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# Level of knowledge and awareness about diabetic retinopathy among population of Al Baha region in Saudi Arabia

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## ABSTRACT

*Background:* Diabetic retinopathy is a complex metabolic disease with a huge prevalence ratio. However, there is a dearth of literature about the importance of knowledge regarding diabetic retinopathy, which can help in the ease of screening and management. *Methods:* The study was conducted in Al Baha region, Saudi Arabia. N = 385 participants, including diabetics and non-diabetics, were recruited through the online questionnaire. The questionnaire was based on 15 questions that were focused on awareness of diabetic retinopathy, participants' satisfaction with the knowledge of disease and the barriers faced by them while seeking access to the treatment. *Results:* Out of N = 385 participants in the present study, 246 were males, and 139 were females. The majority of the participants (69%) reported that Diabetes could lead to eye blindness in affected patients. These participants do have some knowledge of diabetic retinopathy. Furthermore, the participants (60%) reported that they acquired knowledge of diabetic retinopathy from resources other than social media and doctors. Only a few of them (4 participants) had diabetic retinopathy; however, most participants (84%) exhibited the need for a regular annual eye check up. *Conclusions:* Subjects in the present study have significant knowledge of diabetic retinopathy. However, many still remain underdiagnosed in the practical world. Delay onset of diabetic retinopathy in the case of Diabetes mellitus is also because of the under diagnosis. Therefore, it is important to assess the complete knowledge and awareness of the disease and its serious complications.

**Keywords:** Diabetes Mellitus; Awareness; Diabetic Retinopathy; Eye examination

## 1. INTRODUCTION

Diabetes Mellitus (DM) is a serious metabolic disorder characterized by a disruptive carbohydrate metabolism resulting in the hyperglycemic condition.

It progresses into chronic hyperglycemia with consequences of organ damage to the retina, kidney, nerves, and heart (Alam et al., 2014). Worldwide prevalence of Diabetes is reported by the statistical evidence of the International Diabetes Federation, which demonstrated 382 million reported cases for Diabetes worldwide (Alam et al., 2014). The disease is specifically burdened to the Middle East population, where Saudi Arabia tops the list with 7 million reported cases. Diabetes has become the cause of premature deaths, and the trajectory is expected to rise in the next 25 years (Abdulaziz et al., 2016). The condition is caused by the body's inability to produce or utilize insulin for carbohydrate metabolism. The disease has stressed the healthcare to produce reforms against its major challenges.

Diabetes can evolve into many severe complications depending upon the individual's vulnerability to the disease. Diabetic retinopathy (DR) is one significant form of Diabetes with an alarming catastrophe among diabetic patients. A study in Saudi Arabia found that around 36% of diabetic patients experience stressful retinopathy, which is a prolonged disruption of retinal vascular permeability, sometimes resulting in blindness (Ahmed et al., 2016). The disease can be caused by several risk factors such as high blood sugar, chronic progression, and organopathies that are heterogeneous in nature in affected patients. Such kind of abnormalities is responsible for epidemic proportions in the Kingdom of Saudi Arabia (KSA). DR can cause an irreversible systemic abnormality which is followed by the sequelae of ophthalmic blindness (Almotairy et al., 2021; Alghamdi et al., 2021). The condition can vary with respect to geographical heterogeneity. For example, people living in remote areas such as in Al Baha Province, KSA, are more vulnerable to diabetic retinopathy. The relationship is not that simple just because people live at remote sites. Al Baha province is located above sea levels in the Kingdom, which means the risk of low oxygen tension and ethnic disparities subject individuals towards availing diabetes-related severities (Alghamdi, 2016). This indicates that such regions are the focus of prime interest to explore the existing realities about the research problem.

Moreover, population response to disease is the reflection of their awareness about disease risks. Different research studies assessed the awareness of diabetic retinopathy in patients earlier. These studies showed that awareness is a motivational factor that can work as a positive reinforcer to manage diabetic retinopathy (Alzahrani et al., 2018). However, lack of awareness induces challenges of less capacity to control the disease progression. Physical examination, screening, and management intervention of DR require an inherent knowledge about the modifiable risks of diabetic retinopathy both in patients and the general population. Studies have initially focused on the importance of DR knowledge in a patient and how it can assist them in consulting their physician (Alzahrani et al., 2018). However, studying the phenomenon in the general population, including both diabetic and non-diabetic groups in Al Baha, can help in the treatment and prevention of the disease condition.

