Impact of Vitamin D on Acute Ischemic Stroke Prognosis (IVASTO)

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ABSTRACT

Background and Purpose: The correlation between acute ischemic stroke (AIS) and Vitamin D (VitD) was reported in many observational studies. This study aimed to investigate this association, the severity, and the short term outcome of AIS patients with different VitD levels. Methods: The patients were assessed at the onset by clinical and severity scores (National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS)). In follow-ups after 3 months they were assessed by mRS and were classified according to VitD levels into control group 1 (≥ 30 ng/ml) and abnormal group 2 (VitD < 30 ng/ml). Comparison and correlation of the VitD in AIS, NIHSS, and mRS were calculated between both groups. Results: The present single-center prospective cross-sectional study during one-year duration was done on 59 patients with AIS. Vascular risk factors did not show any differences between both groups (P > 0.05). It showed statistically significant differences between both groups regarding VitD level, NIHSS, mRS after 3 months with P-value < 0.001, 0.0035, and 0.0167 respectively. There is a negative correlation between VitD level and NIHSS scores, VitD level and mRS scores at the onset, and after 3 months P < 0.0001, < 0.0001, < 0.00 respectively. Conclusion: AIS patients with VitD deficiency showed more stroke severity and poor outcomes. The VitD serum level should be examined as supplementation may have an important role in the guidelines of cerebral stroke treatment.

Keywords: acute ischemic stroke, Vitamin D, NIHSS, modified Rankin Scale

1. INTRODUCTION

Acute ischemic stroke (AIS) has several non-modifiable risk factors, such as genetics, age, and sex, along with modifiable risk factors like hypertension, diabetes mellitus (DM), dyslipidemia, and a sedentary lifestyle (Mozaffarian et al., 2015). The deficiency of Vitamin D (VitD) is now recognized to be highly prevalent in the U.S and worldwide, impacting between 30% and 50% of the general population (Abuannai and O’Keefe 2011). The most characterized consequence of VitD deficiency has involved the musculoskeletal system. However, it is now recognized that VitD receptors are present on a large variety of cell types, including osteoblasts, immunologic cells, nerve cells, pancreatic beta cells, vascular endothelial cells, and possibly myocytes and cardiac muscle cells (Lee et al., 2008). The association between VitD and AIS has been evaluated in different populations; however, discrepancy findings were reported. Although some trials showed a correlation between low levels of VitD and AIS (Chaudhuri et al., 2014; Tu et al., 2014; Park et al., 2015), as well as its relationship with the outcome and prognosis (Tu et al., 2014; Wang et al., 2014; Turetsky et al., 2015; Brian et al., 2019), others have not found such associations (Bolland et al., 2010; Drechsler et al., 2010; Kühn et al., 2013; Majumdar et al., 2015). It remains to be proven by clinical trials if there is a causal association between VitD deficiency and stroke (Stefania et al., 2014). This study was designed to assess the association between VitD levels and AIS risk factors. We also aimed to investigate the severity and short term outcome of AIS patients with different VitD levels.

2. METHODS

This is a prospective, cross-sectional study, conducted on 59 patients with AIS. It was conducted in the neurology department (stroke unit), Mansoura University hospital, during a 1-year duration (from June 2018 to May 2019) in cooperation with Saudi German Hospital, KSA. Included in this study are patients with AIS within 24-48 hours clinically diagnosed and confirmed with CT or MRI brain scans and of ages ≥ 20. Excluded from our study are patients with intracerebral hemorrhage, endocrine dysfunctions that can disturb bone structural strength and integrity such as parathyroid, thyroid, and adrenal diseases, patients with hepatic or renal impairment, valvular heart disease, and vasculitis.

Ethical approval

All patients or first degree relatives provided written informed consent. The study was approved by the Institutional Review Board of Faculty of Medicine, Mansoura University, Egypt. Also, it was approved by ClinicalTrials.gov (Identifier: NCT03819452).

All AIS patients underwent the following history taking and neurological examination assessment with gathering the related data like age, sex, stroke risk factors (history of hypertension, history of transient ischemic attacks, diabetes mellitus, history of myocardial infarction or any cardiac arrhythmia like atrial fibrillation (AF) and dyslipidemia). Also, brain imaging (either a CT scan and /or MRI) was performed at admission. Electrocardiography (ECG), echocardiography (ECHO), carotid and the vertebrobasilar duplex were done for all participants. We follow the Endocrine Society Clinical Practice guidelines that defined VitD status as the following normal 25-hydroxyvitamin D (25OHD) level ≥ 30 ng/ml, VitD insufficiency 20–30 ng/ml, and VitD deficiency < 30 ng/ml (Holick et al., 2011). The National Institutes of Health stroke scale (NIHSS) used to assess the stroke severity: It is a 15-item impairment scale,
which provides a quantitative measure of key components of a standard neurological examination (Appelros and Terént, 2004; Brott et al., 1989). The scale assesses the level of consciousness, extraocular movements, visual fields, facial muscle function, extremity strength, sensory function, coordination (ataxia), language (aphasia), speech (dysarthria), and hemi-inattention (neglect) (Lyden et al., 2001). The functional neurological outcome was measured by the Modified Rankin Scale (mRS) at the time of admission and after 3 months follow-up. The scale is defined categorically with seven different grades: scores of 0-4 mean no symptoms, scores of 5 mean severe disabilities, and scores 6 mean deaths (van Swieten et al., 1988).

