Original Research Article

Prevalence of Corneal Arcus in Patients Younger Than 50 Years with Non-Alcoholic Fatty Liver Disease in Gorgan, Northeast of Iran

Running title: Corneal arcus in non-alcoholic fatty liver disease

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ABSTRACT

Introduction: Corneal arcus caused by lipid deposition around the cornea has been proposed as an early marker for several metabolic disorders and even cardiovascular events. Non-alcoholic fatty liver (NAFLD) is a common health problem diagnosed by elevated liver enzymes and abdominal ultrasound findings. This study was conducted to assess the prevalence of corneal arcus in patients with NAFLD in Gorgan, northeast of Iran. **Materials and Methods:** This cross-sectional study was performed on 200 NAFLD patients younger than 50 years of age who were referred to hospitals of Gorgan between March 2014 and February 2015. Diagnosis of NAFLD was based on liver function test and abdominal ultrasound examination. Presence of corneal arcus was evaluated by slit-lamp examination.**Results:** Overall, corneal arcus was found in 91 patients (45.5%). Presence of corneal arcus was significantly correlated with smoking, opium use, and family history of NAFLD. After controlling the confounding variables (diabetes, hypertension, smoking, hyperlipidemia, age, gender, ethnicity and body mass index), we found that corneal arcus is significantly associated with history of ischemic heart disease and family history of fatty liver disease. **Conclusion**s: Presence of corneal arcus in patients with NAFLD younger than 50 years is significantly associated with having a history of ischemic heart disease and family history of fatty liver disease.

KEYWORDS: Corneal arcus, Non-alcoholic fatty liver disease (NAFLD), Liver enzymes

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INTRODUCTION

Corneal arcus is a harmless, gray-white circular deposition of cholesterol, triglycerides, phospholipids and a small amount of apolipoprotein B in the peripheral cornea [1-3]. Although it does not usually affect vision, it is a recognized as a sign of hyperlipidemia when observed in individuals younger than 50 years of age [2, 4].

In 1852, Virchow suggested corneal arcus as a risk factor for cardiovascular disease (CVD). Corneal arcus formation shares some similarities with atherosclerotic processes [4]. Previous studies on this issue have limited sample size or lack serial examinations or long-term follow-up. However, prospective follow-ups for CVD events provided the opportunity to examine the relationship between corneal arcus and cardiovascular events in the Framingham Heart Study [4]. A recent study showed that corneal arcus is associated with aging and altered lipid metabolism [3, 5]. Presence of corneal arcus before age of 60 years is related to increased intima-media thickness in the carotid arteries of males with hypercholesterolemia [2]. A prominent corneal arcus could be an indicator of dyslipidemia or familial

hypercholesterolemia. However, it is not clear which component or components of lipid profile correlate with this condition in dyslipidemic patients [2].

No large prospective study has yet investigated whether corneal arcus could predict risk of ischemic vascular disease and mortality in the general population. This is of great clinical importance since diagnosis of corneal arcus is simple and inexpensive [3].

The prevalence of metabolic syndrome and obesity is increasing worldwide. Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome with a rising prevalence [6]. In addition, NAFLD affects cardiovascular, metabolic, renal and endocrine systems [7]. This cross-sectional study was designed to evaluate the prevalence of corneal arcus in individuals younger than 50 years with NAFLD.

MATERIALS AND METHODS

Study population

This cross-sectional study was performed between March 2014 and February 2015, on 200 subjects (80 males, 120 females) younger than 50 years of age with NAFLD in Gorgan, Iran.The ethics committee of Golestan University of Medical Sciences approved the study protocol. All participants signed the informed consent.

Diagnosis of fatty liver disease

Diagnosis of NAFLD was made based on ultrasound examination and liver function test (AST, ALT).

Detection of corneal arcus:

Slit-lamp examination of the eyes was performed by an ophthalmologist. The results were classified into grade 0 (no corneal arcus), grade 1 (corneal arcus in upper or lower part of the cornea), grade 2 (corneal arcus in both upper and lower part of the cornea), grade 3 (corneal arcus as a ring), and grade 4 (overt corneal arcus seen by naked eye).

Statistical analysis

Data were entered into SPSS (version 19) and logistic regression analysis was used to evaluate the association between corneal arcus and variables such as gender, ethnicity, underlying diseases, body mass index (BMI), and past medical and family history. Variables with P-values less than 0.2 in the primary analysis were analyzed by multivariate analysis.

RESULTS

Mean (standard deviation) age of the subjects was 39.74 (6.89) years. Corneal arcus was found in 91 subjects (45.5%). There was no relationship between corneal arcus and gender, ethnicity, BMI, hyperlipidemia and diabetes mellitus. However, corneal arcus was significantly associated with hypertension, smoking, opium use, history of ischemic heart disease, a family history of fatty liver disease, and serum low-density lipoprotein (LDL) and total cholesterol levels (Table 1).