Therefore, the present research aims to evaluate the extent of awareness of diabetic retinopathy in the Al Baha population and factors that contribute towards this awareness. Furthermore, it compares the level of awareness in diabetic and non-diabetic groups under the study focus.

## 2. METHODS

The cross-sectional study design was carried out, followed by approval from the Scientific Research and Ethics Committee at the Faculty of Medicine, Al Baha University. The participants were sought at Al Baha region, Saudi Arabia featuring either Diabetes or non-diabetic condition in the duration from 2021-2022. Participant selection was random and based on the sample size calculation, which resulted in an estimated size of 385, including both males and females with a 95% confidence level (Z statistics = 1.96), margin of error = 5 % and population of 411,888 depending on official governmental statistic was considered with a P-value of 5 or less was used to test significance The following formula was used for the sample size calculation of participants.

$$\text{Sample Size} = \frac{\frac{z^2 \times p(1-p)}{e^2}}{1+\left(\frac{z^2 \times p(1-p)}{e^2 N}\right)} = 385$$

An online questionnaire was customized with respect to the research aims and distributed to participants. The study excluded the groups with existing vulnerabilities (pregnancy, children, and old age). All participants were signed informed consent before proceeding to the evaluation survey. The questionnaire was formed from the data which was collected from existing literature. The literature is motioned in the references that helped to use data for better reproducibility of the content. The questionnaire was comprised of 15 questions and three sections (age, sex, and academic level), as shown in Table 1.

**Table 1** Survey Design

| No. | Details | Survey Response |
|---|---|---|
| **Section 1.** | | |
| **1** | Name | |
| **2** | Age | |
| **3** | Sex | Male/Female |
| **4** | Education/Academic level | Elementary/ Middle School, Secondary School/ College, University/ Higher Education. |
| **Section 2.** | | |
| **A** | Are you diabetic? | Yes/No |
| **B** | If yes, what type of Diabetes condition? | Type 1/ Type 2/ Not Diabetic |
| **C** | How long you possess the diabetes? | <5/ 5-10/ >10/ Not Diabetic |
| **D** | Do you have any relative with diabetic condition? | Yes/No |
| **E** | What do you think about the complications of Diabetes? | Eye disease/ heart disease/ Nephropathy/ Neuropathy/ Stroke/ Peripheral artery disease |
| **F** | Do you think that Diabetes can affect your visual insight? | Yes/No |
| **G** | Do you believe that managing blood sugar can preserve the eyesight of individuals suffering from the condition? | Yes/No |
| **H** | Can Diabetes Lead to blindness in patients? | Yes/No |
| **Section 3.** | | |
| **A** | Do you know what diabetic retinopathy is? | Yes/No |
| **B** | If yes, how did you get knowledge about diabetic retinopathy? | Reading/ social media/ Eye doctor/ Other |
| **C** | Do you have diabetic retinopathy? | Yes/No |
| **D** | In your opinion, is it necessary for a diabetic to get an annual checkup of their eyesight? | Yes/No |
| **E** | Do you receive an annual check of your eyes? | Yes/No |
| **F** | Are you satisfied with your knowledge about diabetic retinopathy? | Diabetic retinopathy satisfaction (1-10) |
| **G** | What are the barriers that affect your attitude toward getting information about diabetic retinopathy? | Lack of knowledge/ lack of access to eyecare/ lack of insurance/ fear of diagnosis |

Furthermore, the research questionnaire was formulated by the researchers of the present study and validated from the Faculty of Medicine, Al Baha University. Researchers used comprehensive information from the previous references for developing questions, and some questions were self-designed by the researchers themselves to achieve the objectives of the study. The first section of the questionnaire, as directed by the standard process, comprised of participants' demographic information. Table 1 lists the demographic elements. The second section of the questionnaire was about checking participants' level of knowledge and awareness about diabetic retinopathy. The questions were as follows (a) are you diabetic, (b) what kind of Diabetes, (c) duration of Diabetes, (d) do you have diabetic relative, (e) your perspective over complications of Diabetes is poorly managed, (f) do you believe that Diabetes can affect eyes, (g) do you believe that controlling blood sugar can help recover your eyesight, (h) can Diabetes result in severe consequences of blindness.

