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Association of diabetes, fasting glucose, and the risk of glaucoma: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: We designed this systematic review to summarize the diabetes-related glaucoma articles produced from 2011 to 2022. We further aimed to perform a meta-analysis to determine the vital association between these two parameters.

MATERIALS AND METHODS: Data sources like PubMed, MEDLINE, and EMBASE were used to find the relevant research. Reviews, case reports, and editorial letters were excluded. Articles inspection was conducted by the main author who extracted the study title and abstract in the first screening by using keywords to find the eligible articles. Heterogeneity was accessed by using the Cochrane Q test and I^2 test.

RESULTS: 10 studies were reported with 2,702,136 cases of diabetes. Out of these, 64,998 incidents of glaucoma were observed. The pooled prevalence of diabetic retinopathy was 11.7% associated with glaucoma. A significant I2 value was achieved (100%) with Cochran's Q of 183.6.

CONCLUSIONS: In conclusion, we found diabetes duration, elevated IOP, and fasting glucose levels are one of the leading risk factors for glaucoma. Fasting glucose levels and diabetes are also major contributors to elevated IOP levels.

Key Words:
Systematic review and Meta-analysis, Diabetes, Glaucoma, Fasting glucose.

Introduction

Glaucoma holds major public health importance as it causes blindness worldwide[1]. It is one of the major healthcare issues in the United States. The rate of diagnosis of glaucoma has increased since 2010. It is expected that by the year 2050, there would be 6.3 million new cases of open-angle glaucoma (OAG) in the United States[2]. According to World Health Organization (WHO) reports[3,4], the major complication of glaucoma is vision loss[3]. Of the five types of glaucoma, primary open-angle glaucoma (POAG) is considered the most frequent. Approximately 70 million people in the world is affected by primary open-angle glaucoma. Elevated intraocular pressure (IOP) and ocular hypertension (OHT) are identified as risk factors for glaucoma. Identification of the risk factors of the disease and increasing the incidence rate would not only help in early diagnosis but would also aid in developing interventions to improve the prognosis of the disease. Although the pathogenesis of this disease is still little understood, its link to the damage to the microvascular network has been reported[5,6]. Diabetes Mellitus plays a major role in damaging microvesicles and cause vascular dysregulation of the retina and the optic disc[7-9]. Uncontrolled diabetes also raises the IOP which enhances the risk of glaucoma. Overall, 476 million cases of diabetes were observed in 2017 and 571 million new cases are expected in the year 2025[10]. Diabetes continues to be one of the key risk factors for glaucoma despite the contradictory and ambiguous link. These contentious findings invite more discussion[11-14].

Diabetic retinopathy (DR) is another risk factor of primary open-angle glaucoma which remains asymptomatic in the early stages. Many advanced, asymptomatic cases of DR were reportedly diagnosed incidentally on fundal screening by ophthalmologists[15].

In 2004 a systematic review and meta-analysis[16] were conducted to evaluate the literature addressing the association of diabetes mellitus with glaucoma before 2002. Later on, meta-analyses was conducted to evaluate the relationship

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between both variables, but they were limited to literature in the early 2000s. So, this systematic review was planned to summarize the diabetes-related glaucoma articles produced from 2011 to 2022. We further aimed to perform a meta-analysis to determine the vital association between these two parameters.

Materials and Methods

This systematic review and meta-analysis followed the protocol of Meta-analysis of observational studies mentioned in Epidemiology guidelines[17]. This meta-analysis was reported according to the preferred reporting items for systematic review and meta-analysis (PRISMA). This reporting system is a minimum set of items that is supported by evidence and intended to assist scientific authors in reporting a variety of systematic reviews and meta-analyses, which are primarily used to evaluate the advantages and disadvantages of a healthcare intervention.

Literature Sources and Search Strategy

Data sources PubMed, MEDLINE, and EMBASE were used to find the relevant research. Search items were based on the established terminologies. We used the following keywords: "diabetes mellitus", "Type 2 diabetes", "insulin resistance", "blood glucose", "fasting blood glucose", "hemoglobin A1c", "intraocular pressure", "intraorbital pressure", "intraocular hypertension", "glaucoma", "diabetic retinopathy", "intraocular tension", and "hyperglycemia". Diabetic Mellitus and glaucoma were the general key terms that were further subdivided for data collection. Furthermore, manual research of reference lists was conducted to retrieve more relevant articles. No language restriction was imposed.