![Diagram of 59 patients with AIS criteria]

### Statistical analysis

All statistical analyses were performed using the SAS University Edition statistical package. The sample continuous variables were checked for normality testing using Shapiro-Wilk and Kolmogorov-Smirnov. Upon the inability to prove normality the exact statistical analyses are applied. All p-values are calculated using the Wilcoxon Exact test where the alpha = 0.05, beta = 0.8 and the significant p-values are equal or less than 0.05. In categorical values, Fisher’s exact test was the analytical test of choice due to 5 or fewer observations being found in different subgroups. The test was set alpha = 0.05, beta = 0.8 and the significant p-value is equal or less than 0.05.

### 3. RESULTS

The age of stroke patients with normal VitD (Group 1 patients - control group) was 43-94 years with a mean age of 67.5. The age of stroke patients with abnormal VitD (group 2 patients) was 53-90 with a mean age of 66.9 years (P-value =0.96). Eleven patients in group 1 were males (42.2%) and nineteen patients in group 2 were males (78.57 %) (P-value =0.030). Thirty patients in group 1 were hypertensive (66.7%). Twenty-nine patients were diabetic (64.4%) and twenty-two patients had ischemic heart disease (48.88%), eight patients had atrial fibrillation (AF) (17.8%), thirty six patients had dyslipidemia (80%) and nine patients had a previous stroke (20%). In group 2, twelve patients were hypertensive (85.7%), ten patients were diabetic (71.4%), six patients had ischemic heart disease (42.9%), three patients had AF (21.4%), eight patients had dyslipidemia (57.1%). There were no statistically significant differences between the 2 groups regarding hypertension, diabetes, ischemic heart disease, AF, dyslipidemia or previous stroke (P > 0.05%) (Table 1, Figure 1 & 2).
Table 1 Summary and comparison of demographic data and vascular risk factors in both groups

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Group 1 (N=14) VitD level ≥ 30 ng/mL</th>
<th>Group 2 (N=45) VitD level &lt; 30 ng/mL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years): mean ± SD</td>
<td>43-94 ± 67.5</td>
<td>53-90 ± 66.9</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>19</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30(66.66)</td>
<td>12(85.71)</td>
<td>0.3103</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>29(64.44)</td>
<td>10(71.42)</td>
<td>0.7529</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>36(80)</td>
<td>8(57.14)</td>
<td>0.1563</td>
</tr>
<tr>
<td>IHD</td>
<td>22(48.88)</td>
<td>6(42.85)</td>
<td>0.7659</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>8(17.77)</td>
<td>3(21.42)</td>
<td>0.7119</td>
</tr>
<tr>
<td>Previous Stroke</td>
<td>9(20)</td>
<td>0(0)</td>
<td>0.0979</td>
</tr>
</tbody>
</table>

VitD: Vitamin D, IHD: Ischemic Heart Disease, Std Dev: standard deviation

Figure 2 Vascular risk factors in both groups. (IHD: Ischemic Heart Disease)

Table 2 Summary and comparison of laboratory values, severity and functional scores in both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (N=14) VitD level ≥ 30 ng/mL</th>
<th>Group 2 (N=45) VitD level &lt; 30 ng/mL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±Std Dev</td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>VitD level</td>
<td>37.95±7.86</td>
<td>31</td>
<td>60</td>
</tr>
<tr>
<td>NIHSS</td>
<td>3.93±2.13</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>mRS (Initial)</td>
<td>2.57±1.16</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>mRS (3 months)</td>
<td>1.50±0.94</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Std Dev: Standard Deviation, Min: minimum, Max: maximum, VitD: Vitamin D, NIHSS: National Institute of Health stroke Scale, mRS: modified Rankin Scale, *: Significant (P < 0.05).

In group 1 (control group), serum VitD levels were 31-60 ng/mL with a mean of 37.95 ± 7.86. In group 2 (control group), serum VitD was 3.6-28.3 ng/mL with a mean of 16.77 ± 7.64 (P-value < 0.0001) with significant statistical differences. At the onset, the NIHSS scores were 2-9 with a mean of 3.93 ± 2.13 in group 1. In group 2 (control group) the NIHSS scores were 2-41 with a mean of 11.51 ± 10.45 (P-value = 0.0035) with significant statistical differences. Initial mRS scores were 1-5 with a mean of 2.57± 1.16 in
group 1. While, in group 2 (control group) mRS scores were 1-5 with a mean of 3.16 ± 1.21 (P-value = 0.1287). After 3 months, mRS scores were 0-4 with a mean of 1.5 ± 0.94 in group 1. In group 2 (control group), mRS scores were 0-6 with a mean of 2.56 ± 1.53 (P-value =0.0167) with a significant statistical difference (Table 2, Figure 3 & 4).

