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RESEARCH ARTICLE

A STUDY OF NON- ALCOHOLIC FATTY LIVER DISEASE [NAFLD] IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Term NAFLD includes fatty liver changes from steatosis to steatohepatitis, cirrhosis, hepatocellular carcinoma; histologically resembling alcohol induced liver damage, in absence of alcohol intake. Metabolic syndrome and associated co morbidities like obesity, T2DM, Dyslipidemia predisposes for NAFLD. Around 70% T2DM have fatty liver, In India, its reported to be 12.5-87.5%. Liver biopsy is gold standard for diagnosis and staging of NAFLD, since its invasive hence not used as a screening tool. Ultrasound detects hepatic steatosis with 89% sensitivity and 93% specificity, can serve as a screening tool to detect NAFLD.

Aims: 1) To Study prevalence of NAFLD in T2DM patients 2) To Study risk factors like age, duration of T2DM, BMI, WHR, Hypertension, Liver enzymes, FBS, PPBS, HbA1C and Lipid profile in both NAFLD and Control groups. 3) To correlate above risk factors in both groups.

Material and Methods: 100 Non-Alcoholic T2DM patients, 30 - 80 years, with evidence of Fatty Liver on ultrasound, formed study group (n=50) and those without Fatty Liver formed control group (n=50). Detailed clinical examination and necessary blood tests were done. 15 NAFLD patients were subjected for histopathology after liver biopsy. SPSS 17 used for analysis of continuous data variables, expressed as Mean ± SD. Student t-test for comparison of mean values. Group comparisons ANOVA and Karl Pearson Correlation was used to find statistical significance of study parameters in NAFLD and Control Groups. 'p' < 0.05 was considered statistically significant.

Results and conclusions: Prevalence of NAFLD in T2DM was 40.32 %, mostly in 5th - 6th decade and increased with duration of T2DM. Ultrasound grade I and II steatosis seen in 88% diabetics. Histopathology grade I and II steatosis seen in 86.67% and NASH grade I in 2 cases and stage I fibrosis in 2 cases. There was significant correlation of prevalence of NAFLD with obesity, abnormal liver function tests, T2DM, Hypertension, Dyslipidemia and Metabolic Syndrome.

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INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is a distinct hepatic condition that includes fatty liver changes from steatosis to steatohepatitis, cirrhosis, hepatocellular carcinoma; histologically resembling alcohol induced liver damage, in absence of alcohol intake. A disease practically unheard 3 decades ago, is now considered as one of the most common causes of chronic liver disease in industrialized world. Overall prevalence of NAFLD in western countries varies from 15-40% and in Asian countries from 9-40%.Epidemiological studies suggest the prevalence of NAFLD to be 12.5-87.5% in general Indian population, with higher incidence amongst overweight/obese and diabetic/prediabetic. Metabolic syndrome and associated co morbidities like type 2 diabetes (T2DM), obesity and dyslipidemia are predisposing factors of NAFLD; and prevalence of NAFLD has increased parallel to these epidemics. Approximately 70% T2DM patients have a fatty liver, Nonalcoholic Steatohepatitis (NASH) and fibrosis, with standardized mortality rate for death greater than that for cardiovascular disease. There is evidence that T2DM patients with NAFLD are at higher risk of developing cirrhosis compared to non-diabetic patients. In the population-based Verona Diabetes Study, cirrhosis was 4th leading cause of death and accounted for 4.4% of diabetes related deaths.[16] Chronic liver disease often identified by asymptomatic elevations of Alanine Transaminase (ALT) and Aspartate Transaminase (AST). Nonetheless, there is evidence to suggest that apparently mild elevation in levels of these enzymes may be a marker for significant liver disease. Elevation of serum transaminases has been found to be in range of 2.8%-13.3% in general populationand 7.8%-31.5%in T2DM patients. Studies have found that liver enzyme abnormalities plus T2DM constitutes a greater risk of CVDand

