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Original Research

Exploring the Impact of Physical Activity on Cryptogenic Steatotic Liver Disease: A Nigerian Case-Control Study.

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Abstract

Background: Cryptogenic steatotic liver disease (CSLD) is a novel subject where the liver has significant steatosis but without a known cause or abnormal cardiometabolic risk factors. It is a growing global health concern with an unclear etiology. Despite the increasing prevalence of CSLD, particularly in regions undergoing rapid urbanization and lifestyle changes, there is limited research on its risk factors in Nigeria. This study investigated the relationship between physical activity and CSLD in a Nigerian population.

Methodology: A case-control study was conducted in tertiary institutions in Zaria, Nigeria. A total of 362 participants were recruited, comprising 181 individuals with CSLD diagnosed via ultrasound and 181 age- and sex-matched healthy controls. Lifestyle, anthropometric, and biochemical data were collected, with physical activity levels classified into sedentary, mild, moderate, and strenuous categories. Statistical analyses, including chi-square tests and logistic regression, were performed to assess associations between physical activity and CSLD.

Results: There was no significant difference in age ($p = 0.5578$) or sex distribution ($p = 0.9160$) between CSLD cases and controls. However, a significant association was observed between CSLD severity and physical activity levels ($\chi^2 = 172.1$, $p < 0.0001$). Sedentary individuals had a higher risk of CSLD, while moderate physical activity was the most protective (OR: 0.001, $p < 0.001$). These findings suggest that an inactive lifestyle is a strong risk factor for CSLD.

Conclusion: Sedentary behavior is an independent risk factor for CSLD, while regular physical activity, particularly moderate exercise, is protective. Public health initiatives promoting physical activity should be prioritized to mitigate CSLD progression and its complications. Further longitudinal research is needed to explore genetic predispositions and assess the long-term impact of lifestyle modifications on CSLD outcomes.

Keywords: Cryptogenic Steatotic Liver Disease; Physical Activity; Sedentary Lifestyle; Case-Control Study; Nigeria.

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Introduction

The accumulation of adipocytes greater than 5% of total liver weight constitutes hepatic steatosis [1]. The CSLD is a novel subject where the liver has significant steatosis but without a known cause or abnormal cardiometabolic risk factors and therefore, the global world is waiting for precise identification of its causal agents by future research [2]. Cryptogenic steatotic liver disease (CSLD) represents a significant public health issue globally [2]. B-mode ultrasound is a non-invasive imaging technique commonly used to assess liver steatosis.

Unlike other liver diseases with well-defined aetiologies (such as viral hepatitis or alcohol-related liver disease), CSLD poses a diagnostic challenge due to its elusive origin [2]. As a major component of steatotic liver disease (SLD), CSLD has become increasingly prevalent worldwide [2]. The rising incidence of CSLD may likely be associated with changing lifestyles, urbanization, and shifts in dietary patterns, making it a critical area of study [2]. Despite the growing burden of CSLD, there is limited research specifically addressing its prevalence, risk factors, and optimal diagnostic approaches in the Nigerian population. Understanding how lifestyle like physical activities influences CSLD could lead to more effective prevention and management strategies tailored to local needs [2].

Ultrasound imaging is a non-invasive, cost-effective method for diagnosing liver steatosis, but its grading and interpretation can vary based on multiple factors [3]. There is a paucity of data on the effect of lifestyle factors such as physical activity on CSLD development and progression worldwide [2].

The relationship between this factor and CSLD severity as determined by ultrasound grading has not been thoroughly explored in this context [2]. CSLD may progress to metabolic dysfunction associated steatohepatitis (MASH), and even to frank liver fibrosis and hepatocellular carcinoma [2]. It is expected in the future to be the major indication for liver transplant from these complications [2]. By focusing on a Nigerian cohort, this study aimed to determine the association between CSLD and physical activity, thereby enhancing understanding and management of CSLD within the regional context.

Methodology

This was a case-control study carried out in the tertiary institutions in Zaria and the environs. A case-control study was the best option for this study to establish the association between physical activities and CSLD. The minimum sample size was calculated using the formula for a binary exposure case-control study by Sainani [4]. Therefore, 181 normal subjects with CSLD and an equivalent number of sex- and age-matched controls (normal subjects without CSLD) were studied, making for a total number of 362 subjects.

Sampling Technique: A consecutive sampling technique was employed for this case-control study. Participants were recruited consecutively as they presented for routine medical check-ups at the General Out-patient/Family Medicine Clinic of ABUTH, Zaria, and the medical centres of Ahmadu Bello University, Samaru, and Kongo campuses. A total of 3,500 individuals were initially screened, and only those who met the strict inclusion criteria after undergoing clinical, laboratory, and abdominal ultrasound evaluations were included in the study. Three hundred and sixty-two (362) apparently healthy participants were enrolled, comprising 181 subjects with ultrasound-detected cryptogenic steatotic liver disease (CSLD) and 181 age- and sex-matched controls without CSLD. This method ensured a systematic and unbiased inclusion of eligible individuals until the required sample size was achieved.

