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# Patent foramen ovale is associated with an increased NAFLD risk for health of young men

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## To cite this article:

Erkan Kibrisli, Sinan İşcen, Salim Ozenc, Adem Parlak. Patent Foramen Ovale is Associated with an Increased NAFLD Risk for Health of Young Men. *American Journal of BioScience*. Special Issue: Chemical Biology. Vol. 2, No. 6-1, 2014, pp. 35-38.

doi: 10.11648/j.ajbio.s.2014020601.16

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**Abstract:** Between March 2012 and July 2013, 1000 asymptomatic young military male underwent hepatic ultrasonography and echocardiography at Medical Check-up Center for general young health screening. Blood biochemistry, arterial blood pressure and anthropometric measurements were studied. All analyses were performed using the statistical package SPSS 15.0, where the statistical significance was assessed at the two-tailed 0.05 threshold. It was found that among 1000 persons, 60 had patent foramen ovale (PFO) and 110 subjects had symptoms of nonalcoholic fatty liver disease (NAFLD). The PFO-group consisted of 20 male with 33.3% of NAFLD symptoms, while the group without PFO consisted of 90 male with 9.6% of NAFLD symptoms only. There were significant differences between two groups:  $p < 0.001$ . Moreover, such factors as the mean age, BMI, triglycerides, hemoglobin, and aspartate aminotransferase level, the mean HDL cholesterol, alanine aminotransferase, platelet count did not differ between the two groups. The main cause of the pathogenesis of nonalcoholic fatty liver disease (NAFLD) has not been sufficiently elucidated. Serotonin of plasma is removed from circulation in capillary beds, predominantly in the lung. Nevertheless, metabolism of serotonin can be by-passed by patent foramen ovale (PFO) that can lead to NAFLD. Therefore, the aim of this study was to test the hypothesis that echocardiographic diagnosed PFO predicts the subsequent NAFLD, which can be diagnosed by ultrasonography. The statistical analysis of the 1000 young male supports the hypothesis that PFO can be associated with increased NAFLD risk for the health of young men.

**Keywords:** Non-Alcoholic Fatty Liver Disease (NAFLD), Patent Foramen Ovale (PFO), Serotonin

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## 1. Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses various stages of the liver injury ranging from hepatic steatosis through steatohepatitis to cirrhosis<sup>1</sup>. Insulin resistance and obesity represent the most important risk factors for the development of NAFLD<sup>2</sup>. The prevalence of NAFLD has been estimated in the range of 20 to 35% of the general adult population in Western countries and it is almost certainly increasing. Excess in liver fat is an independent risk factor for cardiovascular disease, insulin resistance, pre-diabetes and type 2 diabetes (T2DM)<sup>3,4</sup>. Increase the prevalence of obesity and T2DM, particularly

among younger people, ensures that cases of NAFLD-illness will grow also in the future<sup>5</sup>. In a recent study it was shown that serotonin can be implicated in the regulatory process of reactive oxygen species of NAFLD. The decrease in catabolism of serotonin resulted in increased levels of reactive oxidative species and necroinflammation in an animal NAFLD model<sup>6</sup>. Serotonin in plasma is removed from circulation in capillary beds, predominantly in the lung<sup>7</sup>. Nevertheless, metabolism of serotonin can be by-passed by patent foramen ovale (PFO) that can lead to NAFLD.

PFO is a congenital cardiac lesion that frequently persists also into adulthood<sup>8-10</sup>. Although most patients with PFO are asymptomatic, a variety of clinical manifestations may be associated with PFO, most importantly in the case of cryptogenic stroke. Patent foramen ovale was found in 25 to 30 % of people after an autopsy study and community-based transesophageal echocardiography (TEE) study<sup>11,12</sup>. Although most PFO-patients remain asymptomatic, they can suffer from the ischemic stroke due to a paradoxical embolism, migraine and vascular headache, decompression sickness and air embolism platypnea-orthodeoxia syndrome<sup>13,14</sup>.

The aim of this study was to test the hypothesis that echocardiographic diagnosed PFO can predict the subsequent the NAFLD, which can be diagnosed by ultrasonography - the most widely used imaging test for diagnosing hepatic steatosis.

## 2. Methods

### 2.1. Subjects

A cross-sectional statistical analysis was conducted among asymptomatic healthy young men.

Between March 2012 and July 2013, 1000 asymptomatic male subjects underwent hepatic ultrasonography and echocardiography at our Medical Check-up Center for general young health screening. Among them, 110 subjects had NAFLD, 60 had PFO. Besides, none of the young men had got history of stroke, CHD or used antihypertensive, antidiabetic, and antihypercholesterolemic medications and whose lab tests were measured and enrolled in the present study. This was a cross-sectional, retrospective, observational analysis.

