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Research Paper: Frequency of Undiagnosed Diabetes Mellitus Among Patients With Stroke

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Running Title Undiagnosed Diabetes and Stroke

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ABSTRACT

Background: Stroke is one of the common causes of disability and death in the world. Furthermore, diabetes mellitus is among the main risk factors for cerebrovascular events. However, a high percentage of individuals with diabetes mellitus are unaware of their disease.

Objectives: To determine the frequency of Undiagnosed Diabetes mellitus (UD) in patients with stroke.

Materials & Methods: In a descriptive cross-sectional study, all patients with stroke hospitalized in neurology ward of an academic hospital in the north of Iran were included in the study in 2016. A questionnaire was used to collect data including all demographic, laboratory and clinical factors such as high blood pressure, hypercholesterolemia and stroke type. Finally, the data were analyzed using Chi square, Fisher's exact test and multinomial binary logistic regression in SPSS V. 21.

Results: Most samples were male (53.8%) with a mean age of 69.2±10.1 years. The percentage of the UD was 21.7% based on level of HbA1c. The highest percentage of UD was observed in Subarachnoid Hemorrhage(SAH) (66.7%). The frequency of UD in patients with family history of diabetes mellitus (16.7%) was lower than that in patients without that history (27.7%). There was a significant relationship between UD and cholesterol and triglyceride levels and, in general, dyslipidemia (P<0.05).

Conclusion: In this study, a large percentage of patients with stroke suffered UD. Therefore, it is recommended that extensive screening be conducted for diabetes mellitus in the community in order to prevent stroke.

Keywords: Diabetes mellitus, Stroke, Cerebrovascular disorders

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Highlights

- A high percentage of stroke patients suffered undiagnosed diabetes mellitus
- Extensive screening for diabetes mellitus in general population in order to preventing stroke is recommended.

Introduction

Stroke is the third leading cause of death in the world [1, 2]. Annually, 15 million individuals in the world suffer stroke, and one-third of these patients die, and another third suffer permanent disability [3, 4]. In the United States, a stroke occurs almost every 40 seconds that equals 2160 stroke per day, killing about one out of 16 Americans [5]. In Iran, stroke is known as the second cause of death after cardiovascular diseases, and accounts for hospitalization of about 70% of patients in the neurology wards [6]. There are some hidden risk factors responsible for stroke and its disability or improvement including metabolic disorder, hormonal and also environmental and social factors [7-9].

In general, studies have shown that the relative risk of stroke in patients with Diabetes Mellitus (DM) is 1.5 to 3 times higher than that in healthy people [10, 11]. Diabetes is among the most common metabolic disorders with direct effects on the Central Nervous System(CNS) [12]. It is also indirectly involved in some CNC diseases such as stroke as the most important CNS disorder [13, 14]. It is established that patients with diabetes are prone to many psychological disorders [15] which can provoke stroke. Statistics show that stroke causes a higher prevalence, a worse prognosis, more complications and mortality in patients with diabetes [14, 16]. However, it has no effect on hospital stay of patients with stroke [17].

The direct effect of diabetes on hemorrhagic stroke remains unclear [14, 18], however, diabetes has an impact on the development of atherothrombotic cerebrovascular lesions as one of the important risk factors of stroke [19]. It may have an impact on oxidative stress which plays a role in severity of stroke [20]. Currently, DM is spreading around the world as an unprecedented epidemic. In 2016, there were about 29.1 million diabetics in the United States with nearly 1.8 million undiagnosed patients [21]. The Undiagnosed Diabetes (UD) is increasing in many parts of the world, and is detrimental and costly [22].

Patients with stroke represent a large number of UD patients [23]. Determining Hemoglobin A1c (HbA1c) during acute Ischemic Stroke (IS) is of paramount importance to detect undiagnosed glucose abnormalities in patients, and it leads to the identification of many unknown cases of diabetes mellitus [24, 25]. Also, American Diabetes Association stresses the importance of using HbA1c test to identify UD patients admitted to hospitals [26]. Patients with diabetes suffer stroke almost two times as normal people, and they impose higher mortality, disability and economic complications on society. Therefore, the accurate estimate of the prevalence of diabetes mellitus will be essential for health and medical authorities to design effective plans. Diabetes screening programs are one of the most important preventive measures. So, we decided to explore the frequency of UD in patients with stroke and its associated factors.