Inclusion and Exclusion criteria

The major objective of this article was to identify all those studies that define the association between diabetes mellitus and glaucoma. The studies which included patients aged above 18 years were selected. No restrictions were made on demographic information, diagnosis approach, and diagnostic criteria. All diabetic patients were considered, regardless of the type. No restrictions were made on the definition of glaucoma. Reviews, case reports, and editorial letters were excluded. The studies about drug effects, eye surgery, and hemodialysis were excluded from the study. Also, those studies which did not include blood glucose or hemoglobin A1c were not included.

Study Endpoints

Outcomes including intraocular pressure, ocular hypertension, open-angle glaucoma or glaucoma, and diabetic retinopathy were considered as final endpoints. We selected studies with the longest follow-up.

Data Extraction

In the first phase of the articles' screening, the inspection was done. The main author extracted the study title and abstract by using keywords in order to find the eligible articles. Full-text article screening was performed in the second screening, and we extracted the information about year of publication, study type, sample size, inclusion criteria, gender and age of patients', diabetes type, and odd ratios (if meta-regression was performed). Any disagreement was settled by the third author by consensus.

Quality Assessment and Risk of Bias

Quality assessment of included research was conducted by the main author. We used Newcastle-Ottawa Quality Assessment Scale for this purpose. This scale is based on two major points: selection and compatibility. The selection involved the representation of the exposed cohort, selection of the non-exposed cohort, and exposure assessment while compatibility variable involved the analysis of the study design, outcome assessment, and follow-up period.

Statistical Analysis

Meta-analysis was performed by using the random-effect model. We used pool prevalence for measuring weighted mean and proportion with 95 % confidence intervals (CI). Studies are represented in tables. Frequency distribution is used for the representation of age, and other outcomes. Heterogeneity was assessed by using the Cochrane Q test and I^2 test. Heterogeneity was considered significant if the value of I^2 was >50%. We used funnel plot and Egger regression analysis for determining the publication bias across the studies. A p-value less than 0.05 was considered statistically significant.

Results

Characteristics of Included Studies

A total of 563 studies were selected in the initial phase of the meta-analysis. Out of these, 456 duplicate articles were excluded and the remaining 67 were considered for full-text screening (Figure 1). After the full-text screening, 10 studies were selected with 2,702,136 cases of diabetes. A total of 64,998 incidences of glaucoma were observed. Out of ten studies, five studies were cross-sectional[20,21,23-25], while one was a retrospective longitudinal study[26], two were a prospective longitudinal study[19,27], while two were longitudinal cohort study[18,22]. The study population belonged to Denmark, the United States, the United Kingdom, Hong Kong, and India. The age of patients ranged between 20 to 80 years. The study by Goldacre et al[22] did not mention the age of the participants precisely but they involved participants of a pediatric age group.

Associating Risk Factors of Glaucoma

Newman-Casey et al[18] found that diabetes mellitus and hypertension enhance the risk of developing OAG by reporting increased hazard ratios while in the same study, hyperlipidemia had a low hazard ratio of OAG risk. After adjustment of covariates, it was observed that the patient's health status, obesity, ocular conditions, and diabetes were found to be the major factors. Moreover, these factors increased the hazard ratio of developing OAG up to 35% with hypertension independently associated with a 17% increased hazard. Furthermore, co-morbidities were also reported to play an important role in increasing the risk of OAG.

In contrast, a study by Wise et al[19] observed no association between body mass index (BMI) or obesity and the risk of developing OAG. Interestingly, they highlighted a significant correlation between alcohol consumption and the risk of OAG. In the same study, age was another significant factor, the younger age population was more prone to developing glaucoma. They also found a stronger association between diabetes and POAG in multivariate analysis (IRR=1.69, 95% CI: 1.24-2.30).