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renal disease. This makes diagnosis of NAFLD in T2DM patients not only essential for prevention of hepatic complications but also for prevention of CVD and renal impairment. Liver biopsy remains gold standard for diagnosisand staging of NAFLD. However, due to its invasive nature, widespread use as screening tool is not feasible. Ultrasonography hasshown to be an accurate method to detect hepatic steatosis with sensitivity of 89% and specificity of 93%.Computerized tomography, magnetic resonance imaging, and spectroscopy are other alternative techniques used for detection of hepatic steatosis; but have failed to show better accuracy and their cost and adverse effects limit their usefulness as screening tools. Liver enzymes have been used as surrogate markers of liver disease; however, their accuracy is limited. Abdominal ultrasound is widely used for screening asymptomatic patients with an incidental elevation of liver enzymes. However, it cannot establish diagnosis of NASH or stage of hepatic fibrosis. Hence we have undertaken study of NAFLD in Indian T2DM patients.

Aims and Objectives

- To Study prevalence of NAFLD in patients with T2DM.
- To Study risk factors like age, duration of DM II, BMI, WHR, Hypertension, Liver enzymes, fasting and post-prandial blood sugar levels, HbA1C and Lipid profile in both NAFLD (Study) and Control groups.
- Statistical significance of all above risk factors in the NAFLD (Study) and Control group.
- Correlation among above risk factors in NAFLD (Study) group as well as in Control group.

MATERIALS AND METHODS

Study Design: Prospective Case Control StudySAMPLING

Method: Simple Random Sampling

Among the patients attending medicine OPD & IPD of Medical College & hospital, during January 2012 to July 2013, **172** patients were Diabetic diagnosed on the basis of National Diabetes Data Group & World Health Organization criteria for the Diagnosis of Diabetes Mellitus.

The National Diabetes Data Group& World Health Organization Criteria for the Diagnosis of Diabetes Mellitus
1) Symptoms of diabetes plus random blood glucose concentration -11.1 mmol/L (**200** mg/dL) or
2) Fasting plasma glucose - 7.0 mmol/L (**126** mg/dL) or
3) HbA1C > **6.5%** or
4) Two-hour plasma glucose -11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test.

INCLUSION CRITERIA: All patients with Type 2 Diabetes Mellitus, already diagnosed & recently diagnosed, by standard criteria, between 30 to 80 years age, admitted from emergency & outdoor, to Medicine ICU & wards.

EXCLUSION CRITERIA:

1) Type 1 DM
2) Age < 30 &>80 years
3) Direct Patient Interview: For h/o Alcohol (> 20gm/day or two 30ml drinks), Hepatotoxic Drugs, Jaundice, Stroke, TPN, Jejuno-ileal bypass or Bariatric surgery & recent Pregnancy.
4) HBsAg, HCV was done to rule out Viral (or Infectious) Hepatitis.
5) ECG & ECHO was done to look for evidence of ischemic heart disease.
6) Renal Function Tests [Serum Creatinine, Blood Urea] to exclude renal disease
7) Thyroid Stimulating Hormone [TSH], Serum Anti-Nuclear Antibody [ANA] levels, Auto- Immune Hepatitis.
8) Special investigations: Serum Ceruloplasmin, Anti liver kidney mitochondrial antibody, Alpha-1 antitrypsin levels & Serum Transferrin levels. (Only in clinically suspected cases)

48 patients were having either one or more exclusion criteria & hence were excluded from the study; remaining **124** patients of type II DM formed the material of the present study. **21** patients had doubtful H/o alcohol intake having ANI Index > 0 which suggest that these patients can have the liver disease with alcohol as a etiological factor & hence these 21 patients were also not included in the study, so **103** patients of type II DM were subjected for ultrasonography examination.

All these **103** study patients were subjected to **Ultrasonography Examination**

50 non-alcoholic patients had an evidence of Fatty Liver on Ultrasonography, formed Study **Group.**

53 non-alcoholicpatients had No evidence of Fatty Liver on Ultrasonography, among them 50 patients formed **Control Group**

Selection of Study Cases

Methodology

All these patients were subjected to Detailed history and thorough Clinical examination including:

- Detection of Anthropometric Indicators: The Height (cms), Body Weight (kgs), Waist Circumference (WC) and Hip Circumference (HC) were measured. The Waist-Hip Ratio [WHR] and Body Mass Index [BMI] was calculated as:

BMI = Body Weight (kg) /Height^2 (m^2); WHR = WC (inches) /HC (inches)