Materials and Methods

In this descriptive cross-sectional study, medical records of 359 hemorrhagic and ischemic patients with stroke hospitalized in fall 2016 in neurology ward of Poursina Hospital affiliated to Guilan University of Medical Sciences were reviewed by complete enumeration method. UD was detected as above 6.5% based on glycosylated Hemoglobin (HbA1C) when subjects were admitted [27]. Other biochemical tests were requested for patients, who were asked of a complete medical history including demographic data such as age, sex, cigarette smoking habit, having clinical factors like hypertension, hypercholesterolemia, as well as positive family history of DM and hypertension. Then, the questionnaires were filled with data and were analyzed by Chi square, Fisher's exact test and multinomial binary logistic regression, with a confidence interval of 95% and $P<0.05$ in SPSS V. 21.

Results

Most of the 359 patients were men (53.8%) with a mean age of 69.19±10.1 years. The most frequent age group was 60-75 years (58.8%). Statistics show that UD percentage was 21.7% and 34% based on the HbA1C and FBS, respectively. In this study, HbA1C results were used to define UD.

Considering the relationship between the percentage of UD and individual-social variables in the study subjects,

Table 1. Studying undiagnosed Diabetes Mellitus(UD) in terms of individual–social variables

Variables		Undiagnosed Diabetes Mellitus Status Based on HbA1C			
		No Diabetes	Diagnosed Diabetes	Undiagnosed Diabetes	
			N(%)		P
Past cigarette smoking		2(26.8)	35(42.7)	25(30.5)	0.008
Current sigarette smoking		11(19)	24(41.4)	23(39.7)	0.0001
Drug abuse		2(5.9)	16(47.1)	16(47.1)	0.0001
Stroke Type	Ischemic	104(37.5)	111(40.1)	62(22.4)	
	ICH	42(53.2)	23(29.1)	14(17.7)	
	SAH	1(33.3)	0(0)	2(66.7)	0.037
	Total	147(40.9)	134(37.3)	78(21.7)	
Family history of DM		48(32)	77(51.3)	25(16.7)	0.0001
Hyper-cholestrolemia		19(25)	25(32.9)	32(42.1)	0.0001
Hyper triglyceride		18(28.1)	18(28.1)	28(43.8)	0.0001
Dyslipidaemia		34(29.8)	37(32.5)	43(37.7)	0.0001
Sex	Male	83(43)	65(33.7)	45(23.3)	
	Female	64(38.6)	69(41.6)	33(19.9)	
	Total	147(40.9)	134(37.3)	78(21.7)	0.301
Age group	<60 years	25(45.5)	16(29.1)	14(25.5)	
	60-75 years	81(38.4)	85(40.3)	45(21.3)	
	>75 years	41(44.1)	33(35.5)	19(20.4)	0.583
	Total	147(40.9)	134(37.3)	78(21.7)	
Education levels	Illiterate	55(42.6)	44(34.1)	30(23.3)	
	Lower than Diploma	61(36.3)	67(39.9)	40(23.8)	
	Diploma	20(42.6)	20(42.6)	7(14.9)	0.121
	Academic	11(73.3)	3(20)	1(6.7)	
	Total	147(40.9)	134(37.3)	78(21.7)	
Diagnosed history of hypertension		88(39.5)	89(39.9)	46(20.6)	0.428

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the results suggested that the frequency distribution of the UD in terms of former and current cigarette smoking and drug abuse was significant (P<0.001). This means that the percentage of UD in the patients with stroke abusing drug and smoking cigarette currently or formerly was more than those without such a history. Also, there was a significant relationship between the percentage of UD and stroke type. The highest and lowest percentage of UD were observed in SAH (66.7%) and ICH (17.7%), respectively.

Statistical analysis showed that there was a significant relationship between family history of diabetes mellitus and UD in patients with stroke, such that the percentage of UD in people with a family history of DM (16.7%)

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was lower than that in those without the history (27.7%). In addition, there was a significant relationship between UD and cholesterol, TG and, in general, dyslipidemia. On the other hand, the results showed no statistically significant relationship between variables of age, education level and history of hypertension and UD in patients with stroke (P>0.05) (Table 1).

In this study, nominal regression model was used to investigate related factors in multiple analysis. The two diabetic groups (diagnosed and undiagnosed diabetes) were compared to a normal group in terms of the studied variables. The variables of sex (P=0.024), drug abuse (P<0.001), hypertension (P=0.01), education level of lower than high school diploma (P=0.037), Cerebrovascular Accident (CVA) type (P=0.006) and family history of diabetes (P<0.001) were associated with Diagnosed Diabetes (DD), while the variables age (P=0.006), high TG(P<0.001), drug abuse (P=0.001) and education level of illiterate and lower than high school diploma (P=0.042 and 0.031, respectively) were identified as predicting factors for UD (Table 2).