In a study by Ishikawa et al[20] they observed that age, gender, BMI, and hypertension are not significantly involved in enhancing the risk of POAG. A study by Topouzis et al[21] observed a significant association between age factor and IOP with the risk of POAG (OR, 1.04 per year; $p = .048$ and OR, 1.19 per 1 mm Hg; $p < .001$, respectively). Age and duration of diabetes were

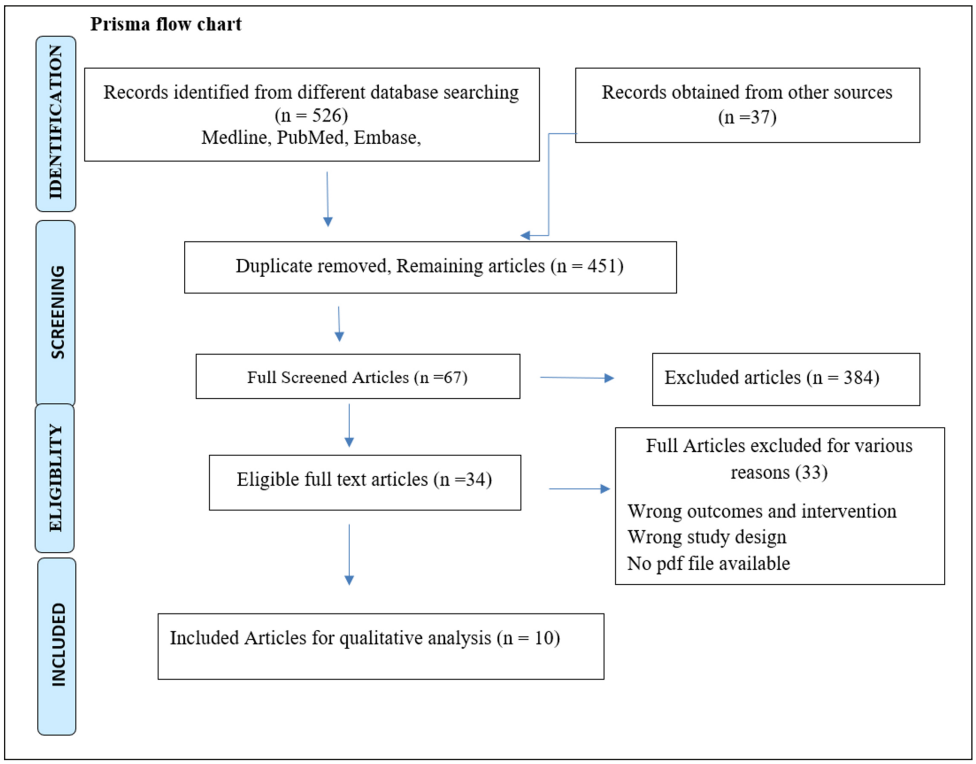

Figure 1. PRISMA technique were used for the selection mechanism schedule of articles in this study.

highly associated with OAG in the study of Dharmadhikari et al[24]. By performing binomial regression analysis, Dharmadhikari et al[24] observed diabetes was a significant predictor of glaucoma (p = 0.02). However, their study failed to demonstrate a statistically significant outcome between glaucoma and diabetes retinopathy. A multicentric study to estimate the incidence of glaucoma in type II diabetic patients was conducted by Behera et al[27]. Although, the majority of POAG cases were reported, the outcome of subtypes was not addressed. Data collected from the eye screening program was measured by the Gangwani et al[25] study and they also reported insignificant association even after adjusting age and sex. Moreover, the longitudinal retrospective study of Horwitz et al[26] found that an increased HR for glaucoma is found in patients having DR, concomitant DR, and diabetic nephropathy and hypertension (hazard ratio 1.40, 95% CI 1.24-1.55) (Table I). Subgroup analysis was performed to analyze the risk factors of glaucoma. It was found that the selected studies observed a significant association between age, hypertension, intraocular pressure, myopia, and ocular perfusion pressure. However, a significant association between diabetes mellitus and glaucoma was only observed in the current study (p = 0.08) (Table II).

Table I. Follow-up duration, diabetes type, adjusted Covariates, and major outcomes of selected studies.