Study Population: The study was carried out in a group of adults (18 - 70 years of age) non-alcoholic and otherwise healthy subjects with ultrasound-detected steatotic liver and another (control) group of healthy subjects without ultrasound-detected steatotic liver. The patients were recruited from those who receive routine medical check-ups in the General Out-patient/Family Medicine Clinic of ABUTH, Zaria, and medical centres of Ahmadu Bello University at Samaru and Kongo campuses. The members of staff and students who fell into either of the two groups were recruited into the study.

Inclusion Criteria: Apparently healthy subjects (18 - 70 years) with ultrasound-detected steatotic liver (subjects) and those without steatotic liver (controls) were recruited at the tertiary institutions in Zaria. Exclusion Criteria: Adult healthy subjects who do not consent to the study, all patients with signs of congestive cardiac failure, previous myocardial infarction, idiopathic cardiomyopathy, pericarditis, and malignancies, severe chronic liver disease, apart from the lone finding of fatty liver on ultrasound, alanine transaminase (ALT) > 30 IU/L in men and ALT > 19 IU/L in women; acute or chronic viral hepatitis which will be ruled out via laboratory screening tests, diabetes mellitus (fasting glucose ≥ 126 mg/dl or HbA1c ≥ 6.5%) or patients on anti-diabetic drugs, particularly metformin, overweight (body mass index [BMI] ≥ 25) and underweight (mal-nourished) with BMI < 18.5, acute or chronic rheumatic, autoimmune, or infectious disease, Chronic alcohol consumption or drug abuse, renal insufficiency, i.e., glomerular filtration rate < 60 mL/min per 1.73 m^2, Human immunodeficiency virus (HIV) infection, pregnancy, systemic hypertension, Homa-IR > 1.0 Unit, waist circumference (WC) > 94 cm and > 80 cm in males and females respectively.

Ethical Considerations: Ethical approval for the study was obtained from the human Research Ethics Committee (HREC) of the Ahmadu Bello University Teaching Hospital, Zaria, Nigeria with reference No: ABUTH/HREC/CL/05. All participants provided signed informed consent before recruitment into the study. The proforma were completed by the researcher and trained assistants.

Abdominal ultrasound scan: The abdominal ultrasound scan was performed using a real-time ultrasound scanner (Mindray diagnostic ultrasound systems, Model DC-3, 2010-12, Nanshan, Shenzen, PR China) fitted with curvilinear array transducer with a frequency range of 3.5MHz. The procedure was carried out by an experienced Radiologist with 20 years in the liver and gastrointestinal radiology sub-specialty. He was blinded to the laboratory and clinical details of the participants at the time of the procedure to avoid bias. The examination of the liver was done in the supine right anterior oblique and left lateral positions in deep inspiration. The intercostal view was also employed for additional information. The presence of fat (steatosis) was recorded as a marked increase in hepatic echogenicity, poor penetration of the posterior segment of the right lobe of the liver, and poor or non-visualization of the hepatic vessels and diaphragm. The quantification of hepatic fat i.e. ultrasound bright liver score (BLS) was graded into four levels (0–3) [5].
Grade 0: normal.
Grade 1: mild steatosis which manifests as a significant diffuse increase in liver echogenicity compared to the kidney with normal visualization of the intrahepatic vessel walls and diaphragm.
Grade 2: moderate steatosis which manifests as a moderate diffuse increase in liver echogenicity compared to the kidney with poor visualization of intrahepatic vessel walls.
Grade 3: manifests as a severe diffuse increase in liver echogenicity with poor visualization of deep liver parenchyma and diaphragm.

The ultrasound BLS has been previously validated by US-guided fine needle aspiration biopsy using 20 Gauge Menghini's needles [6]. The subjects were asked to complete a questionnaire that contained basic demographic and lifestyle data (physical activity). Regarding their physical activity, we used validated tools by O'Donnell *et al* [7] to minimize potential biases. Individuals were classified as physically active if they were regularly involved in mild exercise (walking), moderate exercise (cycling or gardening), or strenuous exercise (jogging, football, and vigorous swimming) for 4 hours or more per week. Others were classified as inactive if they did not engage in any of the above activities.