- Systolic and Diastolic Brachial Blood Pressure (mm Hg)
- **Routine Biochemical Investigations**: Haemogram, Liver function tests, renal function tests, fasting and post-prandial blood sugar levels, HbA1C and Lipid profile.
- **Hepatic Ultrasonography**: Real time ultrasound was performed using LOGIQ-P6 ultrasound machine**,** with 11 L High resolution linear array probe of frequency range from 3.4-11 MHz, depth penetration of 12 cm and a foot print of 39x5 mm. Operating modes used were B mode and Color flow mode (CFM). Technical parameters including gain adjustment, placement of focal zone and optimum location of transducer were optimized for each patient. Transducer was held perpendicular to the skin surface as angling leads to poor sound penetration.
- Coupling of transducer was done with gel which produces images of thin slices of liver on screen. Imaging was performed by an experienced radiologist and images were obtained in at least 2 anatomical planes.

Interpretation of Results: NAFLD was classified based on standard predefined ultrasonography criteria:

Grade 1[Mild Steatosis]: presence of bright echoes and slightly increased heap to-renal contrast with normal vessels and absent posterior attenuation.

Grade 2[Moderate Steatosis]: presence of bright echoes and moderately increased hepato-renal contrast as well as partial blurring of vessels and early posterior attenuation.

Grade 3[Severe Steatosis]: presence of bright echoes and diffusely increased liver echogenicity with absence of visible vessels and heavy posterior attenuation and non-visualization of the diaphragm.

Liver Biopsy: A percutaneous liver biopsy was then performed using the BARD® MAX-CORE® Biopsy Instrument which is a core biopsy device).

RESULTS

In the present study, 103T2DM patients were subjected for ultrasonography for evidence of fatty liver. Among them, 50 patients had Non Alcoholic Fatty Liver Disease (NAFLD Group), and hence Prevalence of NAFLD in T2DM was 40.32 **%.** Age range = 35 - 78 years, Mean age =53.8 ± 10.587 while that in control group = 38 - 78 years, Mean age = 55.5 ± 10.792.

There were 25 males and 25 females in NAFLD group while in control group, 26 males and 24 females. In NAFLD group, 44% cases were overweight and 38% obese with Mean BMI (kg/m^2) was 28.82 ± 4.48. Also, 60% males and 84% females in NAFLD group were having abnormal WHR with prevalence of metabolic syndrome among NAFLD patients was 76%.Ultrasonographically, 25 (50%) had grade I; 16 (32%) had grade II and 9 (18%) patients had grade III steatosis. Liver biopsy done in 15 NAFLD patients were subjected for Histopathological examination, among them 8 had grade I steatosis; 5 had grade II while 2had evidence of inflammation along with Grade III steatosis.

DISCUSSION

In the present study, 124 T2DM patients were subjected for ultrasonography for the evidence of fatty liver disease, among them, 50 patients were having NAFLD, and hence the prevalence of NAFLD in T2DM was 40.32 %. Similar prevalence of 43% was obtained by Banerjee et al. However various Indian and foreign authors quoted the wide range of prevalence of NAFLD in DM type II. In Indian studies, the prevalence of NAFLD ranging from minimum12% by Duseja et al in 2005 and 22% by Amarapurkar *et al* in 2007 to maximum 87% by Prashanth et al in 2009 and 77.4% by Gupte et al in 2004. In foreign studies, the prevalence of NAFLD in general population varied from 10 to 24 percent in various countries but the same prevalence increases to 57.5 percent 25 to 74 percent 19,26 in obese persons. While it is on an average 50 percent ranging from 21 to 78 percent in patients with diabetes had NAFLD. The association of diabetes and obesity may pose an added risk among severely obese patients with diabetes, 100 percent were found to have at least mild steatosis. However in the present study there were 55 patients were obese and among them the prevalence of NAFLD was 64.4 %. These observations also resembled with Silverman JF et al in 1989.