Author (Year)	Follow up duration	Diabetes type	Adjusted Covariates	Exposure assessment	Main outcomes
Newman-casey et al (2011)[18]	6 years	Unclear	DM and HTN	ICD-9 codes	A significant association between diabetes and glaucoma
Wise et al (2011)[19]	12 years	Type 2		Self-report	Significant association
Ishikawa (2011)[20]	1 year	Unclear	Ocular perfusion, age, IOP, gender and DBP	HbA1c≥5.8% and/or previous diagnosis of DM	POAG
Topouzis (2011)[21]	1 year	Unclear	Age, myopia, vascular surgery, BP, and IOP	Self-report	POAG
Goldacre (2012)[22]	Data from 47 years	Unclear	Age, time period, residential area, deprivation score, and sex	Medical records	Glaucoma
Vijaya et al (2014)[23]	6 years	Unclear	Habitation, age, and sex	In-depth medical history	No significant association between glaucoma and diabetes
Dharmadhikari et al (2015)[24]	1 year	Type 2	Unclear	Medical evaluation	lipid parameters
Gangwani et al (2016)[25]	1 year	Unclear	Unclear	Fundus photographs	—
Horwitz (2016)[26]	16 years	Unclear	Hypertension, age, sex, Co-morbidities, pharmaceutical drugs, diabetic nephropathy.	Online database	Co-morbidities enhance the risk of glaucoma, and antidiabetic treatment also raised the risk. Significant association of diabetes with new onset of glaucoma
Behera UC et al (2020)[27]	1 year	Type 2	Hypertension, Neuropathy, age, sex, cardiovascular disorder, stroke, and duration of diabetes	Medical history diabetic neuropathy	Glaucoma and

Values were expressed as number and frequency (%). ASA; American Society of Anesthesiologist.

Table II. Subgroup analysis of Glaucoma risk factors involved in included studies.

	Estimate	Standard Error	Student *t*-test	*p*-value
Age	0.0137	0.8750	0.0156	0.9879
Hypertension	0.0872	1.0679	0.0817	0.9369
Diabtes Mellitus	2.0893	1.0691	1.9543	0.0864
Intraocular pressure	0.0089	0.8760	0.0101	0.9922
Myopia	1.9429	1.0691	1.8173	0.1067
Ocular perfusion pressure	0.0320	1.0691	0.0299	0.9768

Risk of Bias

Newcastle-Ottawa Quality Assessment Scale was used for quality assessment involving two major points of selection and compatibility. The selection parameter involved the representation of the exposed cohort, selection of the non-exposed cohort, and exposure assessment while the compatibility variable was assessed based on the analysis of the study design, outcome assessment, and follow-up period. This scale comprises of 7 points. This scale comprises of 7 points. The highest point was 6 in two studies[24,26], 5 points in three studies[19,20,27], 4 points in two studies[18,23], and the minimum 3 points in three studies[21,22,25] (Table III).

Meta-analysis and Subgroup Regression Model

Overall, 47% association was found between glaucoma and age. The Chi-square value of the age subgroup was observed as 0.17. The results of these studies were homogeneous as we found I^2=0% in our analysis. Meanwhile, the pooled prevalence of hypertension was observed as 49.7% with odd ratios of 0.3 (0.02 to 0.03). Significant heterogeneity among studies was noted. Overall, 39% of glaucoma cases were associated with risk factors like age, diabetes, duration, IOP, hypertension, myopia, and ocular perfusion pressure. Overall, significant heterogeneity was observed among studies as I^2 was noted as 100% (Figure 2).

