family history	Positive	8 (16%)
	Negative	42 (84%)

Data presented as mean ± SD or frequency (%).

Table 2: Medical history of MS of the studied patients

		Total (n=50)
Age at onset of MS (years)		30.78± 9.09
Phenotype of MS at onset	PPMS	5 (10%)
	RRMS	45(90%)
Progression index		0.73 (0.5 - 1.14)
Number of relapse		3 (2.5- 5)
DMT	Highly efficacious DMT	39 (78%)
	Platform DMT	11 (22%)

Data presented as mean ± SD, median (IQR), or frequency (%), MS: multiple sclerosis, PPMS: primary progressive multiple sclerosis, RRMS, relapsing-remitting multiple sclerosis, DMT: disease modifying therapy.

Table 3: Clinical data at interview and disability of the studied patients

	Total (n=50)
EDSS	3 (1.63 -4.50)
25 Foot walk	8.58± 4.65
9 Peg hole	41.64± 10.56

Data presented as mean ± SD, median (IQR), EDSS: expanded disability status score, MS: multiple sclerosis.

Table 4: Radiological findings of the studied patients

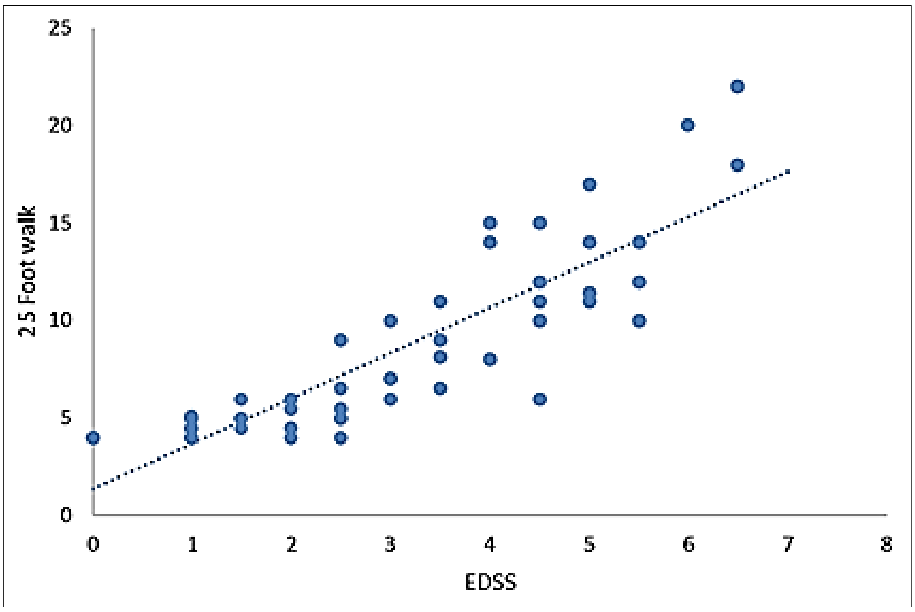
		Total (n=50)
NAGM	CBF	52.07± 19.09
	CBV	4.3± 0.71
	MTT	5.91± 2.16
NAWM	CBF	30.69± 13.21
	CBV	2.22± 0.54
	MTT	5.92± 2.16

Data presented as mean ± SD, median (IQR), MS: multiple sclerosis, NAGM: normal appearing grey matter, MTT: mean transit time. NAWM: normal appearing white matter, CBV: cerebral blood volume, CBF: cerebral blood flow.

Table 5: Correlation between the EDSS and the other parameters

		EDSS		25 Foot walk		9 Peg hole	
		r	P	r	P	r	P
NAGM	CBF	-0.760	<0.001*	-0.759	<0.001*	-0.669	<0.001*
	CBV	-0.808	<0.001*	-0.764	<0.001*	-0.677	<0.001*
	MTT	0.670	<0.001*	0.621	<0.001*	0.612	<0.001*
NAWM	CBF	-0.781	<0.001*	-0.751	<0.001*	-0.680	<0.001*
	CBV	-0.849	<0.001*	-0.785	<0.001*	-0.675	<0.001*
	MTT	0.667	<0.001*	0.621	<0.001*	0.609	<0.001*