Duration of Diabetes Mellitus Type II: In NAFLD group, mean duration of T2DM was 8.63 ± 4.711 years while in control group it was 6.23 ± 4.10. It was observed that prevalence of NAFLD increases along with increased duration of diabetes and it was statistically significant (p = 0.008)

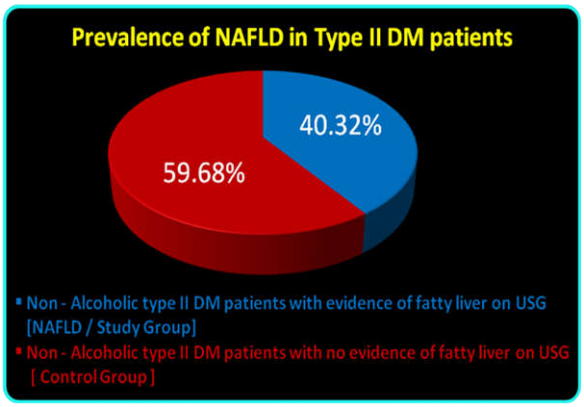
Body Mass Index [BMI]: In NAFLD group, 44% cases were overweight and 38% obese while in control group 50% cases were overweight and 10% obese. Mean BMI (kg/m^2) in NAFLD group was 28.82 ± 4.48 while in control group it was 25.98 w ± 2.82 and it was statistically significant(p = 0.000)

Waist - Hip Ratio [WHR]: 60% males and 84% females in NAFLD group were having abnormal WHR. Mean WHR in NAFLD group was 0.906 ± 0.079 while in control group it was 0.842 ± 0.085. There was high statistical significance of NAFLD with WHR. (p = 0.000)

Parameters of Liver Function Tests: ALT was raised 72% in males and 76% in females and AST was raised 72% in males and 64 % in females in NAFLD group. AST and ALT values were raised more or less same in both sexes in NAFLD group. Mean value of AST was 41.54 ± 13.12 in NAFLD group and 36.42 ± 17.16 in control group while that of ALT was 41.54 ± 13.12 in NAFLD group and 36.42 ± 17.16 in control group. There was high statistical significant correlation of NAFLD with ALT levels (p = 0.000) but it wasnot true with AST levels (p = 0.097).

Table no. 1 - prevalence of nafld in type ii diabetes mellitus patients

Total Number of Type II DM patients	Number of Non Alcoholic Type II DM patients with evidence of Fatty Liver on USG (NAFLD or Study Group)	Prevalence of NAFLD in Type II DM patients
124	50	40.32 %



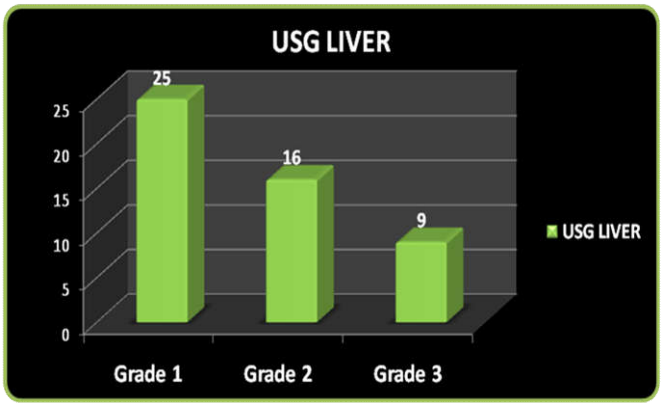
Pie Diagram showing prevalence of NAFLD in total DM II patients

Table no. 4. Histopathological findings in nafld group

HISTOPATHOLOGY FINDNGS [N = 15]		MALE		FEMALE		TOTAL	
		No. of Cases	(%)	No. of Cases	(%)	No. of Cases	(%)
GRADE	Normal	0	00.00	0	00.00	0	00.00
	Steatosis Grade 1	3	20.00	5	33.33	8	53.34
	Steatosis Grade 2	2	13.33	3	20.00	5	33.33
	Steatosis Grade 3	0	00.00	0	00.00	0	00.00
	NASH Grade 1	1	06.67	1	06.67	2	13.33
	NASH Grade 2	0	00.00	0	00.00	0	00.00
	NASH Grade 3	0	00.00	0	00.00	0	00.00
TOTAL		6	40	9	60	15	100
STAGE	Nil	6	40	7	46.67	13	86.67
	Stage 1 Fibrosis	0	00	2	13.33	2	13.33
	Stage 2 Fibrosis	0	00	0	00	0	00
	Stage 3 Fibrosis	0	00	0	00	0	00
	Stage 4 Fibrosis	0	00	0	00	0	00
TOTAL		6	40	9	60	15	100

