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پایان نامه

جهت اخذ دکترای تخصصی

عنوان:

بررسی موارد کبد چرب غیرالکلی و ارتباط آن با شاخص توده بدنی و سندرم متابولیک در اهداکنندگان خون در شهر کرمان در سال ۱۳۸۴-۱۳۸۷

استاد راهنما:

جناب آقای دکتر صدرالدین لهسایی

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نگارش:

دکتر علیرضا قاضی زاده

خرداد۱۳۸۷

تقدیم به همسرم که عاشقانه ترین سرود زندگیم است و صمیمانه در این راه یاریم کرد.

با سپاس از پدر و مادرم که موفقیتم را مرهون تلاش بی وقفه شان هستم.

و با سپاس از استاد گرانقدر دکتر صدرالدین لهسایی که همواره راهنما یم هستند

چکیده

مقدمه: بیماری کبد چرب غیرالکلی بیش از پیش به عنوان شایعترین پاتولوژی درگیرکننده کبد شناخته می شود.این بیماری در حال حاضر بخش در گیر کننده کبد در سندرم متابولیک است که شامل است بر:هایپرلیپیدمی، عدم تحمل گلوکز، چاقی و هایپرتانسیون سیستمیک.

هدف: هدف این مطالعه بررسی بیماران مبتلا به کبد چرب غیرالکلی در شهر کرمان به منظور دستیابی به شیوع این بیماری به عنوان علت افزایش آلانین آمینوترانسفراز در اهدا کنندگان خون در شهر کرمان است.همچنین در این مطالعه به بررسی عوامل خطر بیماری کبد چرب غیر الکلی مانند شاخص توده بدنی و رابطه اش با سندرم متابولیک پرداخته شد .

روش بررسی: ۲۰۰۲ مورد که به طور تصادفی از بین اهدا کنندگان خون انتخاب شدند وارد مطالعه شدند.بیمارانی که بیشتر از ۲ بار سطح آلانین آمینوترانسفراز در خون آنها افزایش یافته بود مورد پیگیری قرار گرفتند.افرادی که سطح آلانین آمینوترانسفراز در خون آنها افزایش یافته بود و تست های آزمایشگاهی به منظور بررسی هپاتیت Bو C، هپاتیت اتوایمیون، کمبود آلفا آنتی تریپسین، سلیاک، بیماری ویلسون، در انها منفی بود و همچنین اشباع ترانسفرین کمتر از ۴۵%و آلکالن فسفاتاز نرمال داشتندو سابقه مصرف الکل و دارو نداشتندو شواهد کبد چرب را در سیتی اسکن کبد نشان دادند به عنوان کبد چرب غیر الکلی تشخیص داده شدند.

یافته ها: ۳۷۸ اهداکننده خون (۲۰/۵%) در اولین اندازه کیری سطح آلکالن فسفاتاز افزایش یافته داشتند. از ۳۵ بیمار که به طور پایدار سطح الانین آمینوترانسفراز خون آنها افزایش یافته بود در ۲۲ مورد (۶۲/۹%)کبد چرب غیرالکلی تشخیص داده شد.میانگین شاخص توده بدنی۵/۷± ۳۱/۱۸در بیماران مبتلا به کبد چرب غیرالکلی بود و کبد چرب غیر الکلی با سندرم متابولیک در ارتباط بود.

نتیجه گیری: کبد چرب غیر الکلی شایعترین تشخیص در اهدا کنندگان خون کرمانی با سطح افزایش یافته آلانین آمینوترانسفراز در خون است.

واژه های کلیدی:کبد چرب غیر الکلی،آلانین آمینوترانسفراز، اهداکنندگان خون، شاخص توده بدنی.

Assessment of NAFLD cases and its correlation with BMI and Metabolic syndrome in Healthy Blood Donors in Kerman.

