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Is Hypothyroidism an Overlooked Risk Factor for Non Alcoholic Fatty Liver Disease: A Cross Sectional Study from South India

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ABSTRACT

Background: NAFLD is emerging as one of the leading causes of end stage liver disease worldwide. Metabolic syndrome is one of the central mechanism in the development of NAFLD. Hypothyroidism is one of the conditions associated with metabolic syndrome. In this study we assess the NAFLD induced by hypothyroidism.
Methods: This cross sectional study was conducted in tertiary care hospitals attached to Bangalore Medical College and Research Institute, India. 44 patients including both clinical and subclinical hypothyroidism, who were non-diabetic and with no significant alcohol intake, were included in the study. The level of NAFLD was assessed by ultrasound and Fibroscan and the same was compared between clinical and subclinical hypothyroid patients.
Results: On comparing the Ultrasonography grading of hepatic steatosis between the clinical and subclinical hypothyroidism group it was found that a significantly higher grade ($p<0.05$) of hepatic steatosis was seen in the clinical hypothyroidism group i.e 11 out of 29 subjects had grade III hepatic steatosis (37.9%)
Out of the 29 subjects in the clinical hypothyroidism group, F2 F3 and F4 fibrosis grade was seen in 5, 5 and 6 individuals respectively. While in the subclinical group 14 out of the 15 individuals had F0 to F1 grade of fibrosis. There was a significantly higher ($p<0.0.5$) fibrosis score in Clinical hypothyroidism group when compared to subclinical group
Conclusion: In our study we observed that Clinical and Subclinical Hypothyroidism are independent risk factors for the development of NAFLD. There was significantly higher level of NAFLD in Clinical Hypothyroidism patients when compared with Subclinical Hypothyroidism subjects. Hence treatment of thyroid dysfunction can serve to prevent the progression of NAFLD

Key Words: *NAFLD; Hypothyroidism; Metabolic syndrome; Fibroscan*

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INTRODUCTION

Non alcoholic fatty liver disease (NAFLD) is currently one of the most common causes of liver dysfunction worldwide. Non alcoholic fatty liver disease has an estimated worldwide prevalence to be around 24%, where in South America has the leading contribution followed by the Middle East, Asia, the USA and Europe in decreasing order [1]. The prevalence of Non alcoholic fatty liver disease is estimated to be around 9-32% in the general Indian population [2]. Hypothyroidism is a condition where in there is deficiency in the production of the thyroid hormones. The Worldwide prevalence of Clinical hypothyroidism is between 0.2% -5.3% in Europe and 0.3%- 3.7% in the USA [3]. Sub clinical hypothyroidism has higher worldwide prevalence ranging from 3-12% [4]. In the Indian population, the prevalence of Clinical Hypothyroidism is around 11% while that of subclinical hypothyroidism is around 8% [5].

Accumulation of fat (first hit) followed by oxidative injury (second hit) has been proposed as the mechanism for the development of Non Alcoholic fatty liver disease [6]. But now it is believed that the actual mechanism is more complex than these mere 'hits'. Thyroid hormones are known to play an important role in the lipid metabolism and insulin resistance, both of which can cause the above mentioned 'hits' and lead to the development of Non Alcoholic fatty liver disease. Hypothyroidism has still not been established as a sole driving factor for the development of Non Alcoholic fatty

liver disease. The results of the many studies have been inconclusive regarding the association between thyroid dysfunction and Non alcoholic fatty liver disease.

AIMS AND OBJECTIVES

Study is being conducted to assess the level of Non alcoholic fatty liver disease among Clinical and Subclinical Hypothyroidism. Also, to correlate the severity of Non alcoholic fatty liver disease between Clinical and Subclinical Hypothyroidism

MATERIALS AND METHODS

Study Design: Cross Sectional study

Study location: Hospitals attached to Bangalore medical college and research institute (BMCRI), Bangalore.

Sample size: 44 patients who gave consent for the study and satisfied the inclusion criteria

Inclusion Criteria:

- All patients who have given written informed consent
- All patients aged 18-60 years
- All Patients clinically and biochemically diagnosed (measured by Chemiluminescence Immunoassay) with Hypothyroidism and subclinical hypothyroidism irrespective of treatment with thyroid replacement medication

F. Exclusion Criteria:

- Patients who did not give written informed consent
- Age less than 18 years
- Presence of Hepatitis B and C infection , HIV infection
- Acute hepatitis
- Patients with Type 2 Diabetes mellitus
- Excessive alcohol consumption – Men more than 30g/day and Women more than 20g/day
- Use of drugs like oral contraceptive, amiodarone, tamoxifen, corticosteroids and methotrexate
- History of any autoimmune disorders

G. Sampling method:

44 patients diagnosed with Clinical or subclinical hypothyroidism attending hospitals attached to BMCRI who were willing to participate in the proposed study after taking informed written consent during the period of November 2019 to May 2021.