Table No 3. Ultrasonographic Grading Of Nafld Group

ULTRASONOGRAPHIC GRADING				NAFLD GROUP	
				No of cases N = 50	Percent (%)
GRADE 1 (mild steatosis)	Slightly increased liver echogenicity	Normal vessels	Absent posterior attenuation	25	50
GRADE 2 (moderate steatosis)	Moderately increased liver echogenicity	Partial dimming of vessels	Early posterior attenuation	16	32
GRADE 3 (severe steatosis)	Diffusely increased liver echogenicity	Absence of visible vessels	Heavy posterior attenuation	9	18
TOTAL				50	100



Bar Diagram showing sonographic grading among NAFLD group

Table No.5. Comparison Of Various Study Variables (Parameters) In Nafld & Control Groups

Study Parameters	NAFLD (STUDY GROUP) n = 50		CONTROL GROUP n = 50		t test	p value
	Mean	± SD	Mean	± SD		
Age (yrs)	53.80	10.587	55.50	10.792	-0.795	0.428
Duration of DM II	8.63	4.711	6.23	4.100	2.717	0.008
BMI (kg/m^2)	28.823	4.486	25.9840	2.825	3.786	0.000
WHR	0.906	0.0799	0.843	0.0858	4.125	0.000
SBP (mm Hg)	133.06	20.952	124.60	15.546	2.293	0.024
DBP (mm Hg)	82.56	10.436	78.20	9.463	2.188	0.031
AST (IU/L)	41.54	13.129	36.42	17.166	1.675	0.097
ALT (IU/L)	49.52	19.289	32.72	12.461	5.173	0.000
AST / ALT Ratio	0.89	.2226	1.10661	0.25	-4.565	0.000
ALP (IU/L)	135.92	35.113	125.46	36.2	1.467	0.146
GGT (IU/L)	37.14	10.577	34.16	10.9	1.387	0.168
Albumin (gm/dl)	3.106	.63965	3.0720	0.62	0.271	0.787
FBS (mg/dl)	175.56	67.932	133.90	49.527	3.504	0.001
PPBS (mg/dl)	261.92	82.115	225.94	65.7	2.419	0.017
HbA1C (gm %)	8.55	1.458	7.3914	1.064	4.539	0.000
CHL (mg/dl)	207.32	78.898	168.96	50.015	2.904	0.005
LDL (mg/dl)	113.44	34.814	107.46	39.951	0.798	0.427
HDL (mg/dl)	37.96	12.787	42.74	10.468	-2.045	0.044
VLDL (mg/dl)	32.76	16.787	29.24	16.556	1.056	0.294
TGL (mg/dl)	199.62	82.892	161.62	72.256	2.444	0.016

Table No. 6. Karl Pearson Correlation among various parameters in the NAFLD Group

CORRELATIONS								
		BMI kg/m^2	WHR	AST IU/L	DBP mmHg	ALT IU/L	AST/ALT Ratio	TGL mg/dl
BMI kg/m^2	Pearson Correlation	1	.552**	.484**	.223	.478**	-.132	.425**
	Sig. (2-tailed)		.000	.000	.119	.000	.362	.002
	N	50	50	50	50	50	50	50
WHR	Pearson Correlation		1	.422**	.078	.456**	-.231	.451**
	Sig. (2-tailed)			.002	.590	.001	.106	.001
	N		50	50	50	50	50	50
AST IU/L	Pearson Correlation			1	.222	.836**	-.141	.256
	Sig. (2-tailed)				.120	.000	.329	.073
	N			50	50	50	50	50
DBP mmHg	Pearson Correlation				1	.208	-.016	.190
	Sig. (2-tailed)					.148	.910	.186
	N				50	50	50	50
ALT IU / L	Pearson Correlation					1	-.617**	.281*
	Sig. (2-tailed)						.000	.048
	N					50	50	50
AST/ALT Ratio	Pearson Correlation						1	-.078
	Sig. (2-tailed)							.592
	N						50	50
TGL mg/dl	Pearson Correlation							1
	Sig. (2-tailed)							
	N							50
** Correlation is significant at the 0.01 level (2-tailed).								
*. Correlation is significant at the 0.05 level (2-tailed).								