Statistical Analysis: Data was analyzed with GraphPad Prism software version 6 manufactured by GraphPad Software, LLC, 225 Franklin Street, Floor 26, Boston, MA 02110, USA. Data was also summarized using the median (and interquartile range [IQR]) for skewed data and mean (±SD) for normally distributed data. Categorical variables were presented as frequencies. A comparison of significant differences between the control group and the three distinct categories of subjects with CSLD: mild, moderate, and severe, was conducted using Kruskal-Wallis with Dunn's post-hoc analysis for skewed variables. The Chi-square test for independence was used to determine relationships between variables. A p-value ≤ 0.05 was considered statistically significant. A multivariate logistic regression analysis model, weighted by years of age and sex

was conducted to establish the significance of the level of physical activity as an independent risk factor in the development of CSLD.

Results

The median (IQR) age of CSLD and control groups were 44.0 (28.5-54.0) and 44.0 (30.0-55.0) years. Wilcoxon matched pairs signed rank comparison test showed no significant difference in the ages of the two study groups ($p = 0.5578$), indicating age matching of the study participants. Table 1 shows the sex-matched distribution of subjects with CSLD and control subjects with an equal number of participants of the same sex in each group. The chi-square test indicated no significant association between the sex of the participants and the development of CSLD ($p = 0.9160$).

Table 1: Sex-matched distribution of subjects with cryptogenic steatotic liver disease (CSLD) and control subjects in Zaria, Nigeria.

Data analyzed	CSLD	Control	Total
Female	98	98	196
Male	83	83	166
Total	181	181	362

Chi-square (with Yates' correction) = 0.011, df = 1; OR = 1.000 (95% CI: 0.6613 to 1.512); p – value = 0.9160

Sociodemographic characteristics of subjects with CSLD and control subjects

One hundred and eighty-one study subjects with CSLD were categorized according to severity into mild (n = 89), moderate (n = 78), and severe CSLD (n = 14). They were studied alongside a healthy control group (n = 181). Of the subjects with CSLD, a total of 98 (54.1%) females constituted 44 (24.3%) with mild, 46 (25.4%) with moderate and 8 (4.4%) with severe CSLD. The 83 (45.9%) males with CSLD constituted 45 (24.9%), 32 (17.7%), and 6 (3.3%) with mild, moderate, and severe CSLD respectively. The chi-square test for independence showed no significant association ($\chi^2 = 1.578$, df = 3, $p = 0.6645$) between sex and development of CSLD (Table 2).

Of the subjects with CSLD, those aged 20-29 years constituted 32 (17.7%) with mild, 14 (7.7%) with moderate, and 1 (0.6%) with severe CSLD; those aged 30-39 years constituted 10 (5.5%) with mild, 13 (7.2%) with moderate and 1 (0.6%) with severe CSLD; those aged 40-99 years constituted 27 (14.9%) with mild, 15 (8.3%) with moderate and 2 (1.1%) with severe CSLD; those aged 50-59 years constituted 19 (10.5%) with mild, 28 (15.5%) with moderate and 4 (2.2%) with severe CSLD; those aged 60-69 years constituted 1 (0.6%) with mild, 5 (2.8%) with moderate and 6 (3.3%) with severe CSLD; those aged 70 years constituted only 3 (1.7%) with moderate CSLD. Forty-one (22.7%) were 20-29 years, 33 (18.2%) were 30-39 years, 40 (22.1%) were 40-49 years and 50-59 years each, 16 (8.8%) were 60-69 years while 11 (6.1%) were aged 70 years. The chi-square test for independence showed a significant association ($\chi^2 = 59.03$, df = 18, $p = 0.0001$) between age and development of CSLD (Table 2).

Bivariate analysis of the association between CSLD and physical activity.

Of the subjects with CSLD, those with mild disease included 11 (6.1%) who were physically inactive, 53 (29.3%) who had mild exercise, 17 (9.4%) who had moderate exercise, and 8 (4.4%) who had strenuous exercise; those with moderate disease included 20 (11.0%) who were physically inactive, 56 (30.9%) who had mild exercise and 2 (1.1%) who had moderate exercise; those with the severe disease include 8 (4.4%) who were physically inactive, 4 (2.2%) who had mild exercise, and 1 (0.6%) each of who had moderate and strenuous exercises. Two (1.1%) of the controls were physically inactive, 42 (23.2%), 106 (58.6%), and 31 (17.1%) had mild, moderate, and strenuous exercises, respectively. The chi-square test for independence showed a significant association ($\chi2=172.1$, df=9; $p < 0.0001$) between subjects' nature of physical activity and the development of SLD (Table 3).