H. Methods of Data Collection:

After obtaining ethical clearance and approval from the Institutional Ethics Committee of BMCRI, written informed consent was taken from the patients. A detailed history and clinical examination was performed to identify all the necessary parameters and relevant investigations was done. Hypothyroidism and subclinical hypothyroidism was clinically and biochemically diagnosed. Nonalcoholic fatty liver disease was diagnosed on the basis of clinical examination and ultrasound of Abdomen. The level of Non alcoholic fatty liver disease will be assessed using Fibroscan fibrosis score. Detailed physical and systemic examination was carried out. Each subject underwent relevant investigations and the data were noted in dedicated proforma.

I .Assessment tools:

- Blood investigation - Thyroid function tests, Liver function tests, Fasting and post prandial sugars, Fasting lipid profile, Serology - HBsAg and HCV, HIV
- Ultrasound Abdomen to look for level of hepatic steatosis
- Fibroscan to assess the level of non alcoholic fatty liver disease using fibrosis score

J. Outcome measures:

Fibroscan will be used to assess the level of NAFLD using Fibrosis score (**Table 1**) as follows:

- Fibrosis score F0 to F1: No liver scarring or mild liver scarring
- Fibrosis score F2: Moderate liver scarring
- Fibrosis score F3: Severe liver scarring
- Fibrosis score F4: Advanced liver scarring (cirrhosis)

Table 1: Fibrosis score interpretation

Disease	Fibrosis stage and approximate cutoff value			
	F0 to F1	F2	F3	F4
Hepatitis B	2 to 7	8 to 9	8 to 11	18 or higher
Hepatitis C	2 to 7	8 to 9	9 to 14	14 or higher
HIV/HCV co-infection	none	7 to 11	11 to 14	14 or higher
Cholestatic liver	2 to 7	7 to 9	9 to 17	17 or higher
NASH or NAFLD	2 to 7	7.5 to 10	10 to 14	14 or higher
Alcohol	2 to 7	7 to 11	11 to 19	19 or higher

ETHICAL CONSIDERATIONS:

This study was approved by the institutional ethics committee of Bangalore medical college and research institute (BMCRI), Bangalore.

RESULTS

The results of the study are summarised in the Tables 2-15 and Figures 1, 2

Table 2: Distribution of the Subjects Based on Age

Age	Frequency	Percent
23 to 30 yrs	11	25.0
31 to 40 yrs	15	34.1
41 to 50 yrs	8	18.2
52 to 60 yrs	7	15.9
> 70 yrs	3	6.8
Total	44	100.0

Table 3: Distribution of the Subjects Based on Gender

Gender	Frequency	Percent
Females	28	63.6
Males	16	36.4
Total	44	100.0

Table 4: Distribution of the Subjects Based on Thyroid Function

	Frequency	Percent
HT	29	65.9
SHT	15	34.1
Total	44	100.0

Table 5: Distribution of the Subjects Based on Bmi

BMI	Frequency	Percent
Normal weight	10	22.7
Overweight	13	29.5
Obesity	21	47.7
Total	44	100.0

Table 6: Distribution of the Thyroid Profile

	N	Minimum	Maximum	Median	IQR
T3 (nmol/L)	44	.08	5.10	1.0500	.50
T4 (pmol/L)	44	1.20	11.00	6.0500	3.11
TSH (mU/L)	44	.49	100.00	6.05	16.08

Table 7: Distribution of the Blood Sugar Levels

	N	Minimum	Maximum	Median	IQR
FBS (mg/dl)	44	79.00	102.0	90.00	4.00
PPBS (mg/dl)	44	82.00	141.0	102.00	13.50

Table 8: Distribution of the Lipid Profile

	N	Minimum	Maximum	Median	IQR
Total cholesterol (mg/dl)	44	132.00	300.00	188.00	96.50
LDL (mg/dl)	44	68.00	261.00	88.00	130.50
HDL (mg/dl)	44	34.00	74.00	44.00	9.75
VLDL (mg/dl)	44	16.00	62.00	38.00	22.00
Triglycerides (mg/dl)	44	79.00	246.00	166.00	38.50