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) has been increasingly recognized as the most common pathological conditions affecting the liver. NAFLD is now recognized as the hepatic component of the metabolic syndrome, which includes hyperlipidemia, glucose intolerance, obesity, and systemic hypertention. The aim of this study was to do an assessment of NAFLD cases to determine the prevalence of NAFLD as a cause of elevated alanin aminotransferas in healthy blood donors in kerman and also the risk factors of NAFLD such as BMI, and its correlation with metabolic syndrome in these subjects.

Methods: 2002 randomly selected blood donors included in this study. Subjects with more than two times elevated serum ALT level chose for further follow up. Subjects with persistently elevated ALT level and negative laboratory results for viral hepatitis B, C, autoimmune hepatitis, alpha 1 antitrypsin deficiency, celiac, wilson's disease, transferrin saturation <45% , normal Alkalin phosphatase and a negative history of alcohol consumption and medication; who had evidence of liver steatosis on CT-Scan were presumed NAFLD.

Results: 378 donors (20.5%) had elevated ALT levels at first measurement. In 35 cases (from 105 subjects) with persistently elevated serum ALT level, in 22(62.9%) NAFLD was the diagnosis. Mean of BMI was 31.18 ± 5.7 in NAFLD subjects and NAFLD was correlated with metabolic syndrome in these subjects.

Conclusion: NAFLD is the most common diagnosis for subjects with elevated serum ALT level in healthy blood donors in Kerman, Iran.

INTRODUCTION

The spectrum of non-alcoholic fatty liver disease (NAFLD) , encompasses simple fatty liver, NASH (non-alcoholic steatohepatitis) and NAFLD-associated cirrhosis. Although large epidemiologic studies of NAFLD are lacking and the prevalence of NAFLD in the general population is undefined, NAFLD probably is the most common liver disorder in the world, affecting 2.8% to 24% of the general population, including overweight children and adolescents.(1)

Non-alcoholic fatty liver disease (NAFLD) has been increasingly recognized as the most common pathological conditions affecting the liver. In concert with the increase in Body Mass Index (BMI) in developed countries that has occurred during the last decades, more and more individuals referred for evaluation of abnormal liver tests are found to have NAFLD.(2-3)

A minority of patients with NAFLD develop liver cirrhosis but NAFLD is probably the most common underlying cause of cryptogenic cirrhosis.(2-5)

Patients with NAFLD have an increased cardiovascular mortality as well as increase in liver related complication compared with matched controls.(2)

Non-alcoholic steatohepatitis is the most common cause of persistently elevated serum ALT in the asymptomatic Iranian blood donors in Tehran.(6)

Most patients with NAFLD have multiple risk factors including obesity,type 2 diabetes mellitus and hyperlipidemia, although some lack all recognized risk factors. NAFLD is now recognized as the hepatic component of the metabolic syndrome, which includes hyperlipidemia, glucose intolerance, obesity, and systemic hypertention.(1)

Management of patients with NAFLD should be aimed at fighting the metabolic risk factors such as visceral obesity, hyperglycemia, type 2 diabetes mellitus and hyper- triglyceridemia.(2)

This study is an assessment of NAFLD cases to determine the prevalence of NAFLD as a cause of elevated alanin aminotransferas in healthy blood donors in kerman and also risk factors of NAFLD such as BMI, and correlation with metabolic syndrome in these subjects.

MATERIAL AND METHODS

A prospective study was carried out in the Blood Donation Center of Kerman, Iran. In one year 2002 healthy blood donors were recruited in this study.

According to the regulations of the Blood Transfusion Organization of Iran, the following individuals are not allowed to donate blood: those who have a major chronic disease, those with any mild to severe acute disease, intravenous drug users and those with a past history of non-neonatal jaundice.

We also excluded persons with positive viral markers and alcohol drinkers (intake of more than 20 g alcohol per day).

