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The Association between Coffee Consumption and Non-Alcoholic Fatty Liver Disease: Is there a Protective Role?

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Abstract

BACKGROUND: Non-alcoholic fatty liver disease (NAFLD) is the main cause of chronic liver disease. Several studies have suggested a protective role of coffee in chronic liver disease, but their results remain controversial.

AIM: The purpose of the study was to investigate the association between coffee consumption and the prevalence and severity of NAFLD in a non-diabetic and non-alcoholic population.

METHODS: This study involved 157 participants. Cases were defined by the presence of steatosis on liver ultrasound, the severity of which was assessed by the Bright Liver Steatosis Score. Controls were defined by the absence of steatosis on liver ultrasound. All patients with cytolysis and/or cholestasis had an etiological investigation (serologic testing for Hepatitis B virus and hepatitis C virus infection, and autoimmune investigation). All participants underwent liver ultrasound, clinical assessment (blood pressure, waist circumference, and body mass index (BMI)), and biological assessment (Complete Blood Count, lipid profile test, liver function tests, and Fasting Blood Glucose [FBG]). Dietary assessment was conducted using a food frequency questionnaire, coffee consumption was dichotomized into present or absent and then categorized according to the number of cups consumed per day.

RESULTS: The study included 94 NAFLD and 63 controls, the two groups were comparable in demographic characteristics. The means of systolic blood pressure, BMI, waist circumference, Aspartate Transaminase, Alanine Transaminase (ALT), Gamma-Glutamyl transferase (GGT), alkaline phosphatase, and FBG were significantly higher in the NAFLD group. The study of the association between coffee consumption and NAFLD showed a significant decrease in the risk of its occurrence (Odds Ratios [OR] = 0.39) and its severity (OR = 0.32) in coffee consumers, mainly in those consuming 3 or more cups. In multivariate analysis, the following factors were associated with increased prevalence of NAFLD: Metabolic syndrome, high mean levels of alkaline phosphatase, GGT, ALT, FBG, BMI, and waist circumference. However, Green tea consumption was not associated with either prevalence or severity of NAFLD (OR = 1.02, p = 0.82).

CONCLUSION: Coffee consumption is inversely associated with the prevalence and severity of NAFLD. Further prospective studies are needed to establish a cause-effect relationship between coffee and NAFLD.

Introduction

Non-alcoholic steatotic liver disease (NAFLD) is the most common chronic liver disease worldwide. It is responsible for hepatic and extra-hepatic mortality and poses diagnostic and therapeutic problems [1].

NAFLD presents a histological spectrum that begins with lipid accumulation in hepatocytes (simple steatosis) without significant inflammation or liver fibrosis, with the potential to progress to non-alcoholic steatohepatitis (NASH) and subsequently to the development of cirrhosis with an increased risk of decompensation and hepatocellular carcinoma [2].

The prevalence is increasing, estimated at between 25% and 30% of the world population [2], with the decline of viral hepatitis C, hepatic steatosis has become the leading cause of chronic liver disease worldwide and the second indication for liver transplantation in the United States of America [3]. Its pathophysiology is complex and mainly related to insulin resistance. Obesity and metabolic syndrome are the main risk factors [4].

Diagnosis of NAFLD requires prior elimination of other causes of hepatic steatosis such as excessive alcohol consumption (≥30 g/d in men, ≥20 g/d in women), steatogenic treatments, and other causes of chronic liver disease [5].

Several pharmacological agents against liver steatosis have been used in practice, such as metformin, Vitamin E, pioglitazone, and pentoxifylline. However, evidence for their efficacy remains limited [6].

At present, no pharmacological treatment is approved for the treatment of this disease, and all therapeutic recommendations are based on compliance with hygienic-dietary rules, weight loss, and physical activity [2].

Coffee is the most consumed beverage in the world and its consumption is said to reduce mortality and the risk of metabolic syndrome and Type 2 diabetes [7].