R: correlation coefficient, NAWM: normal appearing white matter, NAGM: normal appearing grey matter,CBF: cerebral blood flow, MTT: mean transit time, CBV: cerebral blood volume, *: statistically singificant as p value <0.05.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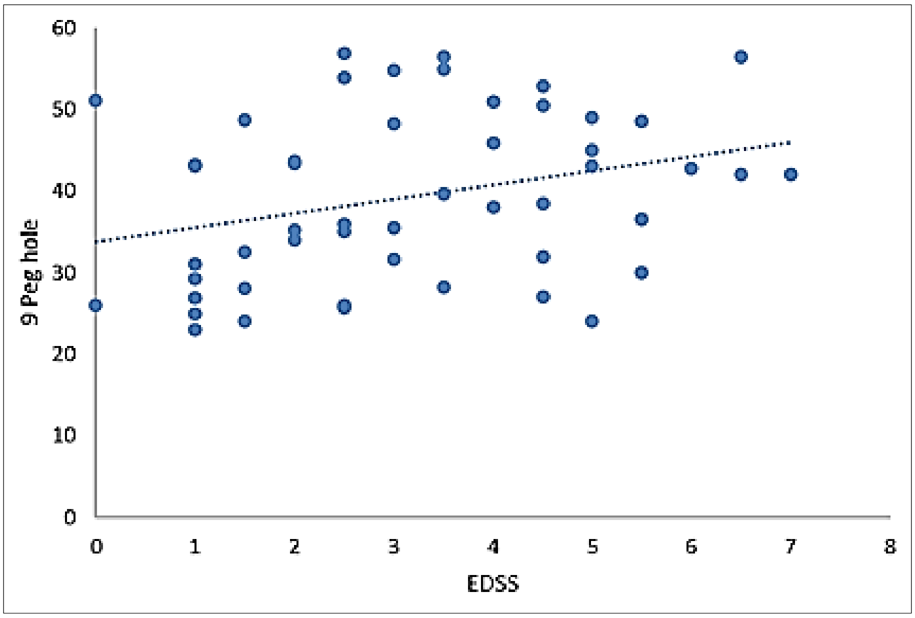
9 Peg hole
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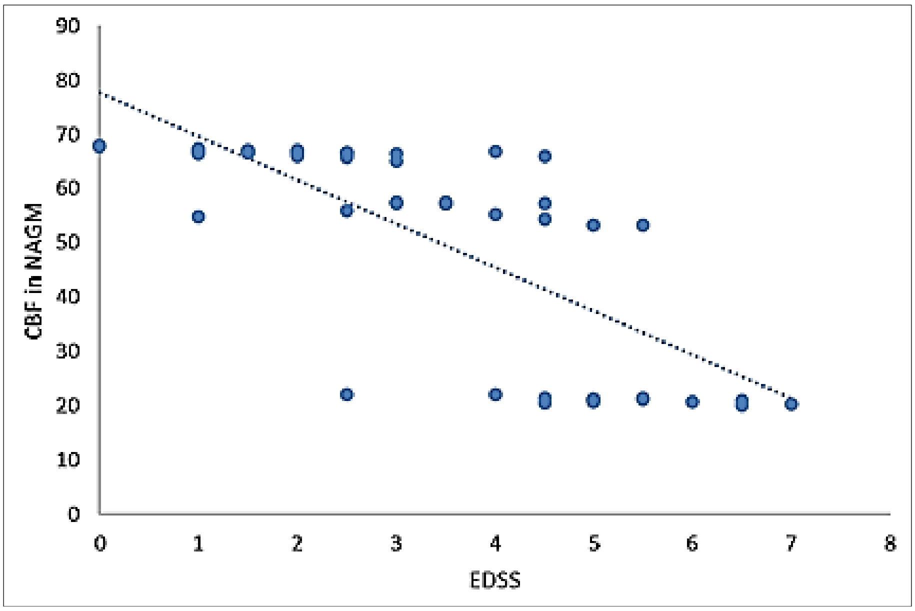
CBF in NAGM
EDSS