The third section assessed the knowledge about diabetic retinopathy. The questions were based on (a) knowledge about diabetic retinopathy, (b) how you got an awareness of the DR, (c) do you have diabetic retinopathy, (d) is it necessary for diabetics to get an annual check of their vision, (e) do you get an annual check of your eyes, (f) how satisfied you are with the knowledge of diabetic retinopathy, and lastly (g) what the biggest barrier is to achieve the knowledge about diabetic retinopathy.

The present questionnaire was performed through online assessment using google forms for creating the survey and giving participants easy access to the survey. Participants were not paid any stipend for taking part in the study. Participants' autonomy to

choose either participating in the study or not was fully respected, and they were made aware of the research aims. All the information was statistically analyzed later by the SPSS Version 21st to perform the quantitative evaluation of the research variables

## 3. RESULTS

A quantitative analysis was conducted with a total sample size comprising 385 participants. The socio-demographic analysis was used to build the characteristics of participants. This added gender, age, academic level, diabetic status, diabetic type, and duration of Diabetes in the questionnaire for the profile building of the respondent. The socio-demographics indicated that 80% of the participants were aged between 18-30 years, and only 4.16% were aged over 60 years. Moreover, 63.90% of the total participants were males, and the remaining 36.1% were females. The response suggested that 77.92% of the participants were college/university/higher qualified, and 2.0% were qualified till elementary school. To achieve the objective of the research, it was revealed that only 12.99% of the respondents had diabetes, while 87.01% were non-diabetic. In addition, 4.94% of participants had type 1 diabetes, and 8.05% had type 2 diabetes. Finally, it was indicated that most of the participants had Diabetes in their relatives, as 85.45% answered yes to this statement (table 2).

Moreover, it was found that Diabetes can affect the eyes, as 90.65% of the participants indicated and said yes to the proposition. Similarly, 89.87% of the respondents indicated that controlling a lump of blood sugar can help preserve vision in a patient with Diabetes (table 3).

**Table 2** Socio-demographic Analysis

| | | N=385 | % |
|---|---|---|---|
| Age in Years | < 18 years old | 18 | 4.68 |
| | > 60 years old | 16 | 4.16 |
| | 18 - 30 years old | 307 | 79.74 |
| | 31 - 60 years old | 44 | 11.43 |
| Gender | Female | 139 | 36.10 |
| | Male | 246 | 63.90 |
| Academic Level | college/University/Higher | 300 | 77.92 |
| | Elementary | 8 | 2.08 |
| | Middle school | 18 | 4.68 |
| | Secondary | 59 | 15.32 |

**Table 3** Survey Regarding Disease Prevalence

| | | N=385 | % |
|---|---|---|---|
| Are you diabetic? | No | 335 | 87.01 |
| | Yes | 50 | 12.99 |
| If you answered yes, which type? | Not diabetic | 335 | 87.01 |
| | Type 1 | 19 | 4.94 |
| | Type 2 | 31 | 8.05 |
| Duration of diabetes in years | < 5 | 13 | 3.38 |
| | > 10 | 21 | 5.45 |
| | 5 – 10 | 16 | 4.16 |
| | Not diabetic | 335 | 87.01 |
| Do you have relatives with Diabetes? | No | 56 | 14.54 |
| | Yes | 329 | 85.45 |

Furthermore, 69.09% said that Diabetes could lead to blindness. In contrast, 57.92% of the participants did not know about diabetic retinopathy. Interestingly, participants, who knew about retinopathy, 66.49% mentioned others as sources. Similarly, there were only 13.51% of participants had diabetic retinopathy. Most important, 84.42% of them supported that it is essential for a diabetic patient to get their eyes checked annually. Moreover, research participants were asked to indicate the biggest barrier for not getting eye screening. It was found that 53.80% of the respondents indicated a lack of knowledge as barrier to such screening.

Similarly, 27.00% highlighted that they had fear of discovery. However, 14.80% and 4.40% mentioned that they had insurance and access to eye care, respectively.

Finally, in response to determining the awareness about diabetics, this study asked participants to rank their knowledge regarding diabetics on a rating scale of 1 to 10. The following results were obtained (table 4).