Finally, the most important related factors predicting UD compared to DD were identified using logistic regression. The model showed that education level (P=0.065), a family history of diabetes (P=0.007), age (P=0.024), cholesterol (P=0.052), and TG (P=0.01) were identified as the most important factors. This means that higher education levels decrease the incidence of UD. Family history of diabetes reduces the risk of UD, such that no family history of diabetes increases UD incidence 2.4-fold. UD decreases with increasing age. People with abnormal total cholesterol levels were 2.2 times more

Table 2. Studying related factors in multiple analysis using nominal regression model

Parameter Estimates						
Undiagnosed Diabetes (UD) Status Based on HbA1C	**Regression Coefficient**	**Standard Error**	**Significance Level**	**Relative Chance**	**Confidence Level of 95%**	
					Lower Limit	**Upper Limit**
Diagnosed Diabetes						
Constant value	-2.525	1.158	0.029			
Age	-0.001	0.015	0.948	0.999	0.970	1.029
Cholesterol-triglyceride	-0.002	0.002	0.298	0.998	0.994	1.002
Male	-0.622	0.275	0.024	0.537	0.313	0.921
Female	Reference Group			1	0	
Drug abuse	2.795	0.792	0.0001	16.365	3.463	77.339
No drug abuse	0b	-	-	-	-	-
Hypertension history	0.744	0.290	0.010	2.104	1.192	3.712
No hypertension	0b	Reference Group		10	-	-
Illiterate	1.015	0.770	0.188	2.759	0.609	12.492
Lower than diploma	1.543	0.740	0.037	4.678	1.096	19.959
Diploma	1.256	0.774	0.104	3.512	0.771	15.994
Academic	0b	Reference Group		10		
Diabetes family history	1.111	0.268	0.0001	3.038	1.796	5.141
No Diabetes family history	0b	Reference Group		1		
Ischemic stroke	0.957	0.351	0.006	2.604	1.310	5.177
Hemorrhagic stroke	0b	Reference Group		1		

Parameter Estimates						
Undiagnosed Diabetes (UD) Status Based on HbA1C	Regression Coefficient	Standard Error	Significance Level	Relative Chance	Confidence Level of 95%	
					Lower Limit	Upper Limit
Undiagnosed Diabetes(UD)						
Constant value	-1.400	1.463	0.339			
Age	0.048	0.017	0.006	0.953	0.922	0.986
Cholesterol-triglyceride	0.008	0.002	0	1.008	1.004	1.012
Male	-0.259	0.323	0.423	0.772	0.410	1.454
Female	0b	Reference Group	1		0b	Reference Group
Drug abuse	2.736	0.805	0.001	15.425	3.186	74.669
No drug abuse	0b	Reference Group	1		0b	Reference Group
Hypertension history	0.427	0.344	0.215	1.532	0.781	3.006
No Hypertension history	0b	Reference Group		1		
Illiterate	2.322	1.141	0.042	10.196	1.089	95.507
Lower than diploma	2.385	1.108	0.031	10.860	1.238	95.262
Diploma	1.464	1.160	0.207	4.322	0.445	41.942
Academic	0b	Reference Group				
Diabetes family history	0.233	0.332	0.482	1.263	0.659	2.421
No Diabetes family history	0b	Reference Group	1		0b	Reference Group
Ischemic stroke	0.333	0.399	0.404	1.395	0.638	3.052
Hemorrhagic stroke	0b	Reference Group		1		

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Table 3. Logistic regression model for related predicting factors of UD compared to DD

Variables in the Equation						
Relative Variable	Regression CoeffSicient	Standard Error	Significance Level	Relative Chance	Confidence Interval of 95%	
					Upper Limit	Lower Limit
Education level	-0.442	0.239	0.065	0.643	0.402	1.028
Diabetes Family history	0.860	0.320	0.007	2.362	1.262	4.423
Age	-0.041	0.018	0.024	0.959	0.925	0.995
Total cholesterol			0.052			
Borderline cholesterol/normal	-0.196	0.446	0.660	0.822	0.343	1.969
Abnormal cholesterol/normal	0.807	0.372	0.030	2.240	1.080	4.647
Triglyceride			0.010			
Borderline triglyceride/normal	0.143	0.405	0.725	1.153	0.521	2.553
Abnormal triglyceride/normal	1.233	0.422	0.004	3.430	1.499	7.852
Constant value	1.254	1.536	0.414	3.503		

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susceptible to UD than normal group. Also, those who had abnormal TG levels were 3.4 times more susceptible to it compared to healthy people (Table 3).