### 2.2. Measurements

#### 2.2.1. Liver

Hepatic ultrasonography was performed in all patients by a single experienced radiologist, who was blinded to the participants' details. Hepatic steatosis was diagnosed on the basis of characteristic sonographic features, i.e., evidence of diffuse hyper-echogenicity of the liver relative to the kidneys, ultrasound beam attenuation and poor visualization of intra-hepatic vessel borders and diaphragm<sup>15</sup>. It is known that ultrasonography has good sensitivity and specificity for detecting moderate and severe hepatic steatosis (90–95%) (14). Grading of hepatic fat content using ultrasonography has been used in previous studies but remains somewhat subjective<sup>15</sup>.

#### 2.2.2. Laboratory

Subjects' heights and body weights were measured barefoot wearing light clothing. The body weight was measured with the subjects wearing light clothes provided by our center and the weight of the clothing was subtracted from the measured body weight. The body mass index (BMI) was calculated as the weight in kilograms divided

by the square of the height in meters. After an overnight fast, blood samples were obtained to measure the blood levels of routinely evaluated laboratory values: plasma glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, hemoglobin (Hgb), blood cell counts, and liver and kidney function tests. The simple qualitative urinalyses were performed with test papers. The chemical measurements were all performed at our center using routine laboratory methods. The estimated glomerular filtration rate (GFR) was calculated as the estimated GFR (MDRD, mL/min/1.73 m<sup>2</sup>). An average systolic blood pressure (SBP) and diastolic blood pressure (DBP) was calculated from two measurements taken with the subjects in a sitting position after a 5 min rest period.

### 2.2.3. Echocardiography

All patients were studied by standard doppler, tissue doppler, and 2-D echocardiography. All echocardiographic measurements were performed using a commercially available ultrasound system (Philips hd7xe) equipped with a harmonic 4.0 - 2.5 MHz variable-frequency phased-array transducer.

Transthoracic 2-dimensional echocardiography (TTE) was performed in all study subjects according to the published protocol adopted from the recommendations of the American Society of Echocardiography. Saline contrast injection (aerated saline solution) with provocative maneuvers (Valsalva maneuver, sniff, and cough) was used for PFO detection. A PFO considered as present, if any microbubble was seen in the left-sided cardiac chambers within 3 cardiac cycles from maximum right atrial opacification.

### 2.3. Statistical Analysis

Data are expressed as means  $\pm$  SD, medians or percentages. All subjects were categorized into PFO and non - PFO group. Results are expressed as subject number with percentage (%) and mean value with standard deviation. The unpaired *t*-test (for continuous variables) and the chisquared test or the Fisher's exact test when appropriate (for categorical variables) were used to analyze the differences among the characteristics of the participants at the time of enrollment in relation to their status of either future development of NAFLD. All analyses were performed using statistical package SPSS 15.0 (SPSS, Chicago, IL, USA) and statistical significance was assessed at the two-tailed 0.05 threshold.

## 3. Results and Discussion

The 1000 asymptomatic subjects were tested (Table 1). The mean age, BMI, triglycerides, hemoglobin, and aspartate aminotransferase level, the mean HDL cholesterol, alanine aminotransferase, platelet count did not differ between two groups.

Among the 1000 participants included in the study, 110

(11%) subjects met the clinical criteria for diagnosis of NAFLD (i.e., hepatic steatosis on ultrasound among persons who drank less than 20 g/day of alcohol, and who did not have viral hepatitis, drug induced liver disease, iron overload or other secondary causes of liver disease) and 60 (6%) subjects had PFO. The PFO group consisted of 20 subjects with 33.3% NAFLD, while the group without PFO had 90 subjects with 9.6% NAFLD. There were significant differences between the two groups ( $p < 0.001$ ).

The main cause of pathogenesis of nonalcoholic fatty liver disease has not been sufficiently elucidated. Nonalcoholic fatty liver disease is a clinic histopathological entity having histological features that resemble alcohol. NAFLD induces the liver injury, but by definition, it occurs in patients with little or no history of alcohol consumption. It encompasses a histological spectrum that ranges from fat accumulation in hepatocytes without concomitant inflammation or fibrosis (simple hepatic steatosis) to hepatic steatosis with a necroinflammatory component (steatohepatitis) that may or may not have associated fibrosis.

The statistical analysis of 1000 young male supports the hypothesis that PFO can be associated with increased risk of NAFLD for the health of young men.

As far as we know, there has not been other study showing the correlation between NAFLD and PFO.

#### 4. Limitation

Our study has some limitations. First, the number of patients having PFO was small. Second, the transesophageal echocardiogram is costly method, which was not available in our center; therefore this method has not been used for PFO detection.

#### 5. Conclusion

PFO is associated with an increased NAFLD risk for the health of young men.

#### Declaration of Interests

There is no conflict of interests.

#### Acknowledgements

This study was designed and analyzed by the author. The database was collected by the author.

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