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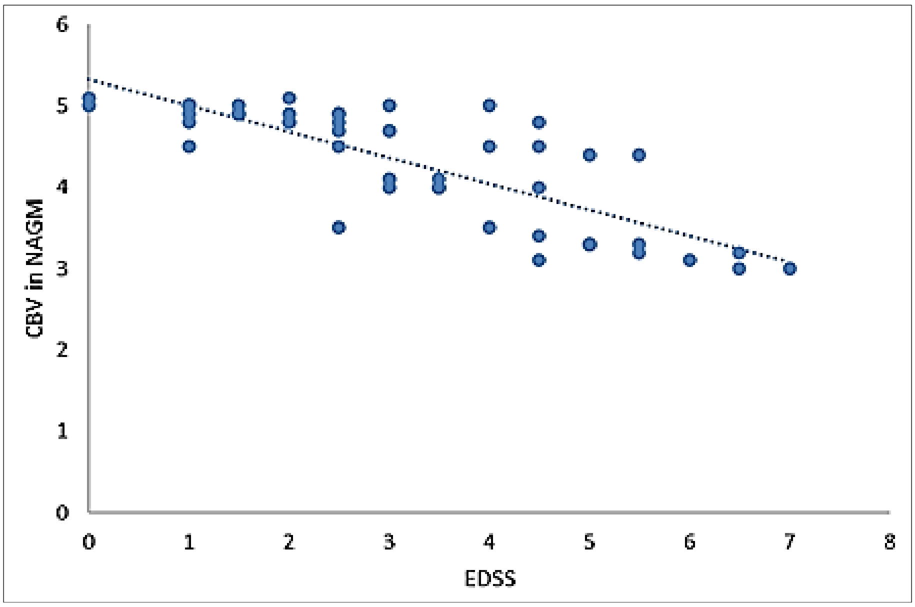
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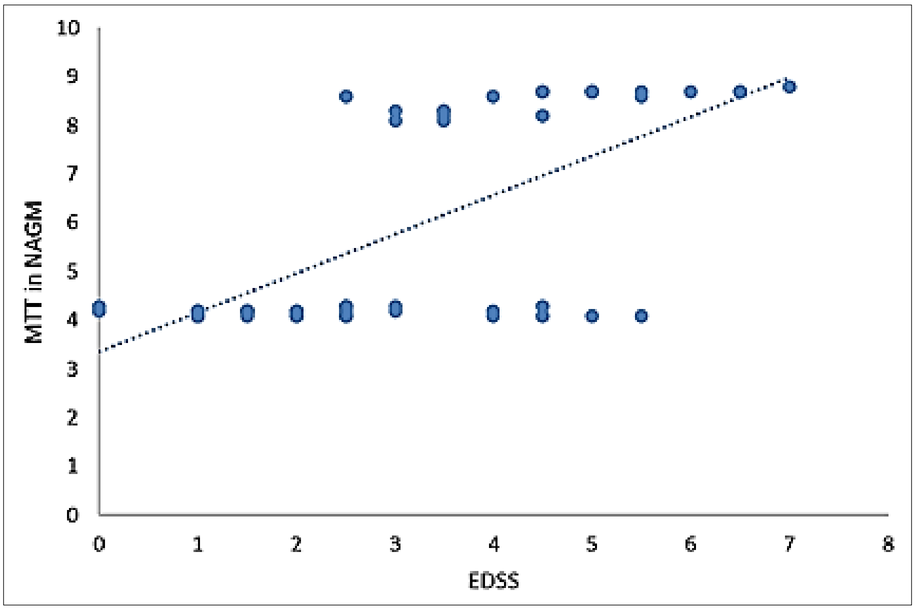
MTT in NAGM
EDSS
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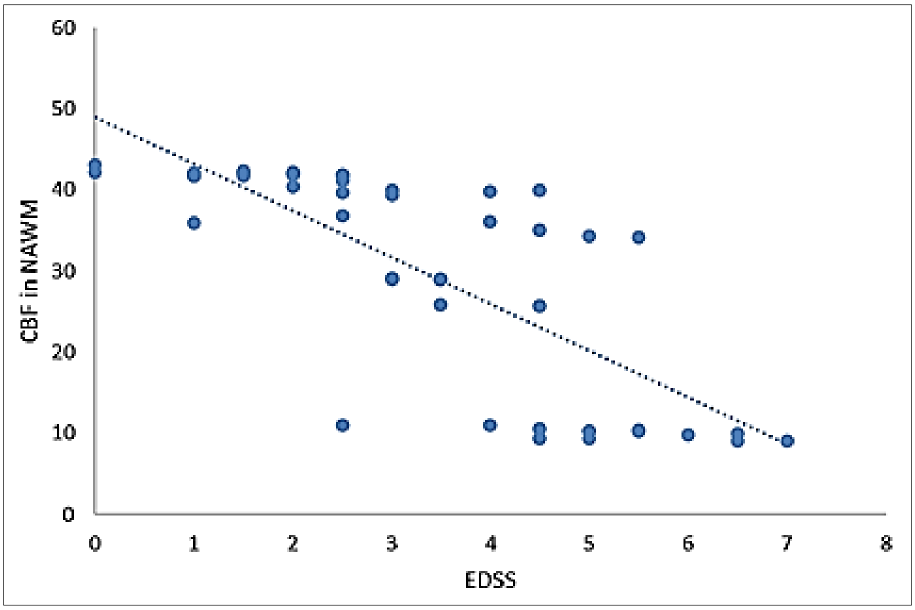
CBF in NAWM
EDSS
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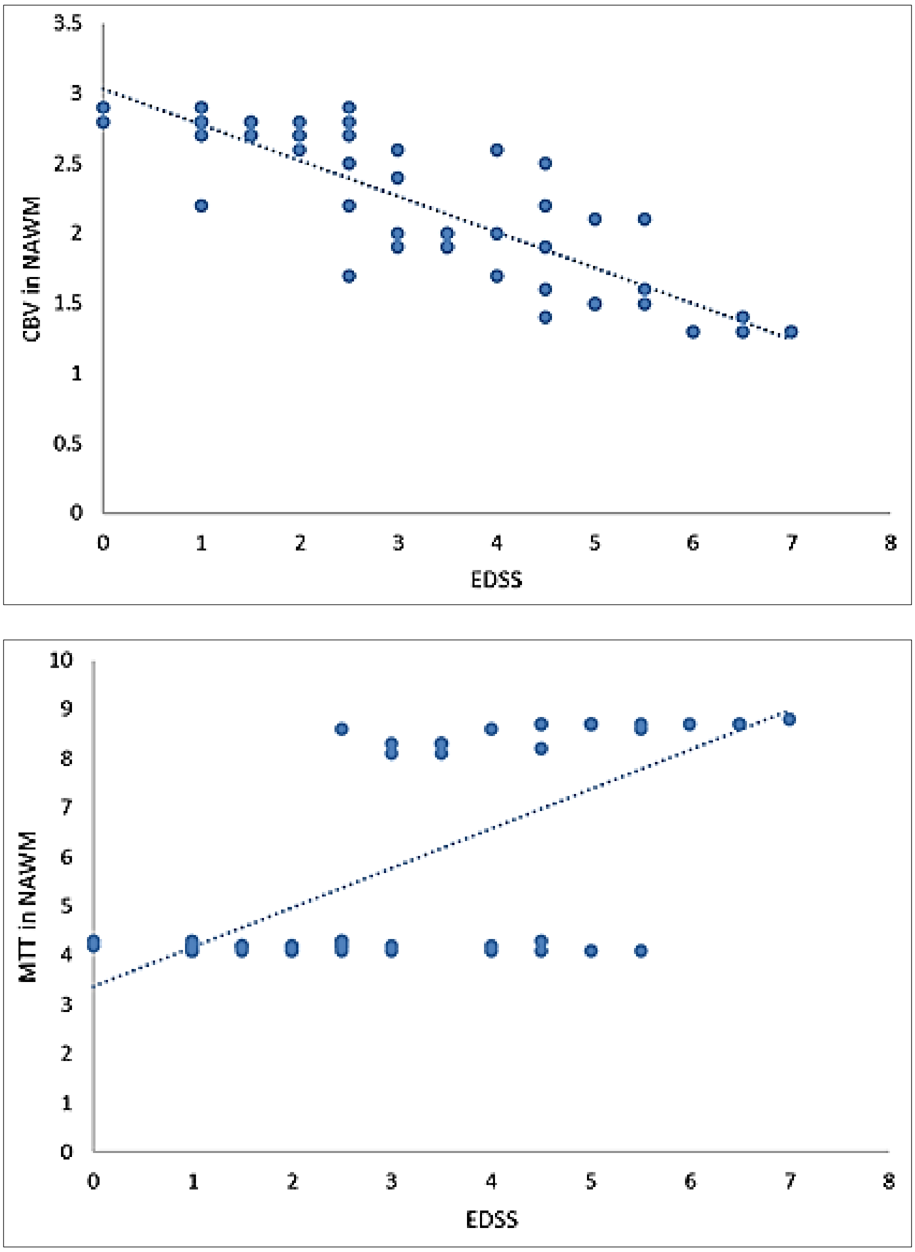
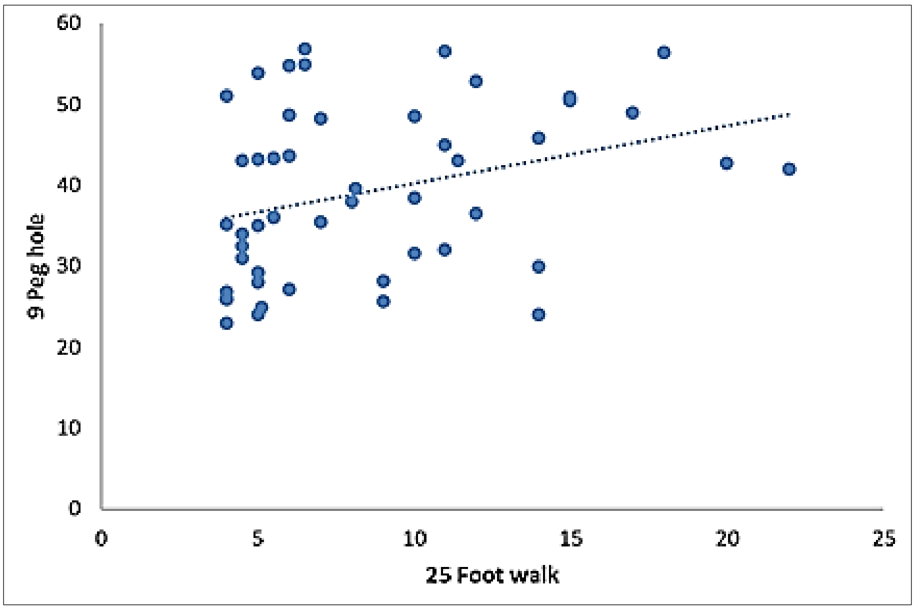
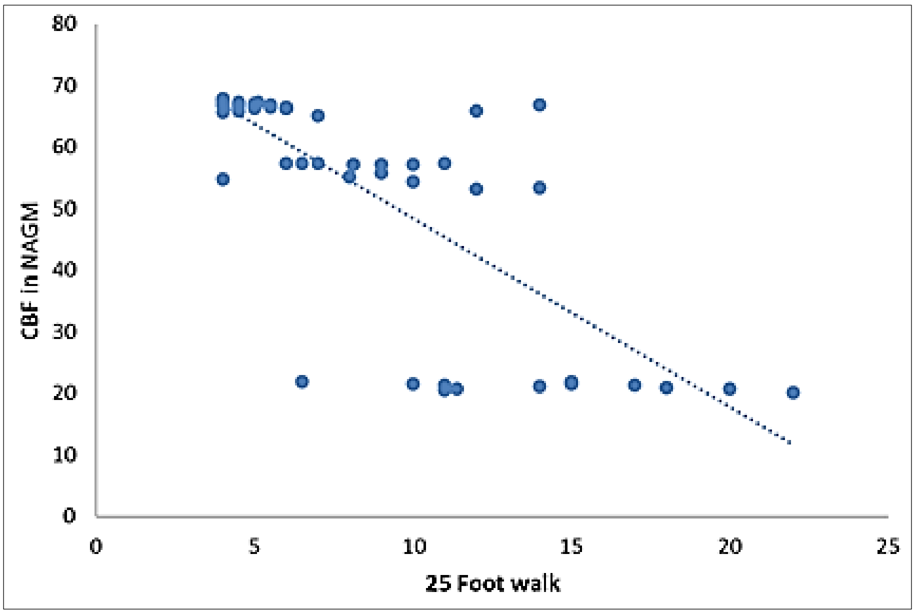