Figure 3 Summary and comparison of Vitamin D level in both groups

Figure 4 Summary and comparison of severity and functional scores in both groups. VitD: Vitamin D, NIHSS: National Institute of Health stroke Scale, mRS: modified Rankin Scale

At the onset, there was a significant negative correlation between serum VitD level and NIHSS scores (P < 0.0001). Regarding the relationship between VitD levels and mRS, there was a significant negative correlation at the onset and after 3 months (P < 0.0001, P <0.00 respectively) (Table 3).

Table 3 Association between VitD, Severity and Functional Scales

<table>
<thead>
<tr>
<th></th>
<th>VitD level (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS</td>
<td></td>
</tr>
<tr>
<td>Pearson correlation</td>
<td>-0.376</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>mRS (Initial)</td>
<td></td>
</tr>
<tr>
<td>Pearson correlation</td>
<td>-0.232</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>mRS (3m)</td>
<td></td>
</tr>
<tr>
<td>Pearson correlation</td>
<td>-0.24</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.00*</td>
</tr>
</tbody>
</table>

VitD: Vitamin D, NIHSS: National Institute of Health stroke Scale, mRS: modified Rankin Scale, *: Significant (P < 0.05).
4. DISCUSSION

The present single-center prospective cross-sectional study during a one-year duration was done on 59 patients (males/females=30/29) with AIS, during their admission to the stroke unit of the neurology department, Mansoura University Hospital. This study stated that there were no statistically significant differences between the control group and AIS patients with abnormal VitD levels in group 2 as regards vascular risk factors (P > 0.05). This study showed highly statistically significant differences between the control group 1 and group 2 as regards VitD level, NIHSS, mRS after 3 months with P-value < 0.001, 0.0035, and 0.0167 respectively. Also, it declared a significant negative correlation between serum VitD levels and NIHSS scores at the presentation (p < 0.0001), serum VitD level and mRS scores on the presentation (p < 0.0001), and after 3 months (p < 0.0). In the current study, the most prevalent modifiable vascular risk factors of stroke in group 2 were hypertension followed by diabetes mellitus, dyslipidemia, ischemic heart disease, and AF. Many previous studies agreed with these results (Kissela et al., 2012; Smajlović 2015). Also, several studies found a strong correlation between low vitamin D and the higher risk of occurrence of cerebral stroke (Zhou et al., 2018; Brondum-Jacobsen et al., 2013). The incidence of cerebral stroke was increased by more than double in the presence of ischemic heart disease, more than triple in the presence of hypertension, more than quadruple in the presence of stroke, and nearly quintupled when AF was present (Tu et al., 2014). Also, AIS patients showed statistically significant lower levels of VitD in comparison to the control group. The previous data agreed with the results established by other studies (Wolf et al., 1991; Alfieri et al., 2017; Chatterjee et al., 2014; Fahmy et al., 2019). Different mechanisms can interpret the role of VitD in the pathogenesis of AIS, especially after the clear evidence for the correlation between VitD deficiency and stroke outcome and severity. VitD plays a crucial role in arterial hypertension by renin-angiotensin-aldosterone system (RAS) suppression. RAS is a key regulator of electrolyte, blood pressure, and normal volume homeostatic mechanisms. The overstimulation of the RAS system causes hypertension, which is one of the most important modifiable vascular risk factors for AIS (Wajda et al., 2019; Kannel and Wolf 2008). Regarding stroke severity and outcome, the multivariable logistic regression analysis showed that high NIHSS score, vitamin D deficiency, and high mRS scores at the onset and after 3 months were the most significant. Our findings were congruent with other studies that stated that the VitD serum level is a valuable biomarker for severity, functional outcome, and death in cerebral stroke (Tu et al., 2014; Santoro et al., 2015). VitD showed a crucial role in neuroprotection by the upregulation of antioxidant mechanisms, activation of detoxification pathways, inhibition of nitric oxide synthase, and regulation of calcium metabolism (Chulho et al., 2020; Michos and Gottesman 2013; Witham et al., 2012). There were some limitations of the current study, different seasons for enrolling the AIS patients as VitD serum levels showed seasonal variation. Also, the present study did not collect data concerning the exposure to sunlight and dietary intake.

5. CONCLUSION

AIS patients with VitD deficiency showed more stroke severity and poorer outcomes. VitD serum level should be examined as supplementation may have an important role in the guidelines of cerebral stroke treatment.

Contributions
All

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The authors declare no conflict of interest.
REFERENCE