First Step:

After explanation about the aim of study and possible need for further blood tests and follow-up; by a general physician, information about demographic characteristics, detailed drug history during the past 3 months, alcohol consumption (the number and type of drinks per day) and cigarette smoking was obtained. BMI (Body Mass Intake) was measured as weight (kg) divided by height squared (m2) and categorized according to the classification of National Heart, Lung and Blood Institute of the USA as follows : under weight (<18.5 kg/m2), normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2), class I obese (30-34.9 kg/m2), class II obese (35-39.9 kg/m2) and class III obese (>= 40 kg/m2).(7)

Serum level of ALT was measured and Alanine aminotransferase more than 41 U/L were considered elevated.

From 2002 blood donors in the first step; 9 subjects were HbsAg+, 1 was HIV+, 14 were HCVAb+, and 95 were alcohol drinker; we excluded these 119 donors and also 50 donors didn't want to participate in our study and excluded too.

As a result 1839 persons included in the first step. From these 1839 donors; 378 had high serum ALT level and followed up at second step of study.

Second Step:

We invited all subjects with elevated ALT levels at the first step, in six months to recheck serum ALT level. Subjects with ≥ 2 times elevated ALT level (high ALT level in re-checking) considered as having persistent elevated ALT (6), and followed in this step.

From 378 persons who must be followed in the second step we could follow 105 persons; because of some problems happened at the time of data collecting in the first step, such as incorrect phone number or incorrect addresses that made some subjects unavailable for follow-up.

Also some of these subjects were living in other cities than Kerman and so didn't come to follow-up.

Another important problem was this fact that we should wait six months after checking serum ALT level at the first step until the second measurement at the second step so we lost some subjects because of unavailable phone numbers or displacement happened in those six months.

As a result we followed 105 subjects from 378 in the second step. From these 105 subjects 35 persons had high serum ALT level in re-checking and followed-up in third step.

Third Step:

All subjects with persistently elevated ALT levels (n=35) were invited for: physical examination, waist circumference measurement, ultrasound of liver and CT-Scan of liver and the complete laboratory tests including: serum protein electrophoresis, aspartate aminotransferase, serum Iron, total iron binding capacity, fasting blood glucose, total cholesterol, high density lipoprotein, low density lipoprotein, alpha 1 antitrypsin, anti TTG, serum ceruloplasmin, ANA and Bilirubin (direct, total), Alkalin phosphatase.

Criteria for metabolic syndrome was defined according to the NCEP ATP3 2005 definition of the metabolic syndrome: ≥3 of these items:

Glucose level ≥ 100 mg/dl or treatment for elevated blood glucose

HDL cholesterol < 40 mg/dl for men; <50 mg/dl for women or drug treatment for low HDL.

Triglycerides ≥ 150 mg/dl or drug treatment for elevated triglycerides

Obesity: waist ≥ 102 cm for men or ≥ 88 cm for women

Hypertension: blood pressure ≥ 130/85 mmHg or drug treatment for hypertension. (8)

The definition of high cholesterol and triglycerides level were based on the National Cholesterol Education Program (ATP III) criteria. (8)

Diabetes mellitus was defined according to the provisional report of the World Health Organization Consultation. (9)

All sonographies were done by an expert sonographist and fatty infiltration of the liver was graded from I to III (mild to severe). (10)

Subjects with persistently elevated ALT levels and negative test results for viral hepatitis B and C, autoimmune hepatitis, transferrin saturation <45% and a negative history of alcohol and medication; with or without fatty infiltration in their liver sonography were invited to do liver CT-Scan.