Fig 1: Correaltion between EDSS and other parameters

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CBF in NAGM
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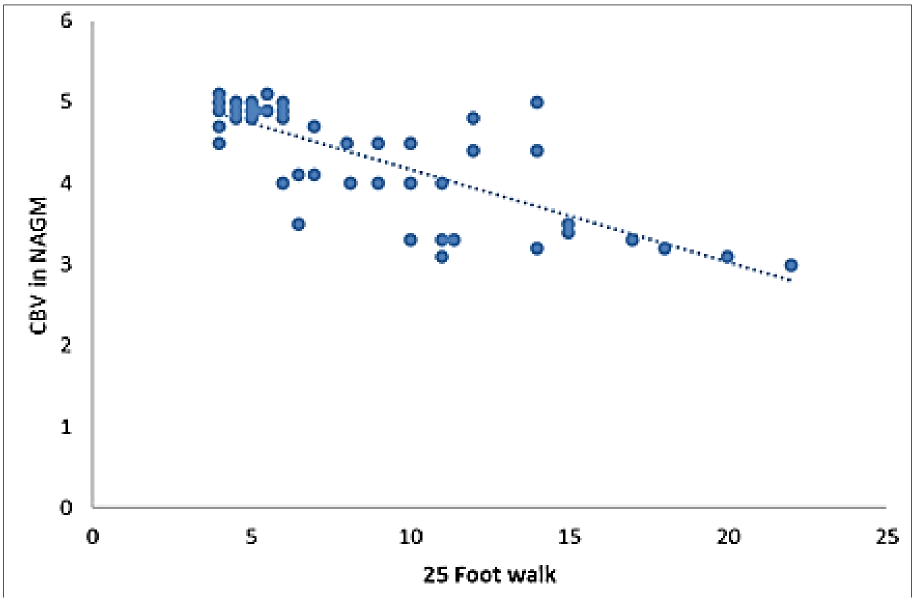
25 Foot walk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CBV in NAGM
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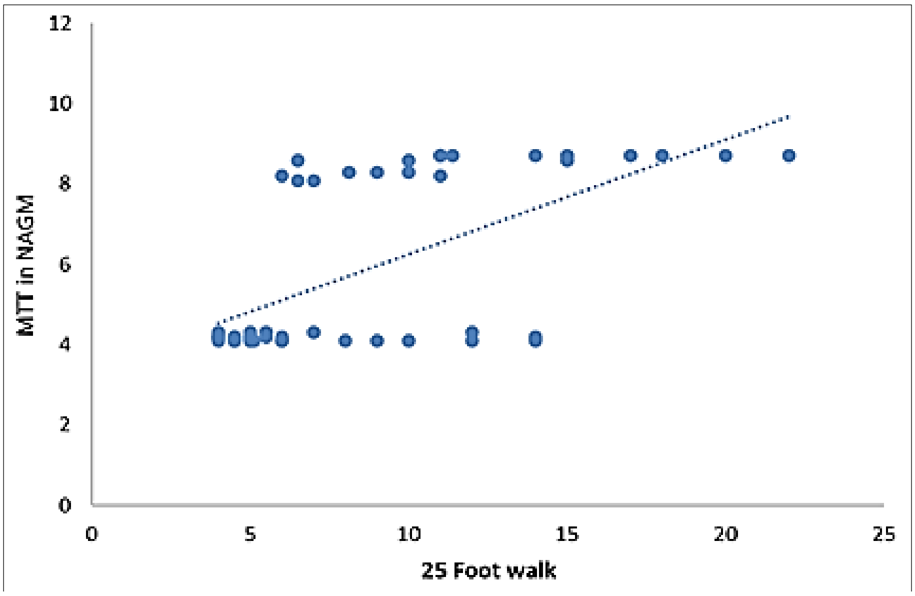
25 Foot walk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MTT in NAGM
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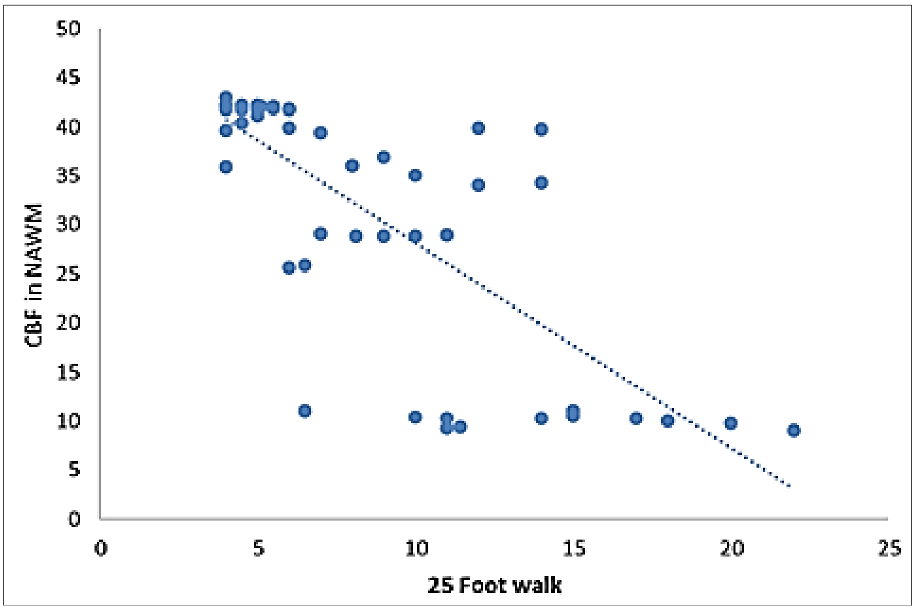
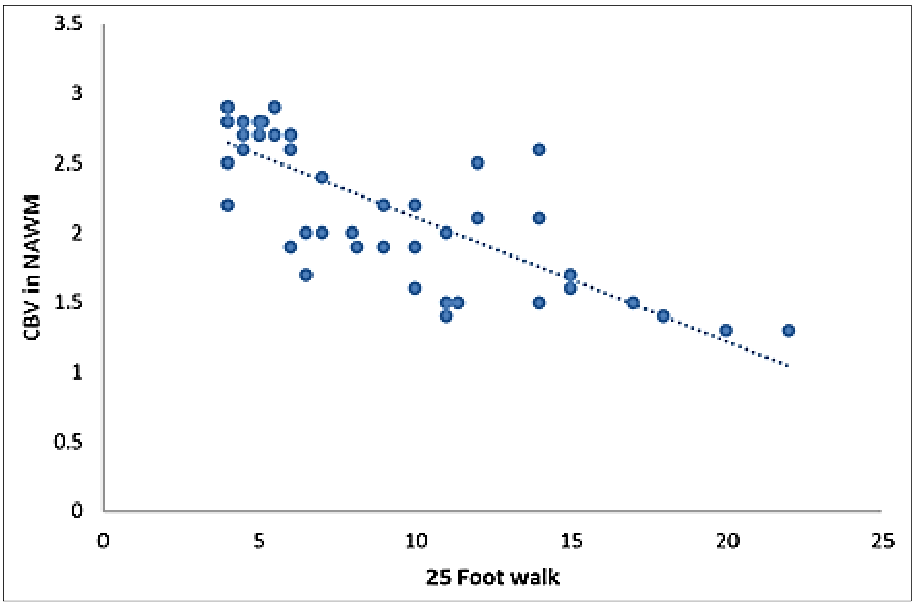
25 Foot walk