Several studies have suggested a protective role for coffee against chronic liver disease, hepatic fibrosis, and hepatocellular carcinoma; however, this finding comes from observational studies and remains controversial, particularly in the presence of confounding factors such as diabetes and low alcohol consumption [8].

This study aims to assess the association between coffee consumption and the prevalence and severity of NAFLD in a non-diabetic population who has never consumed alcohol. Secondarily, we aimed to study the other factors associated with NAFLD.

Methods

This case–control study was conducted from December 2020 to December 2021 at Cheikh Khalifa International University Hospital, Casablanca, Morocco. The target population included 157 participants seeking care in the outpatient and inpatient units of the gastroenterology and internal medicine department. The study protocol was reviewed and approved. All patients were informed and agreed to share in the study.

Patients who had been diagnosed with NAFLD and were at least 18-year-old were eligible for inclusion criteria. We excluded from the study all individuals with viral hepatitis B or C, autoimmune hepatitis, cirrhosis of any origin, taking corticosteroids or chemotherapy or other steatogenic drugs, patients with morbid obesity (body mass index [BMI] ≥40 Kg/m), patients suffering from cancer, kidney failure, and heart failure. Alcoholics (regardless of the amount consumed daily) and diabetics were excluded from the study to eliminate these powerful confounders.

The diagnosis of NAFLD was performed non-invasively according to the presence of fatty liver in ultrasonography, the degree of liver fatty infiltration was evaluated using the bright liver steatosis (BLS) score which classified the severity of the hepatic steatosis into four grades [9] (Table 1).

Table 1: Bright liver steatosis score

Grade 0	Normal liver echogenicity
Grade 1	Diffuse increased hepatic echogenicity, but periportal and diaphragmatic echogenicity is still appreciable
Grade 2	Diffuse increased hepatic echogenicity obscuring periportal echogenicity but diaphragmatic echogenicity is still appreciable
Grade 3	Diffuse increased hepatic echogenicity obscuring both periportal diaphragmatic echogenicity

Patients with steatosis were categorized into three groups according to the BLS score (Group 1: BLS 1; Group 2: BLS 2; and Group 3: BLS 3), the group with BLS 0 was taken as a reference.

The controls were enrolled from the same hospital structure, and during the same period as the cases. We considered as controls any patient with a normal liver ultrasound, and no liver function test abnormalities.

All participants underwent the following clinical and biological assessments: Waist circumference, BMI, blood pressure, blood count, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (PAL), triglycerides (TG), total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-Cholesterol, and fasting blood glucose (FBG).

Liver ultrasound was performed with the same ultrasound machine (General Electric Voluson P8, Boston, USA), and the following parameters were analyzed: The hepatic echotexture, echogenicity, portal vein dimensions, posterior beam attenuation, portal vessel wall distinction, liver diaphragm distinction, and steatosis severity were assessed using the BLS score.

All cases with cytolysis and/or cholestasis had an etiological assessment including viral hepatitis B and C serologic testing, and autoimmune hepatitis workup (Anti-smooth muscle, Anti-mitochondrial M2, antinuclear, Anti-DNA, Anti-SLA, and anti-liver kidney microsomal antibodies).

All participants completed a semi-quantitative food frequency questionnaire. Coffee consumption was the main exposure factor in our analysis, exposure was defined as drinking one cup of coffee per day for at least three consecutive months. Coffee consumption was dichotomized into present versus absent, and then categorized according to the number of cups consumed per day (Group 0: no consumption; Group 1: 1–2 cups/day; and Group 2: ≥3 cups/day), the Group 0 (no consumption) was taken as a reference.

Metabolic syndrome was defined according to the 2009 International Diabetes Federation criteria by the presence of at least 3 of the following 5 criteria [10]: Abdominal obesity (waist circumference ≥94 cm for men and ≥80 cm for women), triglyceride level ≥1.50 g/l (or 1.7mmol/l) and/or use of specific lipid-lowering therapy, HDL-cholesterol level ≤0.40 g/l (1.03 mmol/l) in males and ≤ 0, 50 g/l (1.29 mmol/l) in women and/or specific lipid-lowering treatment, hypertension (systolic pressure ≥130 mmHg and/or diastolic pressure ≥85 mm Hg) and/or antihypertensive treatment, FBG ≥1 g/l (5.6 mmol/l), or antidiabetic treatment.