On CT-Scan, for each case the hepatic attenuation was measured by means of a random selection of 25 circular regions of interest (ROIS) on both lobes on five transverse sections at different hepatic levels (five ROIs per section). For each ROI and avoided areas of visible hepatic vascular and biliary structure to represent liver parenchymal attenuation. Our ROIs ranged from 200 to 400 mm2. the ROI values were averaged as a mean hepatic attenuation to provide an internal control, the mean splenic attenuation was also calculated by averaging three random ROI values of splenic attenuation measurement on three transverse sections at different splenic levels (one ROI per section).the largest possible ROI (size range, 200-400 mm2) was also selected to represent splenic parenchymal attenuation.the liver attenuation index (LAI) derived from the difference between mean hepatic attenuation and mean splenic attenuation, was used as a parameter for prediction of the degree of macro vesicular steatosis. LAI below 5 HU was considered liver steatosis. (11)

These subjects with persistently elevated ALT level and negative laboratory results who had evidence of liver steatosis on CT-Scan were presumed NAFLD and were refered to an expert nutritionist for weight reduction and received medication if necessary.

Table 1: The relative frequency of participants (n=2002) according to demographic characteristics BMI and sex

characteristic	Male (%)	Female (%)	p-value	Total
Mean age± SD (year)	31.65± 11.27	32.29 ±11.75	> 0.3	31.76 ± 11.31
Mean BMI ± SD (kh/m2)	25.7 ±4.4	27.2 ± 4.9	< 0.0005	26.2 ± 4.6
BMI (kg/m2)				
Underweight :<18.5	2.6%	0.6%		2.2%
Normal weight:18.5-24.9	44.8%	37.2%		43.4%
Over weight: 25-29.9	37.3%	33.3%		36,6%
Class I obesity:30-34.9	12.4%	20.7%		13.9%
Class II obesity:35-39.9	2.2%	7.4%		3.2%
Class III obesity: ≥ 40	0.7%	0.8%		0.7%

RESULTS:

In this study, which performed in one year; from 2002 healthy blood donors in the Blood Donatation Center of Kerman, information about demographic characteristics, detailed drug history during the past 3 months, alcohol consumption (the number and type of drinks per day) and cigarette smoking was obtained. BMI (Body Mass Intake) was measured and blood samples were send to the laboratory of the Blood Donation Center for checking serum ALT level.

Demographic characteristics of participants:

The relative frequency of participants (n=2002) according to demographic characteristics BMI and sex is shown in Table 1.

80.8% (n=1617) were male and 18.8% (n=376) were female and 0.4% (n=9) were not defined because of unavailable name or sex in collecting forms.

Mean age of participants was 31.76 ± 11.31 years in all participants, 31.65 ± 11.27 in men and 32.29 ± 11.75 in women which didn't differ on sex ($p>0.3$).

Education level differed from not educated to license. Education level in sex assessed and did not differ ($p> 0.2$).

BMI (Body Mass Index) in these 2002 subjects was different from 15.73 to 57.60 and mean of BMI in all subjects was 26.2 ± 4.6.

Mean of BMI in women was 27.2 ± 4.9 and in men was 25.7 ± 4.4 and so it was different between men and women ($p <0.0005$). Table-3

19.4 (n=388) of 2002 subjects were cigarette smoker, 5.3% (n=107) were opium addict and 4.7% (n=95) were alcohol drinker.

According to the explained details, persons who were HIV+ (n=1), HBSAg+ (n=9), HCVAb+ (n=14) or alcohol drinker (n=95) were excluded from study and also 50 subjects who did not want to participate. As a result, 1839 subjects included to the study.

Of 9 subjects who were HBSAg+, only 6 subjects had elevated serum ALT level (66.66%). In 14 subjects who were HCVAb+, one case had elevated serum ALT level (7.1%). The case who was HIV+, serum ALT level was normal.

Serum ALT level was measured in all subjects it differed from 5 t0 256, the mean of serum ALT level was 34.56 ± 20.22 (standard error 0.48). From 1839 cases, 378 subjects had elevated serum ALT level. The prevalence of once elevated serum ALT level was 20.55% of healthy blood donors.

From 378 persons who had elevated serum ALT level, and followed six months later in the second step for re-checking ALT level, 105 persons completed the second step because of some problems happened at the time of data collecting in the first step, such as incorrect phone number or incorrect addresses that made some subjects unavailable for follow-up.