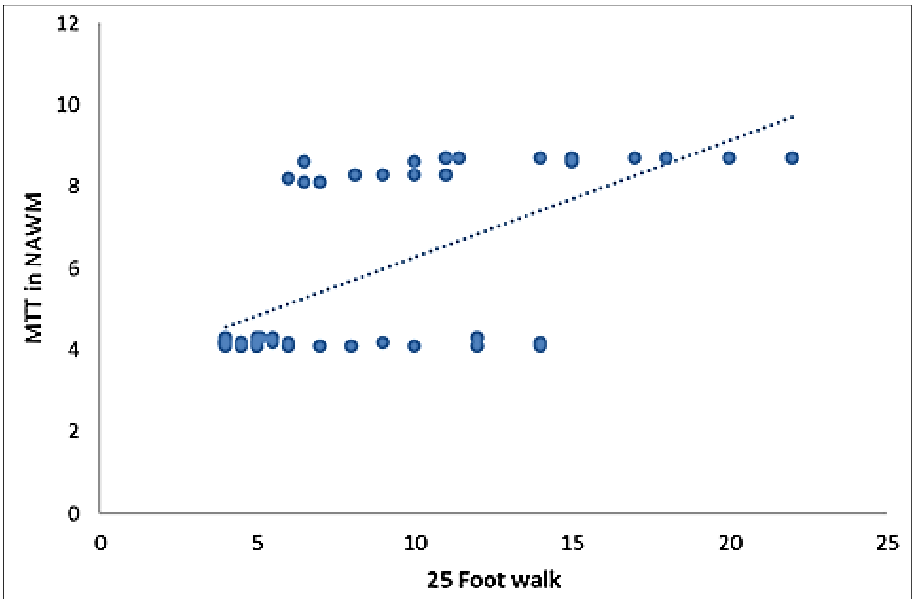
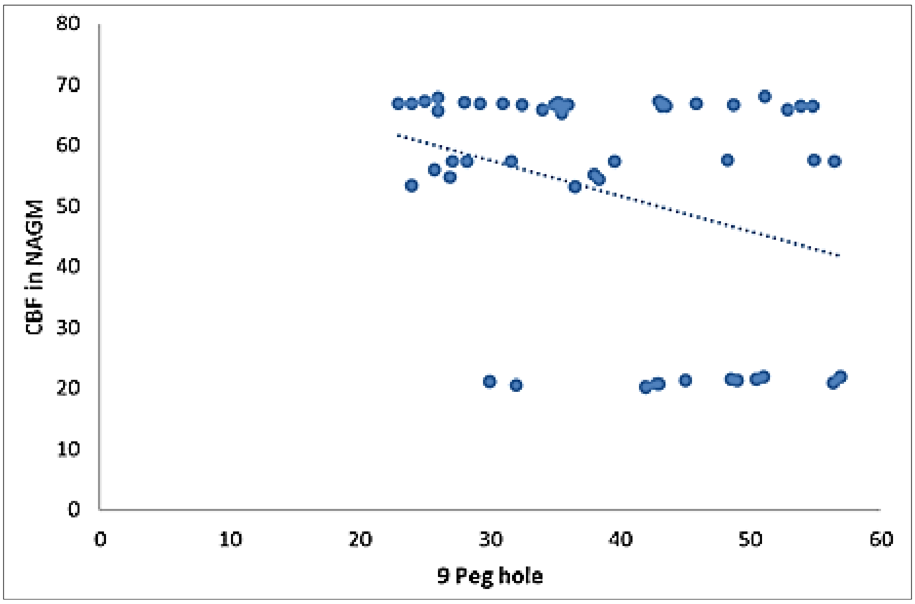


