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RESEARCH

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Baseline vitamin D levels and functional outcome in thrombolyzed stroke patients

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Abstract

Background The primary treatment for acute ischemic stroke (AIS) patients is intravenous recombinant tissue plasminogen activator (IV rt-PA). A link between vitamin D insufficiency and worse post-stroke outcomes and more severe strokes was suggested. The present study aimed to assess the prognostic significance of baseline vitamin D levels in AIS patients treated with rt-PA. The present prospective study was conducted 66 patients with acute ischemic stroke within the therapeutic window and treated with rt-PA. Vitamin D levels were assessed using commercial double antibody sandwich enzyme linked immunosorbent assay. The primary study outcome is patient disability of any degree as assessed by the modified Rankin scale (mRS).

Results The present study included 66 ischemic stroke patients treated with rt-PA. At baseline, there were 37 patients (56.1%) with low vitamin D levels. Comparison between patients with normal and low vitamin D levels regarding baseline data revealed that the former group were significantly younger and had significantly smaller infarct size patients with normal vitamin D had significantly lower NIHSS at day 2 and day 7. Interestingly, patients with low vitamin D levels had significantly higher frequency of rt-PA related hemorrhage, higher frequency of chest infection, longer hospital stay and higher mRS at 90 days. Multivariate logistic regression analysis identified vitamin D level as significant predictor of functional outcome at 90 days.

Conclusions Baseline vitamin D levels is considered a significant predictor of functional outcome in AIS patients treated with rt-PA. It's also related to infarct size and treatment complications.

Keywords Ischemic stroke, Vitamin D, rt-PA, Functional outcome, Treatment complications

Background

Cerebrovascular stroke is the second common cause of death globally with an estimated 5.5 million fatalities per year [1]. Modifiable risk factors of stroke include hypertension, diabetes mellitus, dyslipidemia, cardiovascular disorders, sedentary lifestyle, atrial fibrillation, smoking, and alcohol use. Unmodifiable risk factors are age, gender, race, and genetics [2]. The primary treatment for acute ischemic stroke (AIS) patients is intravenous recombinant tissue plasminogen activator (IV rt-PA) administered within 4.5 h of the onset of symptoms which can dramatically improve functional outcome [3].

Vitamin D is traditionally recognized as a bone metabolism protecting agent. According to reports, vitamin D is essential for maintaining cardiovascular health [4]. The idea that poor vitamin D intake may serve as a predictor of long-term incidence of stroke was also supported by some research. A link between 1,25(OH)D3 insufficiency and worse post-stroke outcomes and more severe strokes was suggested [5].

IGF-1, a neuroprotective protein that fights axon and dendritic degeneration and has antithrombotic properties by activating plasminogen, can be expressed more

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readily when 1,25(OH)2D3 is present. By enhancing the activity of nitric oxide synthase (NOS), 1,25(OH)2D3 may also cause vasodilation, lower blood pressure, and increase post-stroke blood flow to neurons [6].

The present study aimed to assess the prognostic significance of baseline vitamin D levels in AIS patients treated with rt-PA.

Methods

The present prospective study was conducted in the time from May 2021 to September 2021. The study protocol was approved by the ethical committee of Faculty of Medicine. All participants or their legal guardians provided written informed consent before enrollment in the study.

The study included 66 patients with acute ischemic stroke within the therapeutic window and treated with rt-PA. Patients were excluded from the study if they received vitamin D supplementation, anti-inflammatory drugs, estrogen replacement therapy or other drugs that could affect the metabolism of vitamin D. Chronic renal failure and cancer patients were also excluded.

Upon admission, all patients were submitted to careful history taking and thorough clinical examination. The clinical impact of stroke was assessed using the National Institute of Health Stroke Scale (NIHSS). It's an 11-item scale with total scores ranging from 0 to 42 [7]. NIHSS was assessed before initiating rt-PA treatment and at day 2 and 7 after initiation of treatment.

Laboratory assessment included lipid profile, uric acid, complete blood count and random blood sugar.

Vitamin D levels were assessed using commercial double antibody sandwich enzyme linked immunosorbent assay. 25 Hydroxy-vitamin D was added to monoclonal antibody enzyme which was pre-coated with Human 25 Hydroxy Vitamin D monoclonal antibody. 25 Hydroxy Vitamin D antibodies labeled with Biotin were added and combined with Streptavidin-HRP to form immune complex then washed to remove the uncombined enzyme. Chromogen solution A, B then added, and color of liquid became blue, then at the effect of acid, the color finally became yellow.