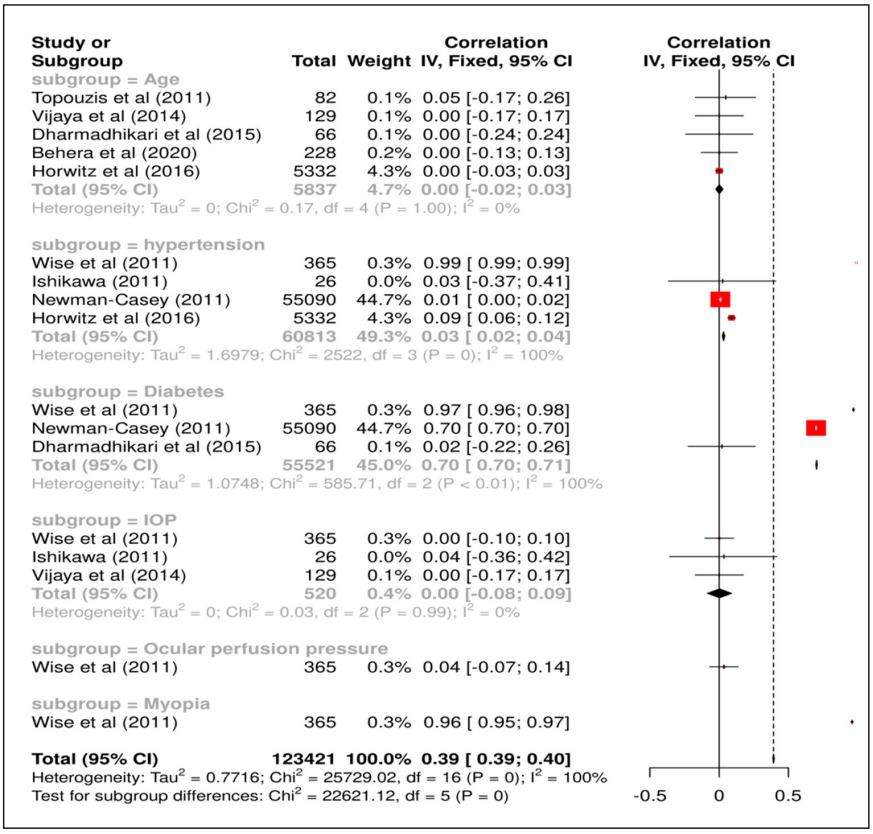

Figure 2. Forest plot of the association between diabetes and glaucoma.

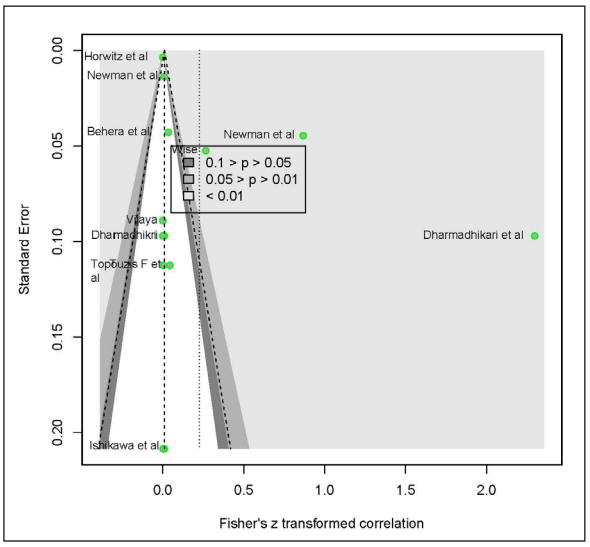

Figure 3. Funnel plot of Egger regression asymmetry analysis.

However, in the Egger regression asymmetry test, no significant publication bias was reported (p = 0.9103) (Figure 3).

Discussion

This systematic review and meta-analysis revealed that the risk of glaucoma increased in diabetic cases. A significant association was found between diabetes, intraocular pressure, and ocular hypertension. We observed that the studies of long-term follow-up had less chance of publication bias due to changes that occurred over time than cross-sectional and case-control studies. Furthermore, we observed that the duration of diabetes is the independent risk factor of glaucoma having a significant statistical association. However, a weak association was found between fasting glucose and high intraocular pressure. None of the studies mentioned glucose biomarkers associated with glaucoma. Furthermore, pre-existing diabetes was also one of the neglecting factors. Future studies should target these areas of research and fill the gap for a better understanding of glaucoma risk.

Although, none of the studies mentioned the mechanism by which diabetes could increase the risk of intraocular pressure a few studies[28,29] claimed that it could be due to hyperglycemia which results in an osmotic gradient and thus draws the excess aqueous humor into the anterior chamber. Significant factors like hyperglycemia and corneal thickness were also described by Horwitz et al[26]. It has also been reported that hyperglycemia causes autonomic dysfunction and disturbance of the trabecular meshwork function which leads to high intraocular pressure[30]. Corneal stiffness and central corneal thickness were also found in diabetic patients which raises IOP[31-33]. However, Horwitz et al[26] reported a weak correlation between increased IOP and diabetes. Studies suggested that diabetes and glaucoma are the independent risk factors for raising IOP. Likewise, the current meta-analysis also emphasizes the association between diabetes and glaucoma as the independent risk factor of increased IOP. These findings corroborate studies in which IOP is used as a defining criterion of glaucoma.

Diabetes also affects the vascular autoregulation of the retina and optic nerve which leads to microvascular damage. This results in reduced blood flow and thus impaired oxygen diffusion[34]. Ultimately, these vascular changes may elevate IOP.