Fig 2: Correaltion between 25 foot walk and other parameters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CBF in NAGM
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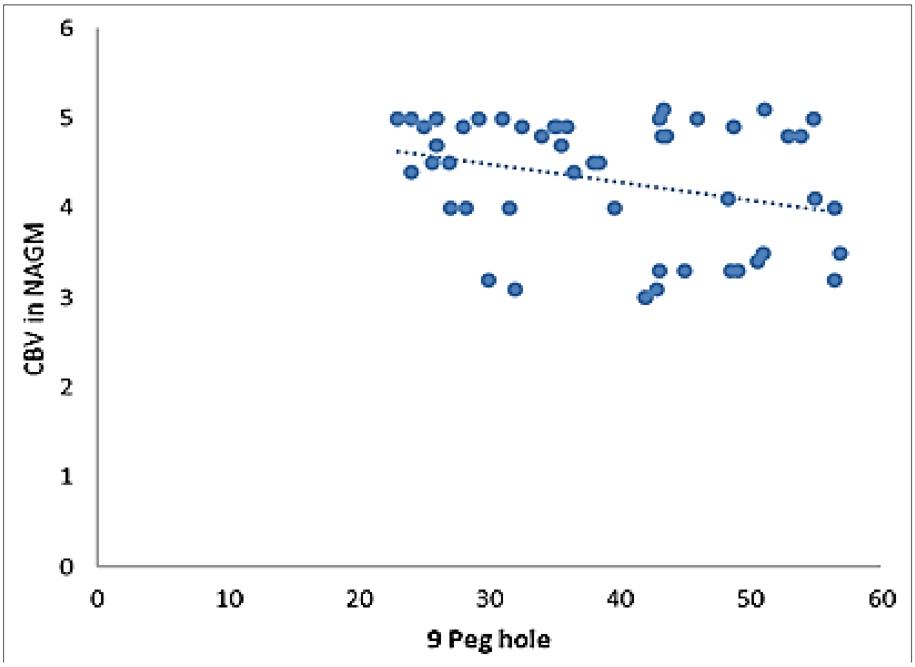
9 Peg hole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CBV in NAGM
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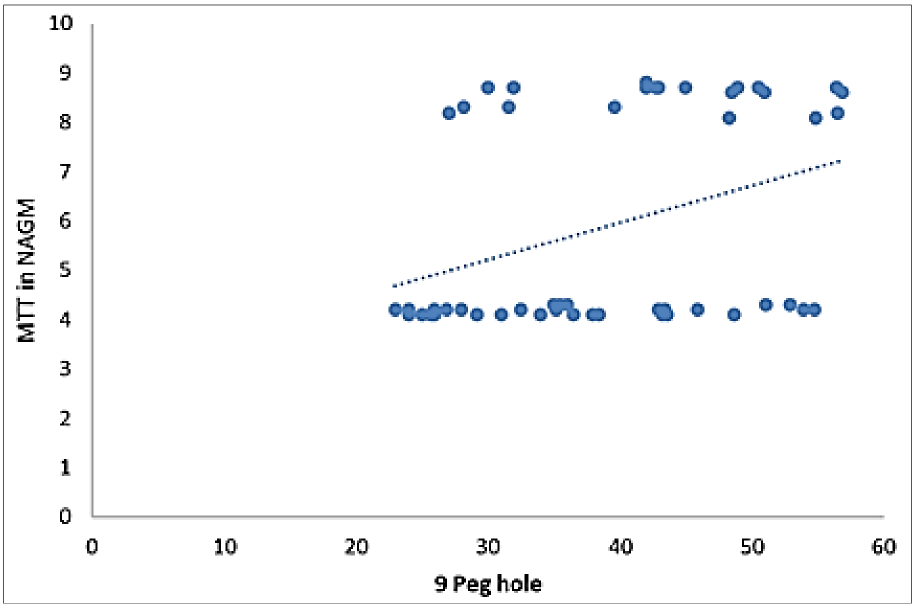
9 Peg hole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MTT in NAGM
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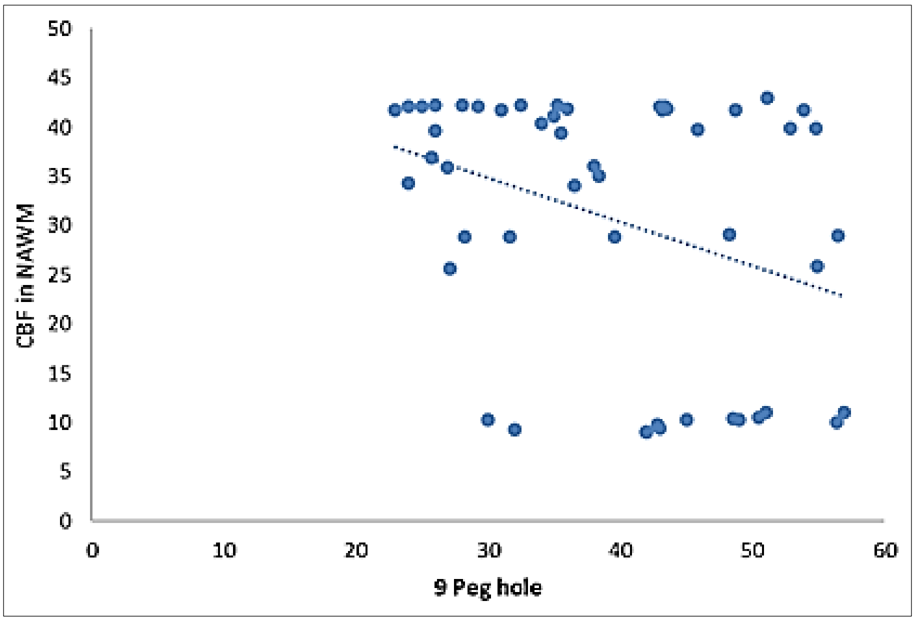
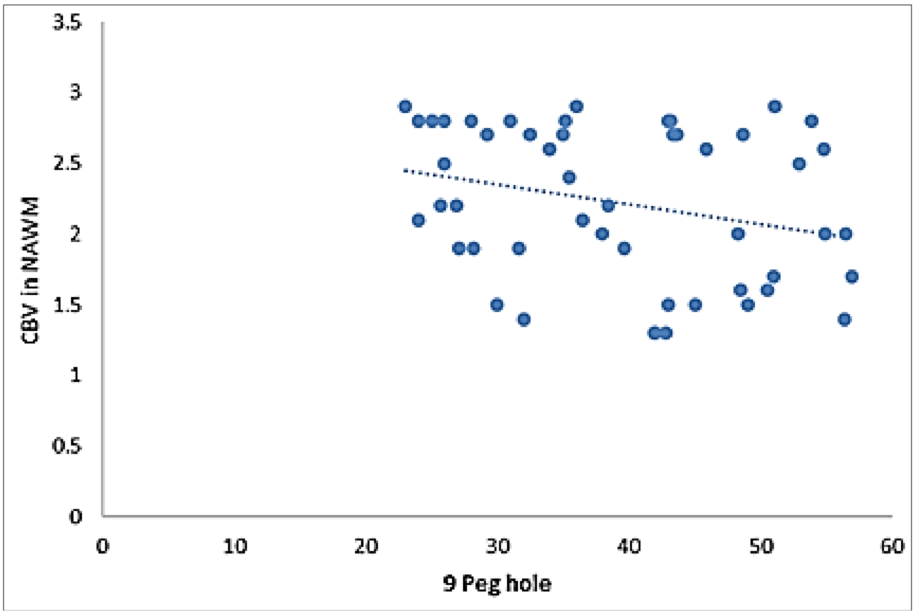
9 Peg hole