The chroma of color and the concentration of Human Substance 25 Hydroxy Vitamin D of samples were positively correlated. Patients with vitamin D levels < 30 ng/mL were identified to have low vitamin D, while those with vitamin D levels ≥ 30 ng/mL were identified to have normal vitamin D levels [8]. Performed imaging studies included brain computed tomography, echocardiography and carotid and vertebrobasilar duplex. Suggested causes of stroke were reported according the Trial of Org 10172 in acute stroke treatment (TOAST) classification [9].

The primary study outcome is patient disability of any degree as assessed by the modified Rankin scale (3 months after stroke onset). The modified Rankin Scale (mRS) is a 6-grades scales where 0 means no disability and 6 means death [10].

Data obtained from the present study were processed using SPSS 25. Numerical data were described in the form of mean and standard deviation (SD) or mean and interquartile range (IQR) and compared using t test or Mann–Whitney U test. Categorical data were presented as number and percent and compared using chi-square test. Binary logistic regression analysis was used to detect factors affecting functional outcome. p value less than 0.05 was considered statistically significant.

Results

The present study included 66 ischemic stroke patients treated with rt-PA. They comprised 31 males and 35 females with an age of 60.6 ± 10.2 years. At baseline, there were 37 patients (56.1%) with low vitamin D levels. Comparison between patients with normal and low vitamin D levels regarding baseline data revealed that the former group are significantly younger (56.6 ± 9.3 versus 63.8 ± 9.9, p = 0.003) and had significantly smaller infarct size (3.6 ± 2.1 versus 5.6 ± 2.6 cm^3, p = 0.001) (Table 1).

After treatment, it was found that patients with normal vitamin D had significantly lower NIHSS at day 2 (6.5 ± 4.0 versus 10.2 ± 6.1, p = 0.004) and day 7 (3.0 ± 2.9 versus 8.4 ± 6.3, p < 0.001). Patients with low vitamin D levels had significantly higher frequency of rt-PA related hemorrhage (27.0% versus 0.0%, p = 0.002), higher frequency of chest infection (35.1% versus 17.2%, p = 0.01), longer hospital stay (10.02 ± 5.81 versus 5.13 ± 3.36 days, p < 0.001) and higher mRS at 90 days [median (IQR): 1.0 (0.0–3.0) versus 0.0 (0.0–0.0), p < 0.001] (Table 2).

Correlation analysis identified significant correlation between vitamin D levels and age (r = − 0.28, p = 0.023), infarction size (r = − 0.36, p = 0.003), NIHSS at day 2 (r = − 0.46, p < 0.001), NIHSS at day 7 (r = − 0.56, p < 0.001) and mRS at 90 days (r = − 0.48, p < 0.001) (Table 3). Multivariate logistic regression analysis identified vitamin D levels as significant predictors of functional outcome at 90 days [OR (95% CI): 0.87 (0.77–0.97, p = 0.013)] (Table 4).

Discussion

The present study revealed remarkable associations between vitamin D levels and many prognostic factors in IS patients treated with rt-PA. Patients with normal vitamin D had significantly lower NIHSS at day 2 and day 7 in comparison to their counterparts with low vitamin D.

In line with these conclusions, [6, 11, 12] concluded that overall stroke severity, assessed using NIHSS, was

Table 1 Baseline criteria in the studied patients (n = 66)

	All patients n = 66	Normal Vit. D n = 29	Low Vit. D n = 37	p value
Age (years) mean ± SD	60.6 ± 10.2	56.6 ± 9.3	63.8 ± 9.9	0.003
BMI (Kg/m^2) mean ± SD	27.9 ± 3.4	28.3 ± 2.8	27.6 ± 3.8	0.38
Male/female n	31/35	12/17	19/18	0.42
Risk factors n (%)				
Diabetes	26 (39.4)	9 (31.0)	17 (45.9)	0.22
Hypertension	37 (56.1)	18 (62.1)	19 (51.4)	0.38
AF	14 (21.2)	6 (20.7)	8 (21.6)	0.93
Valvular heart disease	26 (39.4)	10 (34.5)	16 (43.2)	0.47
Smoking	21 (31.8)	10 (34.5)	11 (29.7)	0.68
Previous stroke	7 (10.6)	–	7 (18.9)	0.013
Family history	8 (12.1)	3 (10.3)	5 (13.5)	0.7
NIHSS at onset	12.0 ± 4.7	11.2 ± 4.4	12.6 ± 4.8	0.21
DNT (minutes) mean ± SD	32.4 ± 8.2	34.0 ± 9.6	31.1 ± 6.8	0.17
TOAST classification n (%)				
Cardio-embolic	14 (21.2)	8 (27.6)	6 (16.2)	0.64
Large artery disease	20 (30.3)	9 (31.0)	11 (29.7)	
Small vessel disease	12 (18.2)	5 (17.2)	7 (18.9)	
Undetermined	20 (30.3)	7 (24.1)	13 (35.1)	
Laboratory findings mean ± SD				
Cholesterol mg/dL	186.53 ± 30.44	179.72 ± 37.62	191.86 ± 22.5	0.11
TGs mg/dL	132.50 ± 38.77	129.41 ± 32.94	134.91 ± 43.08	0.57
HDL-c mg/dL	38.72 ± 7.17	40.03 ± 6.416	37.70 ± 7.64	0.19
Uric acid mg/dL	5.15 ± 0.94	5.11 ± 0.99	5.18 ± 0.914	0.77
RBS mg/dL	180.7 ± 52.7	192.1 ± 53.2	171.8 ± 51.3	0.12
Carotid artery atherosclerosis n (%)				
Right	41 (62.1)	14 (48.3)	27 (73.0)	0.04
Left	40 (60.6)	15 (51.7)	25 (67.6)	0.19
Infarction size (cm^3) mean ± SD	4.8 ± 2.6	3.6 ± 2.1	5.6 ± 2.6	0.001