**Table 4** Questions regarding Diabetic Retinopathy

| | | N=385 | % |
|---|---|---|---|
| **Do you believe that Diabetes can affect the eyes?** | No | 36 | 9.35 |
| | Yes | 349 | 90.65 |
| **Do you believe that controlling a lump of blood sugar can help preserve vision in patients with Diabetes?** | No | 39 | 10.13 |
| | Yes | 346 | 89.87 |
| **Do you believe that Diabetes can lead to blindness?** | No | 119 | 30.91 |
| | Yes | 266 | 69.09 |
| **Do you know what diabetic retinopathy is?** | No | 223 | 57.92 |
| | Yes | 162 | 42.08 |
| **If you answered yes to the previous question, how did you become familiar with diabetic retinopathy?** | Doctor | 24 | 6.23 |
| | Eye Doctor | 25 | 6.49 |
| | Other | 256 | 66.49 |
| | Reading | 71 | 18.44 |
| | Social media | 9 | 2.34 |
| **Do you have diabetic retinopathy?** | No | 329 | 85.45 |
| | Not sure | 52 | 13.51 |
| | Yes | 4 | 1.04 |
| **Do you think it is important for a diabetic to check their eyes annually?** | No | 60 | 15.58 |
| | Yes | 325 | 84.42 |
| **What do you think was the biggest barrier for Lack of knowledge about not getting eye screening?** | Fear of Discovery | 104 | 27.00 |
| | Insurance | 17 | 4.40 |
| | Access to eye care | 57 | 14.80 |
| | Lack of Knowledge | 207 | 53.80 |

The results (figure 1) indicated that there were around 31.69% of participants who rated their knowledge of Diabetes 10 out of 10. In contrast, 4.94% rated 1 out of 10. It was found that a lower number of people had Diabetes in the survey population. Moreover, they had better awareness regarding Diabetes and its types. Importantly, the respondents supported this study's proposition that it is necessary for diabetics to check their eyes annually. The figure 2 represents the biggest barriers regarding lack of getting eyes screened.