Statistical analysis

Sample size was calculated using the sample size formula for the case-control study, the margin of error selected was 0.05, with à 95% confidence interval (CI). Means and standard deviations were used to describe quantitative variables. Numbers and percentages were used to describe qualitative variables. Student's *t*-test and Chi-square test were used to compare variables between cases and controls. The association between coffee consumption and the presence of NAFLD

was estimated using binomial logistic regression and expressed as Odds Ratios (OR) and 95% CI.

Multinomial logistic regression was used to assess the association between coffee consumption (yes vs. no; Group 1, Group 2) and steatosis severity (BLS1, BLS2, and BLS3). The BLS 0 group and the group without coffee consumption were used as a reference.

The correlation between coffee consumption (the number of cups per day) and the other variables were estimated by Spearman's *r*-test for quantitative variables and by linear regression for qualitative variables. The factors that were correlated with coffee consumption and the factors that were associated with the presence of steatosis were included in the multivariate analysis. $p < 0.05$ was considered statistically significant. All analyzes were performed using Jamovi version 2.2.5.

Results

This study included 157 patients, 94 NAFLD and 63 controls, anthropometric and biochemical characteristics of participants were conducted by comparing the NAFLD group and the control group. No significant difference was observed for age and gender. No significant difference was observed for age and gender. Conversely, there was a significant difference between the two groups in the means of systolic blood pressure, BMI, waist circumference, AST, ALT, GGT, Alkaline phosphatase, and FBG. Higher means were observed in the NAFLD group with a $p \leq 0.03$. Table 2 shows the comparison between the general characteristics of cases and controls.

Table 2: Characteristics of non-alcoholic fatty liver disease patients and controls

Variables	NAFLD	controls	p-value
Age (years)	50.52 ± 15.39	45.96 ± 15.51	0.07
Man (%)	57 (60.60)	33 (52.40)	0.30
Woman (%)	37 (39.40)	30 (47.8)	
Coffee (%)	45 (47.90)	37 (58.70)	0.18
Tea (%)	71 (75.5)	47 (74.60)	0.89
SBP (mm Hg)	129.58 ± 14.27	122.41 ± 14.62	0.003*
BMI (kg/m²)	25.72 ± 5.25	22.70 ± 4.86	0.001*
Waist circumference (cm)	93.77 ± 16.60	83.92 ± 17.36	0.001*
AST (UI/l)	28.77 ± 17	23.92 ± 8.70	0.03*
ALT (UI/l)	30.39 ± 20.01	21.08 ± 10.07	0.001*
APL (UI/l)	84.32 ± 28.47	74 ± 28.73	0.02*
Gamma-GT (UI/l)	47.88 ± 20.22	40.87 ± 16.47	0.02*
Triglyceride (g/l)	1.80 ± 0.56	1.40 ± 0.66	0.38
Total cholesterol (g/l)	1.61 ± 0.65	1.44 ± 0.47	0.08
HDL cholesterol (g/l)	0.56 ± 0.38	0.60 ± 0.30	0.50
LDL cholesterol (g/l)	1.01 ± 0.56	0.88 ± 0.49	0.10
FBG (g/l)	1.15 ± 0.74	0.94 ± 0.28	0.02*
Smoking (%)	23 (24.5)	14 (74.60)	0.74
Metabolic syndrome (%)	54 (57.40)	10 (15.90)	0.001*
Arterial hypertension (%)	30 (31.90)	11 (17.50)	0.04*

Values are expressed as mean and SD for quantitative variables and as num numbers percentage for qualitative variables. Student's *t*-test and Chi-square test were used to calculate the p value. *Significant value if $p < 0.05$. NAFLD: Non-alcoholic fatty liver disease, SBP: Systolic blood pressure, BMI: Body mass index, AST: Aspartate alanine transferase, ALT: Aspartate alanine transferase, Gamma-GT: Gamma-glutamyl transferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FBG: Fasting blood glucose, SD: Standard deviation, APL: Alkaline Phosphatase.

