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RESEARCH ARTICLE

IMPAIRED AWARENESS OF HYPOGLYCEMIA (IAH) IN THE KINGDOM OF SAUDI ARABIA

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Abstract

Aims: The current study aimed to identify the prevalence of impaired awareness of hypoglycemia (IAH) in the Kingdom of Saudi Arabia. Also, it aimed to determine the risk factors for IAH.

Methods: This is an analytical cross-sectional study that was conducted through a survey that targeted patients with diabetes mellitus (DM) in Saudi Arabia. The study was conducted from July 10th. 2020 to October 10th. 2020.

Results: The authors got responses from 1080 patients. The mean age was 55.5 years and the mean duration of DM was 11 years. Three hundred and sixty (33.3%) responders stated that they developed symptoms of hypoglycemia, of them, 60 (16.7%) patients developed symptoms weekly, and 60 (16.7%) patients developed symptoms twice weekly. The prevalence of IAH in the sample was 14.8 % (Gold method), and 20% (Pearson method). Our results showed that the prevalence of IAH was higher among patients who were over 65 years of age, female gender, who had DM for over 15 years, and those who did not attend schools.

Conclusion: The problem of IAH is a significant disorder in diabetic patients in the Kingdom of Saudi Arabia. The current study showed that the prevalence of IAH was ranging from 14.8% to 20%.

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Introduction:-

Hypoglycemia is a major problem for patients with diabetes mellitus (DM). Hypoglycemia leads to a variety of symptoms including palpitation, confusion, and loss of consciousness. (1, 2)

Impaired awareness of hypoglycemia (IAH) is a serious consequence of recurrent episodes of hypoglycemia. IAH is a problem in which patients develop an attenuation of their hypoglycemia symptoms, so, they become unable to recognize the occurrence of their hypoglycemia episode. Subsequently, their blood sugar could continue to decrease and lead to other complications, including seizures, coma, and potentially death. (3, 4, 5)

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Hypoglycemia is mainly caused by medications used to treat DM including insulin, sulfonylureas, and meglitinides. Also, other drugs may cause hypoglycemia, such as glucagon, cibenzoline, gatifloxacin, pentamidine, indomethacin, quinine, ethanol, and lithium. Additionally, other conditions could lead to hypoglycemia, including, Addison disease, insulinoma, post-gastric bypass hypoglycemia, and/or noninsulinomapancreatogenous hypoglycemia. (6, 7) Risk factors for hypoglycemia in DM include long duration of the disease, older ages, lower levels of glycemia control, missed meals, the low carbohydrate content of meals, heavy exercises, alcohol ingestion, chronic kidney diseases, and malnutrition. (8, 9)

Early recognition of the warning symptoms of hypoglycemia is very essential to prevent further worsening of the problem. Three methods were suggested to evaluate IAH. They include the 'Gold method' which asks patients if they know when their hypoglycemia was starting. The patient should give a number from 1 (always aware) to 7 (never aware). A score of ≥ 4 refers to IAH. The 'Clarke method' has 8 questionnaires to evaluate the awareness of the patient with hypoglycemia, the frequency of the episodes, and subjective estimation of the glycemia threshold for hypoglycemia occurrence. The answers are classified as either normal (A) or reduced (R). A score of ≥ 4 refers to IAH. The Pedersen method requires the patient to respond to the question "can you feel when you are low?" requiring the selection of one response from "always," "usually," "sometimes," or "never." All answers except always are referred to as IAH. (10, 11)

It was suggested that for patients with a history of IAH, a two- to three-week period of avoidance of hypoglycemia is essential to restore their hypoglycemia awareness. This approach requires an intensive professional involvement from the treating DM team by methods, such as frequent telephone calls, and strict patient education towards blood glucose awareness program. Also, this approach may necessitates higher glycaemic control to avoid hypoglycemia. (12)

Also, real-time continuous glucose monitoring (CGM) devices could provide patients with information about their blood glucose trends. Also, these devices could alert patients to hypoglycaemic events, so they could administer treatment to prevent the episodes. (13)

For those with type 1 DM and IAH, islet transplantation could be considered. Islet transplantation aims to restore hypoglycemia awareness and significantly improve counter-regulatory hormone responses. (14, 15) The prevalence of DM in developing countries is high. In Saudi Arabia, the prevalence of type 1 DM was about 0.1%, and type 2 DM was 20-25%. (16, 16)

The current study aimed to identify the prevalence of impaired awareness of hypoglycemia (IAH) in the Kingdom of Saudi Arabia. Also, it aimed to determine the risk factors for the development of IAH.