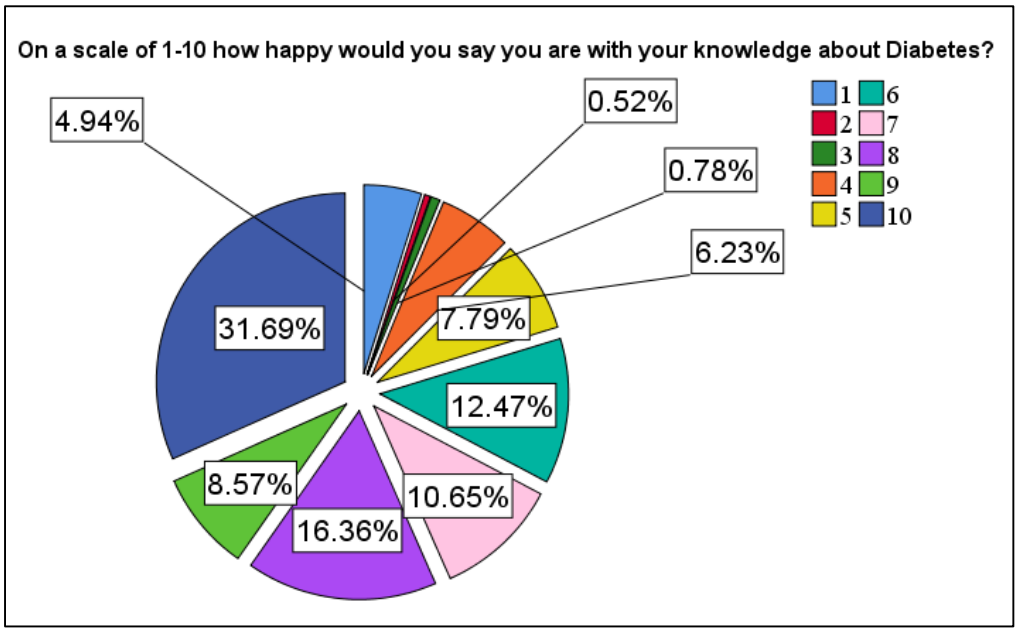


**Figure 1** Knowledge Related to Diabetes Retinopathy

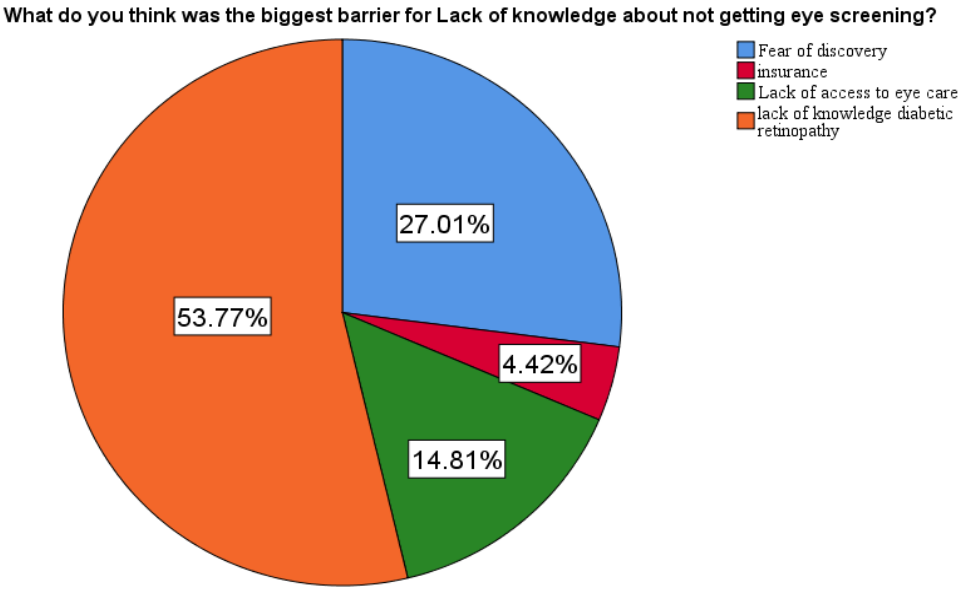


**Figure 2** What do you think was the biggest barrier for Lack of knowledge about not getting eye screening?

## 4. DISCUSSION

Al Baha is a geographic locality situated in the Kingdom of Saudi Arabia. The estimated population size of Al Baha is about 487 thousand inhabitants, including variables of gender and nationality (https://www.statista.com/statistics/617320/saudi-arabia-population-gender-and-nationality-in-al-baha-region. cited on 15.2.2022 at 5:45 pm). Saudi Arabia ranked the top for the prevalence of Diabetes. The total prevalence reported by the statistical report is 22% in adults aged between 20-79 years (https://www.statista.com/statistics/790937/assumed-prevalence-diabetes-and-actual-diabetes-rate-worldwide. cited on 15.2.2022 at 7:00 pm). The condition prevails differently with respect to its types. Furthermore, the global trends about DR prevalence showed the highest prevalence in MENA (Middle East North Africa) than other geographical regions. Among all ethnic groups, Middle Easterners and North Africans showed higher odds for DR prevalence (Teo et al., 2021).

As of the present research interest, it was important to consider the prevalence rate in the Al Baha region. An earlier study reported the prevalence of Type 1 diabetes among children in the Al Baha region with an estimate of around 335 affected children per 100,000 populations (Al-Ghamdi & Fureeh, 2018). Besides children, the overall general population presents a serious health

concern because of Diabetes. Saudi community experienced a heavy financial burden because of Diabetes related comorbidities. Diabetic retinopathy is one among wide health concerning comorbidities that arise in diabetic patients (Dokhaikh et al., 2017). An earlier retrospective study conducted in AL-Baha Diabetic Center showed that diabetic patients experiencing a significant burden of comorbid conditions such as type 1 diabetic patient reported a substantial prevalence of celiac disorder (inflammation of intestinal mucosa). Not only this, but the celiac disorder was found to be the possible risk factor for diabetic retinopathy in patients (Alghamdi et al., 2018). This indicates that diabetic retinopathy is a severe pathological experience for patients who require proper diagnosis and treatment. Such heterogeneity resulted in a considerably high burden of healthcare costs. More so, it also showed the heavy responsibility of the healthcare and researchers to plan for better management and prevention against the disease condition. Hence previously mentioned evidence showed that the risk of diabetes and related comorbidities is significantly higher in the Middle East population, where Saudi Arabia holds a wider proportion. In addition, Al Baha is found to be the suitable area for studying such higher odds of severe consequences because the city entails a quite burden of diabetic retinopathy, which relates to the study objectives.