AF atrial fibrillation, *BMI* body mass index, *NIHSS* National Institute of Health Stroke Scale, *DTN* door to needle time, *TGs* triglycerides, *HDL-c* high density lipoprotein cholesterol, *RBS* random blood sugar. p value ≥ 0.05(non-significant)

Table 2 Outcome parameters in the studied patients

	All patients n = 66	Normal Vit. D n = 29	Low Vit. D n = 37	p value
NIHSS mean ± SD				
Day 2	8.6 ± 5.6	6.5 ± 4.0	10.2 ± 6.1	0.004
Day 7	6.0 ± 5.7	3.0 ± 2.9	8.4 ± 6.3	< 0.001
Complications of rt-PA n (%)				
Cerebral edema	8 (12.1)	2 (6.9)	6 (16.2)	0.45
Hemorrhage	10 (15.2)	–	10 (27.0)	0.002
Other complications n (%)				
Bed sores	21 (35.0)	6 (20.7)	15 (40.5)	0.081
Chest infection	18 (27.3)	5 (17.2)	13 (35.1)	0.0105
Hospital stay (days) mean ± SD	7.9 ± 5.4	5.13 ± 3.36	10.02 ± 5.81	< 0.001
mRS at day 90 median (IQR)	0.0 (0.0–0.2)	0.0 (0.0–0.0)	1.0 (0.0–3.0)	< 0.001
Mortality at 90 days	4 (6.1)	–	4 (10.8)	0.068

NIHSS National Institute of Health Stroke Scale, *mRS* modified Rankin scale p value ≥ 0.05(non-significant)

Table 3 Correlation between vitamin D levels and clinical and laboratory data

	Vitamin D	
	r	P
Age	− 0.28	0.023
BMI	0.05	0.68
Cholesterol	− 0.07	0.56
Uric acid	0.02	0.87
TGs	− 0.09	0.48
HDL	0.18	0.16
Infarction size	− 0.36	0.003
NIHSS at onset	− 0.22	0.074
NIHSS at day 2	− 0.46	< 0.001
NIHSS at day 7	− 0.56	< 0.001
mRS 90 days	− 0.48	< 0.001

BMI body mass index, *NIHSS* National Institute of Health Stroke Scale, *TGs* triglycerides, *HDL* high density lipoprotein, *mRS* modified Rankin scale. p value ≥ 0.05(non-significant)

worse in 25(OH)D3-deficient patients with stroke. Also [13, 14], revealed a strong association between level of 25(OH)D2 and short outcome in acute ischemic stroke patients assessed by NIHSS.

Interestingly, patients with low vitamin D levels had significantly higher frequency of rt-PA related hemorrhage, higher frequency of chest infection and longer hospital stay.

In agreement with our findings, [15] noted that patients with low vitamin D levels experienced more complications than those with normal vitamin D levels [6] found a significant association between low serum vitamin D level and larger infarction volume thus with incidence of complications and poor functional outcome. These results may be explained by many reasons, 1-there is a relationship between stroke functional outcome and inflammatory response, 2-vitamin D acts as anti-inflammatory agent so patients with low vitamin D level have increased inflammatory response [15].