Methods:-

Study design:

This is an analytical cross-sectional study that was conducted through a survey that targeted patients with diabetes mellitus (DM) who were diagnosed between 2000 and 2019 in the Kingdom of Saudi Arabia. The study was conducted from July 10th. 2020 to October 10th. 2020.

Study population:

The authors aimed to survey 1550 patients all over the country. The sample size was calculated using OpenEpi for cross-sectional studies. The sample was randomly selected, through the computer, among DM patients in Saudi Arabia from the Ministry of health data. For inclusion into the current trial, responders had to be either a Saudi citizen or a legal resident in the country. Patients should be diagnosed between 2000 and 2019. Also, they should be over 18 years old at the time of diagnosis.

Sampling method:

The study was carried out through a survey of 10 questionnaires. Responders were asked to give information about their age, gender, the region of residency (western, eastern, central, southern, or northern), and their educational level (university graduate, high school graduate, did not attend schools, or student). When DM was diagnosed, what

type of DM has they (Type 1, or Type 2). If they have ever developed symptoms of hypoglycemia (palpitation, fainting, confusion, loss of consciousness), How often did they notice these symptoms (every 6months [infrequently], monthly, weekly, twice weekly, daily, or none). Also, they were required to respond to the following 2 questions; Do you know when your hypoglycemia was starting?; Patients should give a number from 1 (always aware) to 7 (never aware), and Can you feel when you are low?; The patient should select a response from “always,” “usually,” “sometimes,” or “never.”

Study measurements:

The prevalence was defined as the proportion of people with the target disease among all the studied samples. Also, the current study examined the relationship between IAH and predefined factors including age, the region of residency, educational level, gender, duration of DM, and the type of DM. Then, the study examined the impaired awareness of patients with hypoglycemia (IAH) using both Gold and Pedersen methods.

Statistical analysis:

Statistical analysis was carried out by Statistical Package for the Social Sciences (SPSS) version 17. Continuous data were presented in terms of mean, median, and 95% Confidence interval (CI). Univariate analysis with OR was performed to evaluate the relationship between IAH and predefined factors including age, the region of residency, educational level, gender, duration of DM, and type of DM. Also, multivariate analysis with HR using binary logistic regression was performed to independently investigate such correlations. Statistical significance was set at a P-value of 0.05 or less.

Ethical and financial considerations:

Ethical approval was sought from the ethical committee of the faculty of medicine, King Abdulaziz University, Saudi Arabia. Informed consent was taken from the participants. The authors confirm that this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Results:-

One thousand five- hundred and Fifty patients were contacted and the authors got responses from 1080 (69.4%) patients. The following table 1 showed the sample characteristics. (Table 1)

Three hundred and sixty (33.3%) responders stated that they developed symptoms of hypoglycemia (palpitation, fainting, confusion, loss of consciousness). 120 (33.3 %) responders developed hypoglycemia symptoms every 6months [infrequently], 120 (33.3%) patients developed symptoms monthly, 60 (16.7%) patients developed symptoms weekly, 60 (16.7%) patients developed symptoms twice weekly, zero (0%) patients developed symptoms daily, and 720 (66.7%) patients did not develop hypoglycemia symptoms at all. (P-value 0.06) Concerning the question ‘Do you know when your hypoglycemia was starting?’; 920 (85.6%) patients got a score of 1 to 3.

160 (14.8%) patients got a score of 4-7. With regards to the question, ‘Can you feel when you are low?; 864 (80%) patients selected always, 80 (7.4%) patients chose usually, 70 (6.5%) patients selected sometimes, and 66 (6.1 %) patients chose never. According to the Gold method, the prevalence of IAH in the sample was 14.8%, and based on the Pearson method, the prevalence of IAH was 20%.

Characteristics of the patients with IAH is summarised in Table 2. (Table 2)

Tables 3, 4 showed the univariate and multivariate analysis of the patients with IAH. (Tables 3, 4)

Discussions:-

The current study aimed to investigate the prevalence of IAH among diabetic patients in the Kingdom of Saudi Arabia. Saudi Arabia is the largest country in the Middle East. It has a population of 35 million people. It has a diverse ethnic population, other than Saudi citizens; it has Syrians, Egyptians, Philippines, Indians, Yemini, Pakistanis, and people from Western countries. The population share some risk factors including high glucose level, obesity, high body mass index (BMI), and sedentary life. Knowing the prevalence of the disease and identifying the risk group could help physicians to prioritize patients who require additional care. (18)