Table 9: Distribution of the Lft

	N	Minimum	Maximum	Median	IQR
Total Bilirubin (mg/dl)	44	.02	1.90	0.40	.49
Direct Bilirubin (mg/dl)	44	.01	.50	0.13	.10
Total Protein (g/dl)	44	5.80	8.00	7.10	.40
Albumin (g/dl)	44	3.20	5.30	4.00	.40
AST (IU/L)	44	10.00	41.00	24.00	8.75
ALT (IU/L)	44	9.00	42.00	22.00	8.00
ALP (IU/L)	44	18.00	99.00	46.00	34.00

All the patients included in the study were negative for Hepatitis B, C and HIV infection .

Table 10: Distribution of the Subjects Based On Usg Grade

USG GRADE	Frequency	Percent
GRADE I HEPATIC STEATOSIS	26	59.1
GRADE II HEPATIC STEATOSIS	6	13.6
GRADE III HEPATIC STEATOSIS	12	27.3
Total	44	100.0

Table 11: Distribution of the Subjects Based On Fibrosis Grade

FIBROSIS GRADE	Frequency	Percent
F0 TO F1	27	61.4
F2	6	13.6
F3	5	11.4
F4	6	13.6
Total	44	100.0

Table 12: Comparison of the Tsh, Bmi, Total Cholestrol, Triglycerides Levels Based On Usg Grading of Hepatic Steatosis

	USG	N	Minimum	Maximum	Median	IQR	p value
TSH	Grade I	26	0.49	7.00	3.60	3.35	0.00*
	Grade II	6	5.80	24	19.5	8.83	
	Grade III	12	14.0	100	33.6	21.69	
BMI	Grade I	26	19.6	37.8	24.7	6.31	0.00*
	Grade II	6	20.3	34	29.23	8.9	
	Grade III	12	27.1	41	35.7	7.58	
TOTAL CHOLESTEROL	Grade I	26	132	300	173	73	0.003*
	Grade II	6	162	260	181	50	
	Grade III	12	180	300	240	70	
TRIGLYCERIDES	Grade I	26	132	300	173	73	0.001*
	Grade II	6	162	260	181	50	
	Grade III	12	180	300	240	70	

*significant

Table 13: Comparison of the Tsh, Bmi, Total Cholestrol, Triglycerides Levels Based On Fibrosis Grading

	Fibrosis Grade	N	Minimum	Maximum	Median	IQR	p value
TSH	F0 TO F1	27	0.49	7.00	3.6	3.5	0.028*
	F2	6	16.30	24.00	19.5	5.73	
	F3	5	14.00	29.20	18.00	9.30	
	F4	6	38.0	100.0	38.65	18.50	
BMI	F0 TO F1	27	19.6	37.8	24.7	5.94	0.041*
	F2	6	20.3	34	29.24	6.43	
	F3	5	32	37.1	35.4	3.05	
	F4	6	30.6	41	37.8	9.35	
Total Cholesterol	F0 TO F1	27	132	300	176	106	0.013*
	F2	6	162	280	181	55	
	F3	5	240	300	240	55	
	F4	6	180	300	225	89.3	
Triglycerides	F0 TO F1	27	79.00	246.00	155.00	42.00	0.043*
	F2	6	148.00	192.00	176.00	26.00	
	F3	5	162.00	192.00	180.00	17.00	
	F4	6	154.00	240.00	195.00	50.00	

*significant

Table 14: Cross-Tabulation of Usg Grading with Ht/Sht

USG		HT/SHT		Total
		HT	SHT	
GRADE I hepatic steatosis	Count	12	14	26
	%	41.4%	93.3%	59.1%
GRADE II hepatic steatosis	Count	6	0	6
	%	20.7%	0.0%	13.6%
GRADE III hepatic steatosis	Count	11	1	12
	%	37.9%	6.7%	27.3%
Total	Count	29	15	44
	%	100.0%	100.0%	100.0%
Chi-square value- 11.16				
p value-0.004*				