Fasting and Post-prandial Blood Sugar and Hba1c Levels: In NAFLD group, mean values of FBS (mg/dl) was 175.56 ± 67.93, PPBS (mg/dl) 261.92 ± 82.11 and HbA1C (gm %) 8.55 ± 1.458 while in Control group, mean values of FBS (mg/dl) 133.90 ± 49.527, PPBS (mg/dl) 225.94 ± 65.699 and HbA1C (gm %) 7.39 ± 1.064. There was high statistical significant correlation of NAFLD with FBS (p = 0.001), PPBS (p = 0.017) andHbA1C (p = 0.000) levels.

Hypertension: In NAFLD group, mean SBP (mm Hg) was 133.06 ± 20.952 while in control group it was 124.60 ± 15.546 andmean DBP (mm Hg) in NAFLD group was 82.56 ± 10.436 while in the control group it was 78.20 ± 9.463. There was statistical significance of NAFLD with both systolic and diastolic hypertension. (p = 0.024 for SBP), (p = 0.031 for DBP).

Dyslipidemia: In NAFLD group, mean value of Cholesterol (CHL) was 207.32 ± 78.898 (mg/dl) while in Control group it was 168.96 ± 50.015 (mg/dl). There was statistically significant correlation of NAFLD with Cholesterol. (p = 0.005). In NAFLD group, mean value of HDL was 37.96 ± 12.787 (mg /dl), while in Control group it was 42.74 ± 10.468 (mg/dl). There was statistically significant correlation of NAFLD with HDL levels (p = 0.044). In NAFLD group, mean value of Triglyceride (TGL) was 199.62 ± 82.892 (mg/dl) while in Control group it was 161.62 ± 72.256 (mg/dl). There was statistically significant correlation of NAFLD with Triglyceride levels. (p = 0.016)

Metabolic Syndrome: In NAFLD group, prevalence of metabolic syndrome was 76% while in control group = 30%.

Ultrasonographic Grading of Steatosis: 25 (50%) had grade I; 16 (32%) had grade II and9 (18%) patients had grade III steatosis.

Histopathological Findings in Nafld Group: Only 15 cases were subjected for Histopathological examination, Among them 8 had grade I steatosis (3 males, 5 females); 5 had grade II (2 males, 3 females), while 2 (1 male,1 female) patients had evidence of inflammation along with Grade III steatosis and hence included in the category of NASH Grade I. Among 15 cases, 9 (60%) females and 6 (40%) males had steatosis with and without inflammation, so the prevalence of NAFLD and NASH was more in females than that in males. Moreover fibrosis was not observed in any male patient but stage I fibrosis along with steatosis and inflammation was present in 2 (13.33%) females hence indicating its female predominance.

Correlation of Nafld with Various Study Parameters: There was statistical significant correlation of NAFLD with various study parameters like Duration of DM II, BMI, WHR, SBP, DBP, ALT, AST/ALT RATIO, FBS, PPBS, HbA1C, CHL, HDL andTGL levels. However, there was no statistical significant correlation of NAFLD with various parameters *Age***,** AST, ALP, GGT, Albumin, LDL and VLDL levels.

Conclusion

The prevalence of NAFLD in type II DM was 40.32 %, predominantly seen in 5th and 6th decade, and increased with duration of T2DM. Among NAFLD patients, ultrasonographically grade I and II steatosis was predominant in 88% diabetics; Histopathologically grade I and II steatosis was present in 86.67% with female predominance and NASH grade I in 2 cases and stage I fibrosis in 2 cases. There was significant correlation of prevalence of NAFLD with overweight, truncal obesity and generalized obesity, abnormal liver function tests and AST/ALT ratio, uncontrolled T2DM (FBS, PPBS, HbA1C), Hypertension, Dyslipidemia (Cholesterol, HDL, triglyceride levels) and Metabolic Syndrome.

There was no significant correlation of prevalence of NAFLD with Age, Serum AST, ALP, GGT, Albumin, LDL and VLDL levels.

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