In the present study, multivariate logistic regression analysis identified vitamin D levels as significant predictors of functional outcome at 90 days. This finding is supported by multiple previous studies. While [16] evaluated the short-term prognostic value of serum 25(OH)D (25-hydroxyvitamin D) in Chinese patients with AIS and suggested that 25(OH)D levels as an independent prognostic marker for death and functional outcome within 90 days. Also [11, 17, 18], confirmed the negative correlation between serum vitamin D and modified Rankin Scale. Similar conclusions were also reported by other studies [19, 20].

While [21] found that among acute ischemic stroke patients, 25(OH)D deficiency subjects had a significantly higher NIHSS at admission and 3 months mRS compared with those with normal level.The previous findings may be related to the role of vitamin D in regulation of intracellular calcium in vascular smooth muscle cells.

Also, stimulation of proinflammatory cytokines and inhibition of monocytes and macrophage-derived foam cells and angiogenesis, affecting the renin–angiotensin–aldosterone system, and lowering serum level of 25-OH-D [22].

The protective effect of vitamin D in AIS patients is attributed to several mechanisms. These include antithrombotic capabilities through activation of plasminogen. and anti-inflammation of myeloid and endothelial cells as result of 1,25(OH)2D3 induction of stromal cell derived factor 1α(SDF 1α), vascular endothelial growth factor (VEGF) and endothelial Nitric Oxide Synthase (NOS) [6].

Previous studies found vitamin D deficiency, in hemorrhagic stroke patients. Moreover, vitamin D supplementation improved the outcome. More researches found also that it can induce hemorrhagic stroke through mechanisms, such as endothelial shear stress and inflammation (has a prominent role in stroke pathogenesis). The neuroprotection mechanisms induced by vitamin D including inhibiting

Table 4 Predictors of poor functional impairment (mRS ≥ 1) in the studied patients

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.1	1.03–1.18	0.003	1.06	0.99–1.15	0.12
Previous stroke	5.69	1.0–32.15	0.049	0.72	0.08–6.5	0.77
DNT	1.0	0.94–1.07	0.93	1.03	0.95–1.13	0.48
NIHSS at onset	1.13	1.0–1.26	0.044	1.06	0.91–1.23	0.47
Infarction size	1.45	1.18–1.85	0.001	1.23	0.9–1.68	0.19
Vitamin D	0.84	0.76–0.91	< 0.001	0.87	0.77–0.97	0.013

NIHSS National Institute of Health Stroke Scale, *DTN* Door to Needle time, p value ≥ 0.05(non-significant)

prostaglandin (PG) and cyclooxygenase-2 (COX-2) pathways, matrix metalloproteinase-9 (MMP-9) reduction, and anti-inflammatory cytokine upregulation. Regarding rt-PA related hemorrhage, low vit D levels may be related to the mechanism of action of other inflammatory mediators, coagulation profile or other vascular risk factors [23].

Conclusion: the present study identified vitamin D levels as a significant predictor of functional outcome in AIS patients treated with rt-PA. It's also related to infarct size and treatment complications.

The limitation of this work is the relatively small number of patients due to financial issues and limitation of resources. Further studies with a larger number of patients and for a longer duration to assess the effect of correction of vitamin D deficiency on thrombolyzed stroke patients should be conducted.

Abbreviations

AIS	Acute ischemic stroke
COX-2	Cyclooxygenase-2
NOS	Endothelial Nitric Oxide Synthase
25(OH)D	25- Hydroxyvitamin D
IQR	Interquartile rang
IGF-1	Insulin like growth factor 1
IV rt-PA	Intravenous recombinant tissue plasminogen activator
MMP-9	Matrix metalloproteinase-9
MRS	Modified Rankin scale
NIHSS	National Institute of Health Stroke Scale
NOS	Nitric oxide synthase
PG	Prostaglandin
SD	Standard deviation
SDF 1α	Stromal cell derived factor 1α
TOAST	Trial of Org 10172 in acute stroke treatment
VEGF	Vascular endothelial growth factor

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Author contributions
Conceived and designed the experiments: MMM, AYR, MMA, RHS, NAA, enrolled the patients: MMM, AYR, and NAA Performed the experiments: MMM, MMA and RHS data management and analysis: MMA, RHS and Contributed reagents/materials/analysis tools: MMM, AYR, MMA, RHS and NAA prepared the manuscript: MMM, AYR, MMA, RHS, NAA, read and approve the manuscripts: MMM, AYR, MMA, RHS, NAA. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the ethical committee of Beni-Suef Faculty of Medicine (Approval number: FMBSUREC/06042021/Yassin; date: April, 6, 2021). Informed written consent was obtained from all the patients enrolled in this study.

Consent for publication
Written informed consent was obtained from all patients or their legal guardians before enrollment in the study.

Competing interests
There are no conflicts of interest.

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