The current study is a cross-sectional study that was based on interviewing patients over a 3-month period. The sample was selected by the computer from governmental data for diabetic patients in the last 20 years in the country. The authors decided to conduct a cross-sectional survey. A cross-sectional survey provides the best way to identify a problem and its risk factors in a predefined population. (19)

The authors selected to apply both Gold and Pedersen methods to assess IAH. Studies showed that the Pederson method alone overestimates cases of IAH. Also, the use of both the Gold and Clarke questionnaires to identify the IAH in patients with DM was supported by the study of Lin et al., 2019. Also, new evidence to support our selection came from the study of Chandi et al., 2020, who suggested performing more than one method to assess IAH. Additionally, for patients with type 2 DM, the study of Ling et al., 2019, used a combination of the three methods to evaluate IAH in type 2 DM patients. (20, 21, 22, 23)

Previous research was conducted in this active area. They include the study of Samarkandi et al., 2019, who evaluated the problem of hypoglycaemia in patients with DM in the desert region of Saudi Arabia and showed the prevalence of IAH of 20% of patients. The risk increased in type 1 DM. (24)

Also, the study of Alkhaldi et al., 2019; which was conducted to evaluate the problem in the fasting month of Ramadan in a certain city in the Central region of Saudi Arabia. The authors observed that the problem was associated with young patients, females, longer duration of DM, especially those with DM over 10 years, and those with type 1 DM, although Type 2 DM showed a high prevalence (20%) as well. Also, university graduates showed better awareness of the problem. (25)

Additionally, the study of Al Hayek et al., 2015, which was conducted in a single institute in Riyadh on patients with type 1 DM from June 2013 to February 2014. It showed that the prevalence of the problem was high among older ages, female genders, and a longer duration of type 1 DM. (26)

Moreover, the research of Zanariah et al., 2017, which was run on patients who were 18 years of age at baseline, with T1DM (114 patients) or T2DM (1039 patients) treated with insulin for >12 months in Malaysia. The study showed that 24.8% of patients with type 1 DM and 16.1% of patients with type 2 DM reported symptoms of IAH. (27)

Furthermore, the study of Lamounier et al., 2018, which was conducted in Brazil on 321 patients with type1 DM and 293 patients with Type2 DM on insulin therapy and showed that the prevalence of AIH was 20.0% and 10.3% in type 1 DM and type 2 DM, respectively. They applied the Pedersen method to evaluate AIH. The problem was higher among females, longer duration of DM, type 2 DM, and older ages. (28)

To the knowledge of the authors, the current study was the only research which was conducted on a wide scale in the country. The prevalence of IAH in the current trial based on the Gold method was 14.8%, and according to the Pearson method, it was 20%. This discrepancy between methods was confirmed in previous studies. The authors believe that assessing the problem using more than one method is the best way to evaluate IAH prevalence. The studies of both Chandi et al., 2020, and Ling et al., 2019 agreed with this recommendation. (22, 23)

The studies of Samarkandi et al., 2019, and Lamounier et al., 2018 showed very comparable prevalence rates with the current findings. (24, 28)

Our results showed that the prevalence of IAH was higher among patients who were over 65 years of age, female gender, who had DM for over 15 years. The study of Lamounier et al., 2018 showed similar findings. The reason why females had a higher prevalence of AIH is unknown to us. (28)

Also, the current study showed a higher prevalence among patients who did not attend schools, and those living in the Western region. The study of Alkhaldi et al., 2019, agreed with the former finding. The latter finding may be related to the current patient cohort have a high mean age which may be the cause of that. (25)

The current study showed a higher prevalence for IAH in patients with Type 1 DM. However, those with type 2 DM had a high tendency, as well. The study of Zanariah et al., 2017 showed comparable results. It has to be noted that, we did not investigate the type of diabetic treatment. Further research is required to confirm our findings. (27)

The current study has some limitations. Further trials with a longer follow-up period are required to confirm our results. Also, trials are required to investigate the prevalence of IAH in patients with type 2 DM who are on new antidiabetic medications.

Table 1:-Sample Characteristics.