Table 1. Univariate analysis of variables associated with corneal arcus in patients with NAFLD

Variables	Corneal arcus (%)	P-value
Sex		
Male	48.8	0.18
Female	43.3	
Ethnicity		
Fars	44.4	1
Turkmen	62.1	
Sistani	34.5	
Diabetes mellitus		

+ _	56.8 42.9	0.13
Hypertension + _	 62.2 42.9	 0.04
History of ischemic heart disease + _	 82.9 37.6	 0.001
Smoking + _	 70 43	 0.56
Opium use + +	 71.4 56.5	 0.04
Family history of fatty liver + _	 59.5 35.3	 0.001
Hyperlipidemia + _	 47.9 39.7	 0.29
BMI ≥ 30 kg/m2 <30 kg/m2	 49.6 40	 0.21

After adjusting the confounding factors, multivariate analysis showed that having a history of ischemic heart disease (OR=5.86, CI 95%=2.134-16.092; P=0.001) and family history of NAFLD (OR=2.570, CI 95%=1.322-4.751; P-value=0.005) is significantly correlated with presence of corneal arcus. In addition, a significant statistical relationship was seen between serum levels of total cholesterol and LDL-C and corneal arcus grade (Table 2).

Table 2. Association of serum total cholesterol and LDL-C levels with different grades of corneal arcus in patients with NAFLD

Grade of corneal arcus	Mean (SD)	
	Total cholesterol	LDL-C
0	206.83 (22)	109.85 (22.36)
1	209.25 (23.48)	117.93 (20.84)
2	223.33 (24.63)	131.67 (25.49)
P-value	0.02	0.02

DISCUSSION

In our study, corneal arcus was detected in 45.1% of NAFLD patients younger than 50 years. Having a history of ischemic heart disease and family history of fatty liver disease was significantly correlated with presence of corneal arcus. Detection of corneal arcus in subjects younger than 60 years has been thought to be associated with hyperlipidemia and thickening of the carotid arteries [2,4]. However, the results of previous studies in this regard vary widely. Study of Hashemi et al. estimated the prevalence of corneal arcus as high as 23.3% in 300 randomly selected individuals from north of Iran. They also found that corneal arcus is significantly more prevalent in older subjects and males. Moreover, they found that corneal arcus is significantly correlated with older age, male gender, diabetes, smoking, outdoor activity, and higher systolic and diastolic blood pressure [8].

Another study in Iran reported the prevalence of corneal arcus as 74% among 165 recent myocardial infarction patients (mean age: 62 years). The mentioned study reported that the degree of corneal arcus is significantly associated with older age and high levels of total cholesterol. However, after adjusting for age, they found no association between presence of corneal arcus and gender, hypertriglyceridemia, fasting blood sugar, and systemic hypertension [9].

Similar results have been reported by studies from other parts of the world. In a population-based study on 40-80 years old South Asian Indians, Ang et al. performed slit-lamp examination on 3397 cases to examine whether corneal arcus could predict CVD. They found that older age, male gender, high total cholesterol level, hypertension, and cigarette smoking are significantly associated with corneal arcus. After adjusting the mentioned risk factors, corneal arcus was found to be significantly associated with CVD (OR: 1.31) even in cases with a low Framingham risk score [10]. It is worth noting that most of the aforementioned studies had no follow-ups. In a large cohort study in Denmark, Christoffersen et al. followed-up 12745 individuals aged 20-93 years for about 22 years to examine the predictive role of xanthelasma and corneal arcus in ischemic vascular disease. At baseline, ischemic vascular disease was absent and 24.8% of the patients had corneal arcus [3]. They concluded that corneal arcus is not an independent predictor of CVD.

Our results showed a significant positive correlation between grade of corneal arcus and dyslipidemia, indicating that cases with high grades of corneal arcus have higher serum level of LDL-C and total cholesterol. These results are similar to the results of some previous studies [2, 11].

CONCLUSION

We found that corneal arcus in NAFLD patients aged younger than 50 years is significantly associated with dyslipidemia, history of ischemic heart disease, and family history of NAFLD. Since this was a cross-sectional study, we could not conclude the presence of corneal arcus as a sign of hyperlipidemia or cardiovascular disease. Therefore, cohort studies should be conducted to determine whether corneal arcus is associated with dyslipidemia and cardiovascular events in young individuals.

CONFLICT OF INTEREST

This article has been derived from a medical doctorate thesis approved by the Golestan University of Medical Sciences, Iran.

AUTHORS' CONTRIBUTIONS

NB performed physical examination for diagnosis of corneal arcus. AN performed

physical examination for diagnosis of liver disease and interpreted the data regarding the NAFLD diagnosis. SB wrote the manuscript. RH collected the data and interviewed the patients. All authors read and approved the final manuscript.

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