Our study formulated an appropriate sample size that included both male and female genders with some variable differences in their proportion. Males were considerably greater in numbers than females. Participants' responses showed that a large number of proportions had a non-diabetic health profile. Those with diabetic profiles reported higher cases of type 2 diabetes. However, 87% of all participants reported that they have diabetic relatives. This means that a considerable ratio of sample is exposed to individuals with a diabetic condition. Diabetes was surely the prevalent condition in the region. Apart from this, the target population was school-going or university students, which might be the reason for the odds of disease prevalence since the earlier studies showed children and vulnerable adults to be more prone to the disease (Al-Ghamdi & Fureeh, 2018; Dokhaikh et al., 2017; Alghamdi et al., 2018). Furthermore, the participants were quite aware of the symptoms of Diabetes as most of them responded yes to the states where they were being asked if they have a diabetic relative.

Besides, even though greater numbers of responders said that Diabetes could lead to blindness, most of the responders still did not have some knowledge about diabetic retinopathy. Unlike the earlier studies, diabetic patients presented an appropriate response regarding the disease knowledge. Research in Jeddah reported that 82% of patients were aware of their retinal abnormality due to diabetes (El Khatib et al., 2017). Likewise, another research in the USA reported that the vast majority of enrolled diabetic patients had knowledge that Diabetes can affect their ophthalmic function (Al Zarea, 2016). One reason can be that these studies were carried out while considering diabetic patients under focus.

Diabetic retinopathy is a consequence of diabetic severity in patients. Since most of the participants were non-diabetic, it is possible to not have knowledge about DR as well. This fact can be supported by the evidence where diabetic patients had more knowledge about diabetic retinopathy. One research included 202 participants comprised of diabetic and non-diabetic groups. These participants were tested for their knowledge and attitudes regarding diabetic retinopathy. Results showed that diabetic patients had more potential knowledge about Diabetes, hypertension, and diabetic retinopathy (Lingam et al., 2018). The possible reasons could be the frequent exposure of the patient to diabetic centres while seeking their treatment.

However, many responders stated that Diabetes could lead to blindness like the recent research conducted in the same geographical entity. In Saudi Arabia, an awareness questionnaire carried out among students showed satisfactory knowledge about diabetic retinopathy (Alamri et al., 2021). There were different studies that suggested that diabetic eye disease is a frequent condition in the affected patient (Al-Ghamdi & Fureeh, 2018; Dokhaikh et al., 2017; Alghamdi et al., 2018). Early research focused on the diabetic eye screening program to screen for eye abnormality in patients. Prevention of this condition has been widely addressed in the theoretical context of the research (Stefánsson et al., 2000). It was well documented that Diabetes can cause blindness. In addition, when participants were asked about their views on diabetic examination, most of them (84%) reported that it is necessary to get the annual eye check up in diabetic patients. Diabetic patients were aware of their complications in the eyes in most cases.

Primary evidence supported that many diabetic patients, especially those possessing a tertiary level of education; seek examination and management from their ophthalmologist. Physicians also recommended the patients to the eye clinic for a careful check up to avoid eye complications in diabetics (Tajunisah et al., 2011). Diabetic patients were studied to be highly susceptible to corneal edema, and the symptoms were not uncommon in patients, which meant that the consequences were common and expected in patients. Even though the symptoms were frequent, these were not avoidable. The diabetic eye can get a serious complication of internal eye bleeding and impose surgical challenges (Berrocal et al., 2016). Pathological changes in diabetic patients subject them to these eye-related abnormalities. To further support our findings of why diabetics need an eye examination, we investigated more details of pathological mechanisms of Diabetes related to eye damage by the existing research references. Hyperglycemia is a primary change induced in diabetics, which affects almost all the body cells of affected individuals. Hyperglycemia is more chronic

to the corneal and retinal cells. The toxicity to the cells increased due to the early loss of vascular permeability in diabetics causing micro vasculopathy, which is a characteristic marker of diabetic retinopathy (Lutty et al. 2013). Diabetic retinopathy is the well-known cause of blindness in patients aged over 50 years and may result in fatal consequences. It is, therefore, useful to have comprehensive knowledge about such health complexities.