	Number	Percentage %	P- value
Age: (Years)			
18-30	150	13.9	
31-50	200	18.5	
51-65	330	30.6	
Over 65	400	37.0	
Mean	55.5 years		0.06
Median	55.1 years		
95% CI	20-76 years		
Gender:			
Male	486	45	0.06
Female	594	55	
Region of residency:			
Western		32	
Eastern	345	23.6	
Central	255	18.6	
Northern	200	12	
Southern	130	13.8	
Mean, Median	150		0.06
	Western		
Educational level:			
-University graduate	270	25.0	
-High school graduate			
-Did not attend schools	300	27.8	
-Student (School or university)	310	28.7	
Mean, Median	200	18.5	
	Did not attend schools		
Duration of DM			
Less than 1 year:	100	9.2	0.05
1-5 years:	180	16.7	
5-10 years:	250	23.2	
10-15 years:	350	32.4	
>15 years:	200	18.5	
Mean	11 years		
Median	11.1 years		
95% CI	6 months -20 years		
Type of DM			
Type 1	350	32.4	0.04
Type 2	730	67.6	
Mean, median	Type 2		

Table 2:-Characteristics of patients with IAH.

	Number	Percentage %	P- value
Age: (Years)			
18-30	40	18.5	
31-50	46	21.3	
51-65	55	25.5	
Over 65	75	34.7	
Mean	68.5 years		0.05
Median	68.1 years		
95% CI	22-76 years		
Gender:			
Male	101	46.7	0.06
Female	115	53.3	
Region of residency:			
Western			
Eastern	66	30.6	
Central	50	23.1	
Northern	40	18.5	
Southern	20	9.3	
	40	18.5	
Mean, Median			0.05
	Western		
Educational level:			
-University graduate	16	7.4	
-High school graduate			
-Did not attend schools	50	23.1	
-Student (School or university)	100	46.4	
Mean, Median	50	23.1	
	Did not attend schools		
Duration of DM			
Less than 1 year:	0	0	
1-5 years:	0	0	
5-10 years:	36	16.6	0.04
10-15 years:	80	37	
>15 years:	100	46.4	
Mean	11.4 years		
Median	11.5 years		
95% CI	2-20 years		
Type of DM			
Type 1	110	51	0.05
Type 2	106	49	
Mean, median	Type 1		

Table 3:-The univariate analysis of patients with IAH.

Factor	IAH	No IAH	OR (95% CI)	P- value
Age 18-50 years	86	264	0.09 (0.06-2.00)	0.06
Age 51-65 years	55	275	0.05 (0.03-2.0)	0.06
Age: Over 65 years	75	325	0.035 (0.02-1.6)	0.04
Regions Western, and Eastern	116	484	0.03 (0.01-2.00)	0.04
Other regions	100	380	0.06 (0.04-2.1)	0.06
Male	101	385	0.07 (0.05-2.2)	0.06
Female	115	479	0.05 (0.03-2.0)	0.06
Educational level: University graduate, and students	66	404	0.04 (0.02-2.2)	0.06
High school graduate	50	250	0.03 (0.01-2.0)	0.04
Did not attend schools	100	210	0.03 (0.02-2.2)	0.04
Duration of DM Less than 1 year to 10 years	36	494	0.05 (0.2-2.2)	0.06
10-15 years	80	270	0.05 (0.2-2.2)	0.06
Over 15 years	100	100	0.03 (0.02-2.0)	0.04
Type of DM: Type 1	110	240	0.03 (0.02-2.0)	0.04
Type 2	106	624	0.05 (0.03-2.2)	0.04

Table 4:-The multivariate analysis for patients with IAH.

Factor	HR (95% CI)	P- Value
Age 18-50 years	0.9 (0.6-1.5)	0.06
Age 51-65 years	0.7 (0.6-1.5)	0.06
Age: Over 65 years	0.3 (0.2-1.0)	0.04
Regions Western, and Eastern	0.3 (0.2-1.0)	0.04
Other regions	0.7 (0.6-1.5)	0.06
Male	0.7 (0.6-1.5)	0.06
Female	0.6 (0.4-1.2)	0.06
Educational level: University graduate, and students	0.8 (0.6-1.5)	0.06
High school graduate	0.5 (0.3-1.2)	0.04
Did not attend schools	0.3 (0.01-1.0)	0.03
Duration of DM Less than 1 year to 10 years	0.9 (0.7-1.5)	0.06
10-15 years	0.7 (0.6-1.5)	0.06
Over 15 years	0.3 (0.0-1.0)	0.04
Type of DM: Type 1	0.3 (0.0-1.0)	0.04
Type 2	0.4 (0.2-1.2)	0.05

Conclusions:-

The problem of IAH is a significant disorder in diabetic patients in the Kingdom of Saudi Arabia. The current study showed that the prevalence of IAH was ranging from 14.8% to 20%. Further research is required to confirm our findings.

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