The duration of diabetes is strongly associated with an increased risk of glaucoma. Diabetes imposes damage to neuronal functions which enhances the risk of glaucoma. Regular eye examinations followed by adequate management should be conducted for patients with long-standing diabetes. Furthermore, we observed that diabetes is one of the major risk factors for ocular diseases. It was observed that diabetic patients with glaucoma had frequent ophthalmologic visits.

We included three studies[24,25,25] of diabetic retinopathy in our systematic review with a total of 255,614 diabetic patients. Interestingly, no significant correlation was found between diabetic retinopathy and primary open-angle glaucoma (POAG). On the contrary, previous scientific literature claims that diabetes is one of the leading risk factors for primary open-angle glaucoma[35,36]. Moreover, the association between diabetic retinopathy and visual defects was also observed in two studies[24,25]. These studies ascertain that diabetic retinopathy could result in visual field defects. This could be due to the overdiagnosis of glaucoma. One of the included retrospectives study[26] observed that during diabetes screening 22% of patients reported an incidence of glaucoma.

While the current study reports a pooled prevalence between 0.38 and 0.38, the systematic review by Zhou et al[36] reports a pooled odd ratio of 1.35 that spans from 1.06 to 1.74. Furthermore,

Table III. Quality assessment of included studies.

Author (Year)	Representativeness of the exposed cohort	Selection of the unexposed cohort	Exposure assessments	The outcome of interest does not present at the start of the study	Control for important factors or additional factors	Outcome assessments	Follow-up period long enough for outcomes to occur	Total quality score
Newman-casey et al (2011)[18]	No	Yes	Yes	No	No	Yes	Yes	4
Wise et al (2011)[19]	Yes	Unclear	Yes	No	Yes	Yes	Yes	5
Ishikawa (2011)[20]	Yes	No	Yes	No	Yes	Yes	Yes	5
Topouzis (2011)[21]	Yes	No	Yes	Unclear	Unclear	Yes	Unclear	3
Goldacre (2012)[22]	Yes	No	Yes	Unclear	Unclear	Yes	Unclear	3
Vijaya et al (2014)[23]	Yes	No	Yes	No	Unclear	Yes	Yes	4
Dharmadhikari et al (2015)[24]	Yes	No	Yes	Yes	Yes	Yes	Yes	6
Gangwani et al (2016)[25]	Yes	Unclear	Yes	Unclear	Unclear	Yes	Unclear	3
Horwitz (2016)[26]	No	Yes	Yes	Yes	Yes	Yes	Yes	6
Behera et al (2020)[27]	Yes	No	Yes	No	Yes	Yes	Yes	5

they observed a statistically significant link between diabetes and an increased risk of POAG, but in our analysis, the *p*-value for POAG was insignificant ($p > 0.05$). As a result, our study demonstrates that diabetes is one of the independent significant risk factors and that the development of diabetic retinopathy does not necessarily imply the presence of POAG. According to a study by Abikoye et al[37] glaucomatous diabetic eyes have three times increased chance of developing diabetic retinopathy. The results of different research by Griffith et al[38] showed that POAG had the highest likelihood of DR of any subtype. Furthermore, Nakamura et al[8] observed that POAG had the highest likelihood of DR of any subtype.

Conclusions

In conclusion, this meta-analysis found strong evidence in support of a positive association between glaucoma and diabetes. We determined that fasting glucose levels and diabetes are also independent contributors to elevated IOP levels. Patients suffering from diabetes for a long time period show elevated IOP. Among these patients fasting glucose levels were one of the leading risk factors for developing glaucoma. However, no significant association was found between diabetes retinopathy and POAG. We recommended regular eye screening for patients having diabetes since age to reduce morbidity.

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Conflict of Interest
The authors declare no conflict of Interest.

Ethics Approval
Not applicable.

Authors' Contribution
Conceptualization: Abdulrahman AlDarrab, Othman Jarallah Al Jarallah and Hani Basher AlBalawi; data collection: Othman Jarallah Al Jarallah; Data Analysis: Hani Basher AlBalawi, Manuscript write up and review: Abdulrahman AlDarrab and Othman Jarallah Al Jarallah, Project administration and supervision: Hani Basher AlBalawi.

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