Besides, our findings also suggested that satisfaction with the knowledge of the disease can enhance participants' potential to challenge the disease and look for its prevention. Satisfaction to education facilitates the screening and early diagnosis of the disease. Early evidence reported that educational programs for diabetic retinopathy were potentially significant for diagnosis. Educational aid assisted in the follow-up in routine screening procedures hence ensuring the compliance of patients to proper diagnosis and management. These educational programs are necessary for both patients and physicians for ease of screening and testing. Lack of information and poor access to the resources are found to be the major barriers while seeking treatment. It was evident from the study of Moinul et al., (2020) that the education model for screening improved the compliance in high-risk patients as well who found difficulty to persistence. Ultimately, adherence will contribute to the wellbeing of patients. Our findings were in correspondence with the goals of achieving quality of care in diabetic patients.

The majority of the participants (around 32%) reported their satisfaction and anticipation with the knowledge of diabetic retinopathy. The focus of the study was on the assessment of awareness about DR. Good awareness of DR in patients was in congruence with appropriate control of the disease (Al Hargan et al., 2019). Furthermore, present research also studied some barriers that hindered with the eye care in diabetic patients. These barriers were lack of knowledge access, fear of discovery, and lack of access and insurance of medical services. It was deduced that lack of knowledge was the most dominant contributing factor in diabetic and non-diabetic individuals which can subject them to severe eye disease (diabetic retinopathy).

Our study included the participants, with the majority of students enrolled in different academic levels. Awareness of diabetic retinopathy, therefore, resulted in a positive response since participants were quite knowledgeable. Even though some participants did not respond positively to the questions, there could be certain factors that might cause their lack of access to knowledge and care of diabetic retinopathy. One important thing was that majority forced upon the need for an annual eye check up. Among different types of diabetes-related complications, eye complications remained consistent in all participants' responses. Likewise, many of them believed that controlling the blood sugar can help in the recovery of poor eyesight in diabetic patients.

Previous literature also indicated that managing sugar levels can be helpful for controlling diabetes-related eye complications (Boyer et al., 2013). Since hyperglycemia was the responsible contributor to cause toxicity to the eye and inducing macular edema, therefore reduced blood sugar can counter the hyperglycemic condition, and the health status can be adjusted in patients. It is because anti-VGF therapy was administered to the patients to control hyperglycemia and improve outcomes in the case of diabetic retinopathy (Boyer et al., 2013).

## 5. CONCLSUION

Our results have provided many considerations for patients with diabetic eye disease. Firstly, it is very important to have wide knowledge about diabetes and its relatable complications. Secondly, since diabetic eye disorder is a commonly faced challenge in the general population in Saudi Arabia, subjects must know the importance of receiving annual checkups for their eyes while suffering from diabetes. Most importantly, satisfaction with the extent of knowledge that individuals possess leads to the positive directions of achieving good health recovery. The present study was reliable, with a 95% confidence interval in the results. All the previous findings ensured the need for understanding the diabetic retinopathy in both patients and non-diabetics in the Al Baha region, Saudi Arabia, for improving the annual eye check up by their regular ophthalmologist.

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**Disclosure**

Statement: we would like to state that this work is our own and no information is copyrighted or infringed.

**Ethical Consideration**

The study was approved by Research Ethical Committee of Faculty of Medicine, Al Baha University, under approval number (REC/SUR/BU-FM/2022/6). The ethical considerations included in the maintaining the confidentiality and anonymity of the respondents. A consent form was duly signed by the respondents specifying the aims and objectives of the study and voluntary

participation in the study. The ethical considerations also aimed towards ensuring that the studies published by the previous authors were given full credit and due acknowledgment through in-text citation and generation of a complete reference list at the end of the research.

**Author Contribution**

Ali conceived the original idea, Mahadi and Alhassan designed the study, Alhassan and Osama collected the data, Mahadi and Alhassan analyzed the data, Mahadi drafted the manuscript, and Ali revised it. All were equally contributed. All authors revised and approved the version to be published and agreed to be accountable for all aspects of the work.

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**Conflicts of interest**

The authors declare that there are no conflicts of interests.

**Data and materials availability**

All data associated with this study are present in the paper.

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