*significant

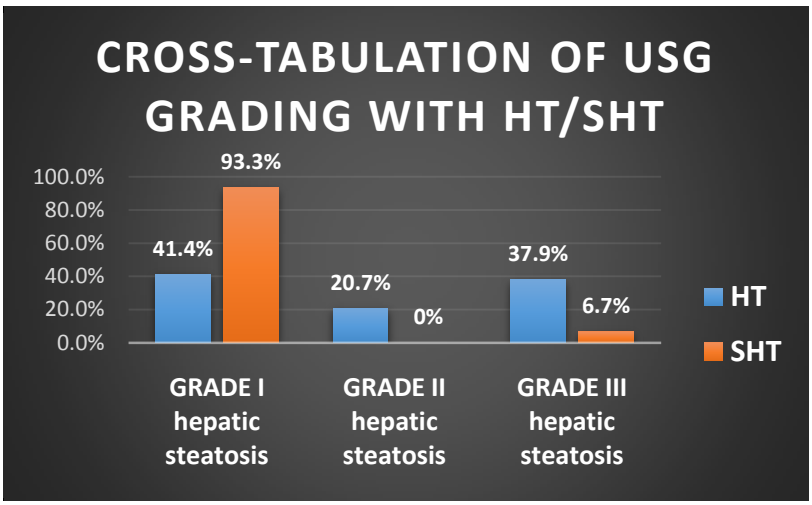

Figure 1: Cross-Tabulation of Usg Grading with Ht/Sht

Table 15: Cross-Tabulation of Fibrosis Grading with Ht/Sht

Fibrosis Grade		HT/SHT		Total
		HT	SHT	
F0 TO F1	Count	13	14	27
	%	44.8%	93.3%	61.4%
F2	Count	5	1	6
	%	17.2%	6.7%	13.6%
F3	Count	5	0	5
	%	17.2%	0.0%	11.4%
F4	Count	6	0	6
	%	20.7%	0.0%	13.6%
Total	Count	29	15	44
	%	100.0%	100.0%	100.0%
Chi-square value- 10.29				
p value-0.016*				

*significant

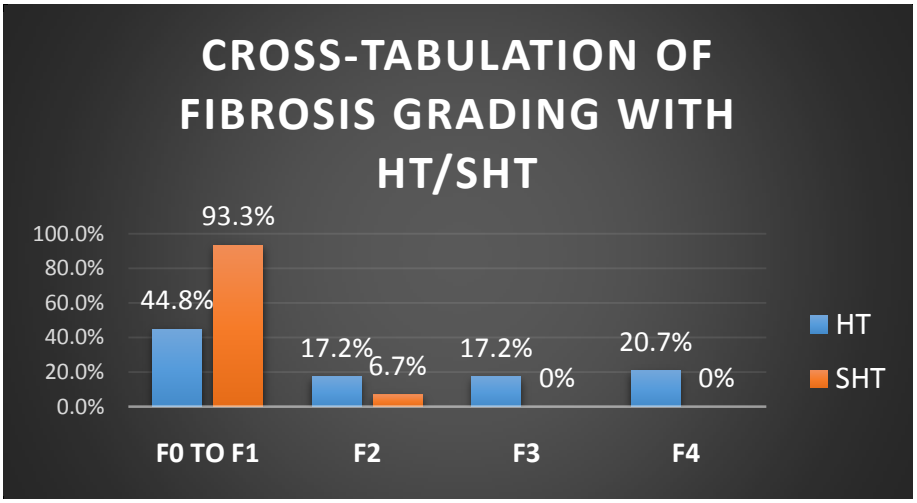

Figure 2: Cross-Tabulation of Fibrosis Grading with Ht/Sht

DISCUSSION

The first proposed mechanism for NAFLD was attributed to 'two-hit' hypothesis wherein a first hit stage of hepatic steatosis is followed by a second hit of oxidative injury to ultimately lead to NAFLD. The current view is that the actual pathogenesis is much more complex rather than a simple step wise process. It is believed to be an interplay of many pathogenic pathways varying between individuals. This can also explain the varied phenotype of the disease among different individuals. A state of excess glucose and fatty acids can exceed the liver's capacity to metabolize them . This will

lead to their accumulation and generation of toxic metabolite products which include free radicals and toxic lipid products. These cause Endoplasmic reticulum stress in hepatocytes , leading to hepatocellular injury [7-12].

The free fatty acids in the hepatocytes acts as reactive oxygen species and increases the mitochondrial β-oxidation and cytochrome P-450 4A and cytochrome P450 2E1 levels. The mitochondrial oxidative stress leads to steatohepatitis and fibrosis by three main mechanisms, namely (i) lipid peroxidation, (ii) cytokine induction, and (iii) Faslig and induction [13, 14].