In addition, some of these subjects were living in other cities than Kerman and so did not come to follow-up.

Another important problem was this fact that we should wait six months after checking serum ALT level at the first step until the second measurement at the second step so we lost some subjects because of unavailable phone numbers or displacement happened in those six months.

From 105 subjects who completed the second step, 70 persons had normal serum ALT level in re-checking and 35 subjects had elevated serum ALT level. In these 70 subjects with normal ALT level on re-checking, 15.7% (n=11) were female and 84.3% (n=59) were male. Mean of age in these 70

subjects was 35.2 ± 11.7 and it was different from 19 to 69 years. Mean of age in women was 34 ± 12.95. In men, it was 35.4 ± 10.9 it did not differ ($p > 0.7$). Education level was under diploma in 31.4% (n=22), diploma to license 67.1 %(n=470 and 1.4 % (n=1) after license.

Mean of BMI in this group was 25.6 ± 3.9 kg/m2 in women, 27.7 ± 3.9 in men and it did not differ between men and women ($p > 0.2$).

At third step, there were 35 subjects with persistently elevated serum ALT level. One of these 35 subjects was female (2.9%) and 34 subjects were male (97.1%). In education level 25.7% (n=9) were under diploma and 74.3% (n=26) were diploma to license.

8.6% (n=3) of these 35 subjects were cigarette smoker. Mean of BMI for this group was 28.84 ± 5.7 (SD).

We assessed these 35 subjects with liver ultrasound and liver CT-Scan according to methods we explained before. These subjects with persistently elevated ALT level and negative laboratory results for viral hepatitis B and C, autoimmune hepatitis, alpha 1 antitrypsin deficiency, celiac, wilson's disease, transferrin saturation <45% , normal Alkalin phosphatase and a negative history of alcohol consumption and medication; who had evidence of liver steatosis on CT-Scan were presumed NAFLD.

As a result 22 of these 35 (62.9%) persons presumed NAFLD and 13 subjects (37.1%) had normal CT-Scan. Only 45.7% (n=16) of these persons had evidence of steatosis on sonography. Demographic characteristics and BMI of subject with NAFLD diagnosis is shown in Table 2.

Table 2: Demographic characteristics and BMI of subject with NAFLD diagnosis

characteristic	Value
Mean age± SD (year)	36.41 ± 10.27
Mean BMI ± SD (kh/m2)	31.18 ± 5.73
BMI (kg/m2)	
Underweight :<18.5	–
Normal weight:18.5-24.9	3 (13.6%)
Over weight: 25-29.9	7 (31.8%)
Class I obesity:30-34.9	7 (31.8%)
Class II obesity:35-39.9	4 (18.2%)
Class III obesity: ≥ 40	1 (4.5%)

Although the gold standard test for diagnosis of NAFLD is liver biopsy, since we could not use biopsy as a diagnostic test in voluntary blood donors; we used liver CT-Scan as the last step of our study for diagnosis of NAFLD in subjects whose laboratory tests were negative for other etiologies of elevated ALT. By using CT-Scan as diagnostic test for NAFLD, sensitivity of sonography for diagnosis of NAFLD in our study was 72.7%, the specifity was 100%, positive predictive value was 100% and negative predictive value was 68.4%. Table 3, Fig 1.

Table 3: Liver ultrasonography on NAFLD

			NAFLD Evidence of steatosis on CT-Scan		Total
			yes	no	yes
Liver ultrasonography	normal	Count	6	13	19
		% within liver ultrasonography	31.6%	68.4%	100.0%
	NAFLD	Count	16	0	16
		% within liver ultrasonography	100.0%	.0%	100.0%
Total		Count	22	13	35
		% within liver ultrasonography	62.9%	37.1%	100.0%

Fig 1 : NAFLD on liver ultrasound and CT-Scan