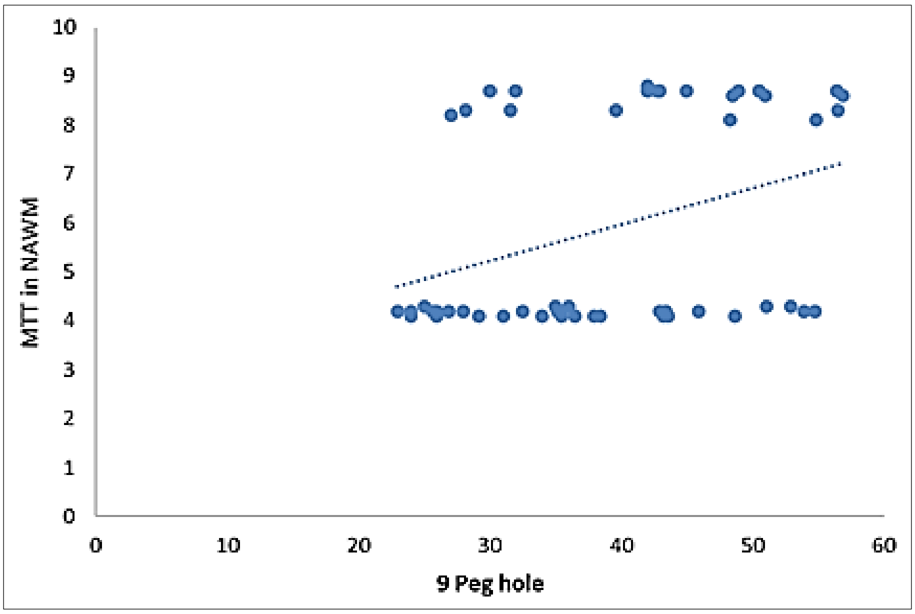


Fig 3: Correaltion between 9 peg hole foot walk and other parameters

Discussion

In absence of structural differences, prior research has shown that brain perfusion is capable of detecting cortical abnormalities. The cerebral perfusion test has potential to indirectly analyze the neurodegeneration that is a component of this disease by assessing the oxygenation and metabolism of various brain regions [18, 19].

We discovered that there was a significant negative correlation between CBF and EDSS in both NAGM and NAWM, also CBV in both NAGM and NAWM. Additionally, we observed a significant positive correlation between EDSS and 25 Foot walk, 9 Peg hole, MTT in both NAGM and NAWM. There was a significant negative correlation among 25 Foot walk and CBF in both NAGM and in NAWM, and CBV in both NAGM and in NAWM and In both NAGM and NAWM, there was a significant positive correlation between 25 Foot walk and 9 Peg hole, MTT. In both NAGM and NAWM, there was a significant negative correlation between 9 Peg hole and CBF, and CBV in both NAGM and NAWM. In both NAGM and NAWM, there was a significant positive correlation between 9 Peg hole and MTT.

Hammad *et al.*, [20] it was shown that the periventricular NAWM of RR MS patients exhibited a significantly reduced CBF and CBV, while MTT was significantly prolonged in comparison to white matter of controls.

Additionally, Varga and colleagues [21] who used DSC-MRI to evaluate twelve cases had CIS, twelve cases had RRMS, and twelve healthy individuals (controls) were examined for cerebral perfusion parameters in the NAWM (periventricular and frontal areas).They reported a significant decrease in CBF of periventricular NAWM of CIS patients and RRMS cases in comparison to controls.

Steen and colleagues [22], in a study, pseudo-continuous arterial spin labeling was employed to measure the CBF of 25 MS cases had varying disability degrees10 healthy controls and (16 with RRMS and 9 with progressive MS). There was no correlation among disability assessed by EDSS and decrease in CBF in NAWM. The results' discrepancies may be due to the fact that the author selected a diverse collection of MS cases with EDSS values that were not correlated with CBF and variable disease activity. Furthermore, disability measures may show diminished sensitivity in predicting disease severity. As an illustration, EDSS frequently illustrates motor disability that is a result of spinal cord lesions and may vary among clinicians.

De la Peña *et al.*, [23], in accordance with the McDonald 2010 criteria, conducted a cross-sectional study that included healthy controls and cases had RRMS [24], and SPSM according to Lublin 2013 criteria [25], and a significant reduce in CBF has been observed in frontal thalamus, cortices, and caudate of MS cases, nevertheless, there is no indication of a reduction in gray matter volume or cortex thickness. Furthermore, in disability context, In the basal ganglia and frontal cortex, a negative correlation was observed between EDSS and CBF, also among EDSS and BAT in thalamus. Causes of these variations in cerebral perfusion in MS are not entirely comprehended. These findings may be addressed by a variety of hypotheses. First and foremost, hypoperfusion may be associated with neuronal atrophy. On the other hand, majority of study has not identified any relation between brain atrophy and perfusion [26, 27], Conversely, although other articles have only described a partial relation to T2 lesion burden [28, 29].

In De la Peña *et al.*, [23] study, their findings further support the idea that these modifications are the result of alternative mechanisms, as decrease in perfusion was not correlated in brain atrophy measurements. Alternative explanations may involve a decrease in metabolic consumption or energy demand, primary ischemia, cerebrovascular reactivity dysfunction, mitochondria dysfunction, or a preceding stage in the neurodegenerative process prior to tissue loss. In the present scenario, this parameter may provide more therapeutic opportunities than identification of a more severe and extensive injury [30, 31].

Additioally a significant negative correlation among CBF/CBV and EDSS was reported [32]. However, Doche *et al.*, [33] also found a significant positive correlation among thalamic CBF and global Multiple Sclerosis Functional Composite Measure, also nine-hole peg test sub-score.

Testu *et al.*, [10], cerebral perfusion reduced during disease duration ($p = 0.009$) and follow-up period ($p < 0.001$); however, EDSS disability marginally rised ($p = 0.023$). Reduced global perfusion was significantly related to an increase in disability in 9-Hole Peg Test, Timed 25-Foot Walk, and EDSS.

Study is limited by a brief follow-up period, a study design that may induce bias and a comparatively small sample size.

Conclusion

Our findings corroborate that physical disability severity is related to brain hypoperfusion, as evidenced by a negative correlation between CBF and disability parameters (EDSS, 25 Foot walk, 9 Peg hole) in a variety of GM and WM regions. Specifically, 25 Foot walk, 9 Peg hole and higher EDSS, were related to prolonged transit time and brain hypoperfusion in several GM amd WM.

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Conflict of Interest: Nil.