Discussion

About one-third of the patients with diabetes have UD [28]. DM is a major risk factor for cerebrovascular accidents [29]. Studying the frequency of UD in patients with stroke and related factors has led to the identification of risk factors for stroke, which can primarily be a big step to prevent stroke. In the current study, most patients were male (53.8%), and our results were consistent with other studies [24, 30], while Kumar et al. showed that women with UD were more than men with UD [31]. The results of this study demonstrated that the mean age of the samples was 69.2±10.1 years, and they were mostly in the age group of 60-75 years. Patients in Kumar et al. study were divided into diabetic, pre-diabetic and unknown UD groups with above 50 years old [31]. Considering the relationship between UD and individual-social variables, no significant relationship was observed between age and the frequency of UD. Huisa et al. study in 2013 also had such results [32].

Although there was no significant difference between the frequency of DM (diagnosed, undiagnosed and no diabetes mellitus) and patient's age in our study, age was identified as a predictor factor of UD compared to DD, such that the chance of UD incidence decreased with age. This result may be due to screening at a later age. In our study, education level was determined as a predicting factor related to UD compared to DD, such that the incidence of UD decreases with higher education levels. Also, in a study conducted by Eslami et al. education was reported as an underlying variable that strongly increased screening prevalence of diseases such as diabetes and hypertension, as increasing levels of society health literacy, self-awareness and self-care rise at the primary level of prevention [33].

In this study, the criterion for a definite diagnosis of UD was the HbA1C more than 6.5%, and the results showed that 21.7% of patients suffered UD, while Roquer et al. showed that 11.5% of patients with newly diagnosed DM [25]. Another study by Huisa et al. found that only 15% of 166 patients without a history of DM had this disease, according to HbA1c classification [32].

In the present study, the frequency of UD in patients with stroke with current or past smoking cigarette was more than twice(2:1) as that in non-smoking patients with stroke; this ratio was almost 2.5:1 in drug abusers. In a study conducted in 2012, Zahra et al. reported a statistically significant relationship between cigarette smoking and the incidence of UD in patients with stroke, and it is considered as the second most common risk factor in patients with stroke with DM [23]. In fact, cigarette smoking has been known as a possible risk factor for insulin resistance, a precursor to DM. Cigarette smoking also impairs glucose metabolism, which in turn leads to the onset of type 2 DM [34], thus quitting smoking in these patients seems necessary.

In the current study, there was a statistically significant relationship between the frequency of UD and stroke type, such that the highest and lowest percentages of UD cases were observed in patients with subarachnoid hemorrhage (66.7%) and intracranial hemorrhage (17.7%), respectively. Our analysis was consistent with other studies reviewed [25, 32]. It should be noted that there were a few patients with subarachnoid hemorrhage in our study, therefore, it cannot be concluded that the frequency of UD in subarachnoid hemorrhage was higher in all cases.

Considering other variables, we found people with a family history of DM had a lower percentage of UD than that in those with no such history, showing patients' awareness of the adverse consequences of DM, which leads to timely screening and self-care measures. Therefore, a positive family history of DM reduces the frequency of UD.

In this study, a statistically significant relationship was observed between cholesterol, TG levels (dyslipidemia) and the frequency of UD, such that the percentage of UD in people with abnormal TG was 2.5 times higher than that in healthy people. In a study by Kumar et al. patients had low HDL levels, but their level of total cholesterol was high [31]. Also, Todd et al. (2013) found that patients with UD had a higher LDL level compared to patients with DD. However, patients had no awareness of their high cholesterol levels and no plan to control cholesterol levels [35]. According to the findings, dyslipidemia like DM may have no clinical symptoms; thus, diagnosis and subsequent treatment will not be taken without screening tests.

Conclusion

Given the results of this study, it can be concluded that despite the high frequency of UD in patients with stroke, many of them are not aware of their DM. Therefore, it is recommended that training, timely screening and assessment of HbA1c be planned in general population

particularly among people with a family history of DM, dyslipidemia, and smoking.

Ethical Considerations

Compliance with ethical guidelines

All the study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki 1957.

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Authors contributions

Writing, revision, and editing the manuscript: Alia Saberi and Samaneh Kazemi; Data collecting: Zahra Rezaei; Providing resources: All authors; and Study Supervision: Yaser Moaddabi and Babak Bakhshayesh

Conflict of interest

The authors declared no conflict of interest.

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