There are various pathways via which the beneficial effects of thyroid hormone on NAFLD risk can be mediated. Thyroid dysfunction is related to several cardiovascular risk factors that are in turn associated with an increased NAFLD risk (eg, higher BMI and dyslipidemia). When we add BMI and triglycerides into the model, the risk estimates of the association between thyroid function and NAFLD attenuate, indeed suggesting a mediating role of these factors.

Thyroid hormone induces intrahepatic lipolysis through lipophagy, that involves the sequestration and degradation of lipid droplets within hepatic lysosomes . Moreover, TR-mediated lipophagy enhances fatty acid oxidation, which may accelerate the clearance of liver lipids and reduce hepato-steatosis [15]. Conversely, the decreased activity of hepatic lipases that occurs under hypothyroid conditions can promote NAFLD via decreased triglyceride clearance and hepatic triglyceride accumulation [16]. In addition, the insulin resistance state associated with hypothyroidism can contribute to NAFLD by concomitantly inducing “de novo” lipogenesis and generating a flux of free fatty acids from adipose tissue to the liver [17, 18].

Major advances in molecular pathogenesis of hypothyroidism-induced NAFLD ,Significant discoveries in metabolomics, cell imaging, lipophagy, autophagy and genetically engineered mouse models have recently contributed to promoting our understanding of the TH- and TRH-mediated molecular regulation of hepatic lipid metabolism. Lipidomic signature is key to the risk of NASH progression or resolution. A consistent line of research has identified T3 as a factor protecting from lipotoxic compounds, such as ceramides and diacylglycerol, which derive from excess intracellular palmitate. Further to its action mediated by increased expression of mRNA and enzymatic activity of hepatic lipases, T3 promotes FA catabolism through hepatic lipophagy (namely autophagy of FAs in hepatocytes) to traffic lipids to lysosomes and stimulate FA-oxidation. Furthermore, autophagy may promote cell survival during starvation and upon challenge by either inflammatory or pro-apoptotic injuries. Sirtuin-1 (SIRT1) is required for TH-mediated autophagy.

Viability of hepatocytes and pancreatic beta cells critically depends on the organisms’ capacity to prevent the degeneration of mitochondria via normal mitophagy. In this regard, confocal microscopy studies showed that T3 increased both mitophagy and mitochondrial biogenesis mediated by Peroxisome proliferator activated receptor gamma coactivator 1a (PGC1a). Importantly, liver-tissue specific hypothyroidism may be a feature of NAFLD, as supported by the finding that hepatic T3 concentrations (rather than those of T4 and rT3) are decreased in rats developing NAFLD after a 12-week methionine- and choline-deficient diet. Finally, Yan et al., by leveraging a genetically engineered mouse model knock-out for TSH receptor, documented a novel extra-thyroid role of TSH in regulating triglyceride metabolism via decreased AMPK and increased activity of hepatic SREBP (Sterol regulatory element binding protein) through the cAMP/PKA/PPAR-alpha pathway .Collectively, these innovative experimental studies offer new insights into the potential molecular mechanisms and sub-cellular/molecular targets for HIN, providing strong rationale for using TH and/or thyromimetic agents to treat liver and metabolic disorders.

Subclinical hypothyroidism is characterised by elevated TSH levels with normal thyroid hormone levels. Subclinical hypothyroidism is also associated with development of significant hepatic steatosis .One mechanism being TSH mediated promotion of hepatic steatosis by upregulation of activity of SREBP. The level of Insulin resistance seen in Subclinical hypothyroidism is comparable with that of clinical hypothyroidism except for the absence of significant hyperglycemia. Insulin resistance is a well established risk factor of NAFLD which participates in the molecular pathogenesis of NAFLD. Hence Subclinical hypothyroidism is also an important aetiology for the development of NAFLD.

In our study it was found that higher BMI was associated with significantly higher grade of hepatic steatosis and higher fibrosis score. Higher TSH levels were also associated with significantly higher grade of hepatic steatosis and higher fibrosis score. Dyslipidaemia in the form of high LDL cholesterol and triglycerides was also associated with significantly higher grade of hepatic steatosis and higher fibrosis score. (Table 12 & 13)

Grade III hepatic steatosis was seen in 27.3% of the subjects while most of the subjects had Grade I hepatic steatosis (59.1%). Most of the patients had F0 to F1 fibrosis grade on fibroscan with a distribution of 61% of the total population. 6 out of 44 subejcts had F4 fibrosis grade (13.6%)

In a study conducted in The Netherlands done by Bano et al [19] it was found that lower thyroid hormone levels was associated with increased risk of developing NAFLD. Ultrasonography of liver was used to assess the level of NAFLD. Similarly a study done by Manka et al [20] found that subnormal thyroid hormone levels was associated with a higher grade of NAFLD. In this study Fibroscan was used to assess the level of NAFLD.