References

1. Nociti V, Romozzi M, Mirabella M. Challenges in diagnosis and therapeutic strategies in late-onset multiple sclerosis. Journal of Personalized Medicine. 2024;14:8-36.
2. Mohammed EMA. Understanding multiple sclerosis pathophysiology and current disease-modifying therapies: A review of unaddressed aspects. Frontiers in Bioscience (Landmark Edition). 2024;29:386-397.
3. Monti L, Morbidelli L, Rossi A. Impaired cerebral perfusion in multiple sclerosis: Relevance of endothelial factors. Biomarker Insights. 2018;13:117-136.
4. Rocca MA, Preziosa P, Barkhof F, Brownlee W, Calabrese M, De Stefano N, *et al*. Current and future role of MRI in the diagnosis and prognosis of multiple sclerosis. Lancet Regional Health - Europe. 2024;44:100-115.
5. Elahi R, Taremi S, Najafi A, Karimi H, Asadollahzadeh E, Sajedi SA, *et al*. Advanced MRI methods for diagnosis and monitoring of multiple sclerosis (MS). Journal of Magnetic Resonance Imaging. 2025;87-93.
6. Arteaga-Noriega A, Castro-Álvarez JF, Benjumea-Bedoya D, Gutiérrez-Vargas J, Segura-Cardona A, González-Gómez D, *et al*. Factors associated with time to disability progression in patients with multiple

sclerosis. Revista Peruana de Medicina Experimental y Salud Pública. 2022;39:442-449.
7. Sisco NJ, Borazanci A, Dortch R, Stokes AM. Investigating the relationship between multi-scale perfusion and white matter microstructural integrity in patients with relapsing-remitting MS. Multiple Sclerosis Journal - Experimental, Translational and Clinical. 2021;7:205-223.
8. Lagana MM, Pelizzari L, Baglio F. Relationship between MRI perfusion and clinical severity in multiple sclerosis. Neural Regeneration Research. 2020;15:646-652.
9. Eshaghi A, Marinescu RV, Young AL, Firth NC, Prados F, Cardoso MJ, *et al*. Progression of regional grey matter atrophy in multiple sclerosis. Brain. 2018;141:1665-1677.
10. Testud B, Delacour C, El Ahmadi AA, Brun G, Girard N, Duhamel G, *et al*. Brain grey matter perfusion in primary progressive multiple sclerosis: Mild decrease over years and regional associations with cognition and hand function. European Journal of Neurology. 2022;29:1741-1752.
11. Lapointe E, Li DKB, Traboulsee AL, Rauscher A. What have we learned from perfusion MRI in multiple sclerosis? American Journal of Neuroradiology. 2018;39:994-1000.
12. Hostenbach S, Raeymaekers H, Van Schuerbeek P, Vanbinst AM, Cools W, De Keyser J, *et al*. The role of cerebral hypoperfusion in multiple sclerosis (ROCHIMS) trial: Insights from negative results. Frontiers in Neurology. 2020;11:674-698.
13. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurology. 2018;17:162-173.
14. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology. 1983;33:1444-1452.
15. Lynch S, Baker S, Nashatizadeh M, Thuringer A, Thelen J, Bruce J. Disability measurement in multiple sclerosis patients 55 years and older: What is the Expanded Disability Status Scale really telling clinicians? Multiple Sclerosis and Related Disorders. 2021;49:102-115.
16. Oosterveer DM, Wouda NC, Volker G, van den Berg C, Terluin B, Hoitsma E. Reliability parameters of the Timed 25-Foot Walk (T25FW) in patients with multiple sclerosis: Lower walking speed is associated with greater smallest detectable change. Multiple Sclerosis and Related Disorders. 2024;88:105-117.
17. Kellor M, Frost J, Silberberg N, Iversen I, Cummings R. Hand strength and dexterity. American Journal of Occupational Therapy. 1971;25:77-83.
18. Vollmer T, Huynh L, Kelley C, Galebach P, Signorovitch J, DiBernardo A, *et al*. Relationship between brain volume loss and cognitive outcomes among patients with multiple sclerosis: A systematic literature review. Neurological Sciences. 2016;37:165-179.
19. Granziera C, Wuerfel J, Barkhof F, Calabrese M, De Stefano N, Enzinger C, *et al*. Quantitative magnetic resonance imaging towards clinical application in multiple sclerosis. Brain. 2021;144:1296-1311.
20. Hammad AB, El Din EMS, Abdel Azim GS, Abboud MA. Cerebral perfusion and its association with serum endothelin-1 in multiple sclerosis. Egyptian Journal of Basic and Applied Sciences. 2022;9:296-307.
21. Varga AW, Johnson G, Babb JS, Herbert J, Grossman RI, Inglese M. White matter hemodynamic abnormalities precede sub-cortical gray matter changes in multiple sclerosis. Journal of the Neurological Sciences. 2009;282:28-33.
22. Steen C, D'haeseleer M, Hoogduin JM, Fierens Y, Cambron M, Mostert JP, *et al*. Cerebral white matter blood flow and energy metabolism in multiple sclerosis. Multiple Sclerosis Journal. 2013;19:1282-1289.
23. de la Peña MJ, Peña IC, García PG-P, Gavilán ML, Malpica N, Rubio M, *et al*. Early perfusion changes in multiple sclerosis patients as assessed by MRI using arterial spin labeling. Acta Radiologica Open. 2019;8:205-219.
24. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Annals of Neurology. 2011;69:292-302.
25. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, *et al*. Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology. 2014;83:278-286.
26. Vitorino R, Hojjat SP, Cantrell CG, Feinstein A, Zhang L, Lee L, *et al*. Regional frontal perfusion deficits in relapsing-remitting multiple sclerosis with cognitive decline. American Journal of Neuroradiology. 2016;37:1800-1807.
27. Hänninen K, Viitala M, Paavilainen T, Karhu JO, Rinne J, Koikkalainen J, *et al*. Thalamic atrophy predicts 5-year disability progression in multiple sclerosis. Frontiers in Neurology. 2020;11:606-617.
28. Eshaghi A, Prados F, Brownlee WJ, Altmann DR, Tur C, Cardoso MJ, *et al*. Deep gray matter volume loss drives disability worsening in multiple sclerosis. Annals of Neurology. 2018;83:210-222.
29. Lie IA, Weeda MM, Mattiesing RM, Mol MAE, Pouwels PJW, Barkhof F, *et al*. Relationship between white matter lesions and gray matter atrophy in multiple sclerosis. Neurology. 2022;98:1562-1573.
30. Chandler HL, Stickland RC, Patitucci E, Germuska M, Chiarelli AM, Foster C, *et al*. Reduced brain oxygen metabolism in patients with multiple sclerosis: Evidence from dual-calibrated functional MRI. Journal of Cerebral Blood Flow and Metabolism. 2023;43:115-128.
31. Klistorner S, Barnett MH, Klistorner A. Mechanisms of central brain atrophy in multiple sclerosis. Multiple Sclerosis. 2022;28:2038-2045.
32. Zhang X, Guo X, Zhang N, Cai H, Sun J, Wang Q, *et al*. Cerebral blood flow changes in multiple sclerosis and neuromyelitis optica and their correlations with clinical disability. Frontiers in Neurology. 2018;9:305-317.
33. Doche E, Lecocq A, Maarouf A, Duhamel G, Soulier E, Confort-Gouny S, *et al*. Hypoperfusion of the thalamus is associated with disability in relapsing-remitting multiple sclerosis. Journal of Neuroradiology. 2017;44:158-164.