Table 2: Sociodemographic characteristics of subjects with cryptogenic steatotic liver disease (CSLD) and control subjects in Zaria, Nigeria

Characteristic	CSLD			Control (n=181)	Statistics
	Mild (n=89)	Moderate (n=78)	Severe (n=14)		
Sex (%)					
Female	44 (24.3)	46 (25.4)	8 (4.4)	98 (54.1)	χ^2=1.578, df=3, p=0.6645
Male	45 (24.9)	32 (17.7)	6 (3.3)	83 (45.9)	
Age-group (%)					
20-29	32 (16.6)	14 (7.7)	1 (0.6)	41 (17.7)	χ^2=59.03, df=18, p<0.0001*
30-39	10 (5.5)	13 (7.2)	1 (0.6)	33 (18.2)	
40-49	27 (14.9)	15 (8.3)	2 (1.1)	40 (22.1)	
50-59	19 (10.5)	28 (15.5)	4 (2.2)	40 (22.1)	
60-69	1 (0.6)	5 (2.8)	6 (3.3)	16 (8.8)	
70	0 (0.0)	3 (1.7)	0 (0.0)	11 (6.1)	

Table 3: Bivariate analysis of the association between SLD and physical activity.

Parameter	Control (n=181)	SLD			Statistics
		Mild (n=89)	Moderate (n=78)	Severe (n=14)	
Physical activity					
Physically inactive	2 (1.1)	11 (6.1)	20 (11.0)	8 (4.4)	χ^2=172.1, df=9; p<0.0001*
Mild exercise	42 (23.2)	53 (29.3)	56 (30.9)	4 (2.2)	
Moderate exercise	106 (58.6)	17 (9.4)	2 (1.1)	1 (0.6)	
Strenuous exercise	31 (17.1)	8 (4.4)	0 (0.0)	1 (0.6)	

Multiple logistic regression model of lifestyle risk factors: notably, an inactive (sedentary) lifestyle was a single independent risk factor for developing CSLD. Conversely, increasing physical exercise was less associated with CSLD, with the strongest protective effect observed in moderate exercise (OR, 95% CI: 0.001 [0.00-0.002], $p < 0.001$).

Discussion

The index study shows that there is no gender factor in the relationship between physical activity and development of CSLD in the cohort which was well matched for age and sex in both CSLD and the control groups. There is no previous study yet to compare the factor of gender in the development of CSLD. However, the previous studies [8,9] on non-alcoholic fatty liver disease (NAFLD) which is a general term for steatotic liver disease (SLD) without adjustment for confounders reported a significant association between the females' gender and the development of non-alcoholic fatty liver disease (NAFLD),

The difference in the findings between their studies and the index study could be attributed to the fact that in the index study was carried on novel CSLD after adjustment for the major confounders.
The index finding on the factor of age and the development of CSLD agrees with the study by Tseng *et al* [10] on NAFLD in which age is a significant factor in the development of NAFLD. They found that the association between age and NAFLD was stronger in middle-aged individuals compared to younger individuals. Also, Park *et al* [11] study on NAFLD suggested that NAFLD may be less pronounced in

younger individuals due to their higher metabolic rate and potential for greater recovery. Most patients with CSLD are asymptomatic which is also evident from the index study as the subjects who constituted the cases group were all apparently healthy. However, malaise, fatigue, and right upper quadrant pain have been reported in a previous study on NAFLD [12].

In the index study, the Chi-square test for independence showed a significant association between subjects' nature of physical activity and development of SLD. The index study also shows that a sedentary lifestyle is an independent risk factor for CSLD. Multiple logistic regression analysis shows that increasing physical exercise is less associated with CSLD, with the most potent protective effect observed in moderate exercise. These findings agree with a comprehensive review by Stine *et al* [13], which found that Regular physical activity has been shown to reduce liver fat accumulation, improve insulin sensitivity, and decrease inflammation, which is crucial in the context of liver diseases characterised by steatosis. The same review also highlighted that engaging in at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity exercise per week can significantly reduce liver fat and improve overall liver function.

Furthermore, the index study also agrees with a study by Ryu *et al* [14] who examined the relationship between sedentary behaviour and liver health, that increased sitting time is associated with a higher risk of developing liver steatosis. Conversely, higher levels of physical activity were linked to reduced risk, emphasizing the importance of an active lifestyle in liver disease prevention and management.

Conclusion: A sedentary lifestyle is a significant independent risk factor in the development of CSLD. This factor is easily modifiable and should be emphasized to reduce the burden of hepatic failure from cirrhosis and hepatocellular carcinoma, which is the natural pathway of progression of the CSLD. The study recommends public health initiatives promoting physical activity and awareness programs to reduce CSLD prevalence. Future research should explore genetic predispositions and longitudinally assess the impact of lifestyle changes on CSLD progression.

Limitation: The index study was conducted at the tertiary health facilities. More broad-based community studies with larger sample sizes in various geopolitical zones of Nigeria are recommended to validate the index findings.

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