It was found in our study that BMI, total cholesterol and triglyceride levels were significantly higher in the Clinical Hypothyroidism than in the Subclinical group which suggests the effect of thyroid hormone on fat metabolism and metabolic syndrome

On comparing the USG grading of hepatic steatosis between the clinical and Subclinical Hypothyroidism group , it was found that a significantly higher grade of hepatic steatosis was seen in the clinical Hypothyroidism group i.e 11 out of 29 subjects had grade III hepatic steatosis (37.9%). Although most of the Subclinical Hypothyroidism patients had grade I hepatic steatosis, one patient in the group had grade III steatosis. (Table 14)

Out of the 29 subjects in the clinical Hypothyroidism group, F2 F3 and F4 fibrosis grade was seen in 5, 5 and 6 individuals respectively. While in the Subclinical group 14 out of the 15 individuals had F0 to F1 grade of fibrosis. There was significantly higher level of fibrosis in the clinical Hypothyroidism group when compared to the Subclinical group. (Table 15)

A study done by Ludwig et al [21] found similar results where in the level of NAFLD was found in both Clinical Hypothyroidism and Subclinical Hypothyroidism group. The study doesn't compare the level of NAFLD between both groups. The study used ultrasonographic grading of hepatic steatosis. Kim et al [22] found in their study that even subclinical hypothyroidism is a significant independent risk factor for the development of NAFLD. In the study, the importance of TSH levels in the association with NAFLD was emphasized.

With the rising burden of end stage liver disease due to NAFLD, it becomes pertinent to assess the risk factors which cause NAFLD. [23] There are not many studies comparing Clinical and Subclinical hypothyroidism in terms of severity of NAFLD. Hence this area is still in active research in elucidating the causal mechanisms and associations.

Study limitations

The study doesn't include the duration of thyroid dysfunction to associate with the severity of NAFLD. The study doesn't exclude patients on thyroid hormone supplementation. The study had a relatively small sample size owing to the cost of fibroscan. There was no follow up of patients to assess the response to treatment with thyroid hormone supplementation

CONCLUSION

Metabolic syndrome and its associated dyslipidemia is the main driving force for the development of NAFLD. Thyroid dysfunction in the form of Hypothyroidism is one of the major causes of Metabolic syndrome. The interplay of this puts forth Hypothyroidism as one of the potential risk factor for NAFLD. In our study we found that both Hypothyroidism and Subclinical Hypothyroidism was associated with NAFLD. And the level of NAFLD was higher in Hypothyroid patients when compared with Subclinical Hypothyroid patients. Further studies are required to establish the fact that Hypothyroidism is an independent risk factor for NAFLD.

DECLARATION

We declare that this manuscript is original, has not been previously published, and is not currently under consideration by any other journal. All authors have made substantial contributions to the study, and we have read and approved the final manuscript. We also declare that the study complies with the ethical guidelines for human research and that all necessary approvals were obtained from the relevant authorities. Any conflicts of interest have been disclosed. The study was self-sponsored.

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LIST OF ABBREVIATIONS

AMPK	Adenosine monophosphate activated protein kinase
BMI	Body mass index
CAP	Controlled attenuation parameter
CREBP	Carbohydrate response element binding protein
DNL	De novo lipogenesis
FA	Fatty acid
HDL	High density lipoprotein
IHC	Immunohistochemistry
IKK B	Inhibitor of nuclear factor kappa B
IL	Interleukin
LDL	Low density lipoprotein
LSM	Liver stiffness measurement
MDB	Mallory denk body
NAFLD	Non alcoholic fatty liver disease
NASH	Non alcoholic steatohepatitis
OR	Odds ratio
PGC1a	Peroxisome proliferator activated receptor gamma coactivator
PKA	Protein kinase A
PLPLA	Patatin like phospholipase
SIRT	Sirtuin
SREBP	Sterol regulator element binding protein
TE	Transient elastography
TG	Triglycerides
TSH	Thyroid stimulating hormone
TNF	Tumor necrosis factor
TR	Thyroid receptor
TRH	Thyrotropin releasing hormone
VLDL	Very low density lipoprotein
FBS	Fasting Blood Sugar
PPBS	Post Prandial Blood Sugar