Coffee consumption (cups per day) was associated with smoking (β =1.25, CI 95% [0.45; 2.06]; p = 0.002), we found also a significant inverse correlation between the number of cups of coffee and waist circumference, BMI, AST, and PAL levels (Table 3).

Table 3: The correlation between coffee consumption and patient characteristics

Patient characteristics	Coffee consumption (cups/day)	
	Pearson's *r*	p-value
SBP (mmHg)	−0.12	0.12
Waist circumference (cm)	−0.17	0.03*
BMI (kg/m²)	−0.20	0.01*
HDL cholesterol (g/l)	0.08	0.30
LDL cholesterol (g/l)	−0.07	0.36
Total cholesterol (g/l)	−0.01	0.83
FBG (g/l)	−0.07	0.36
AST (UI/l)	−0.19	0.01*
ALT (UI/l)	−0.12	0.12
Gamma-GT (UI/l)	−0.10	0.19
Alkaline phosphatase (UI/l)	−0.17	0.03*
Triglyceride (g/l)	−0.04	0.60

*Significant value if $P < 0.05$. SBP: Systolic blood pressure, BMI: Body mass index, AST: Aspartate alanine transferase, ALT: Aspartate alanine transferase, Gamma-GT: Gamma-glutamyl transferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FBG: Fasting blood glucose.

Association assessment between coffee consumption and the prevalence of NAFLD

In simple logistic regression, coffee consumption assessed as a binary qualitative variable (yes vs. no) was not associated with any decreased odds of NAFLD occurrence (OR = 0.60; CI 95% [0.31; 1.15]; p = 0.12). However, when we looked at coffee consumption as a quantitative variable (number of cups drunk per day) we found a significant decrease in odds of NAFLD occurrence (OR = 0.77; IC 95% [0.65; 0.90]; p = 0.002). Taking those not consuming coffee as a reference, subjects who drank three or more cups of coffee had a reduced risk for NAFLD (OR = 0.39; CI 95% [0.19; 0.83]; p = 0.015). Conversely, drinking 1 to 2 cups of coffee per day was not associated with a reduced risk of developing NAFLD (OR = 0.98; CI 95% [0.57; 3.48]; p = 0.45).

Association assessment between coffee consumption and NAFLD severity

Using BLS 0 group as reference, coffee consumption was significantly associated with a decreased odds of severe steatosis (OR = 0.38; IC 95% [0.15; 0.94]; p = 0.03). A reduction in odds was mainly observed in those who drank three or more cups per day (OR = 0.32; 95% CI [0.11; 0.89]; p = 0.03) (Table 4).

Table 4: Association between coffee consumption and severity of nonalcoholic fatty liver disease[β]

Coffee parameters	BLS[a] score		
	BLS 1	BLS 2	BLS 3
Coffee consumption□ (yes/no)	1.08	0.66	0.38
	(0.43–2.69)	(0.28–1.52)	(0.15–0.94)
	p = 0.89	p = 0.33	p = 0.03*
Group 1 (1–2 cups/day)□	3.15	1.28	0.57
	(1.03–9.62)	(0.41–3.95)	(0.15–2.15)
	p = 0.06	p = 0.66	p = 0.41
Group 2 (≥ 3 cups/day)□	0.42	0.46	0.32
	(0.12–1.37)	(0.17–1.21)	(0.11–0.89)
	p = 0.15	p = 0.11	p = 0.03*

[β]Multinomial logistic regression was used, [a]The BLS 0 group was taken as a reference, □Noncoffee consuming group was taken as a reference, *Significant if $p < 0.05$. BLS: Bright liver score.

Association assessment between NAFLD and other factors

In the multivariate analysis, the folling factors were significantly associated with an increased risk of NAFLD: Metabolic syndrome, increased mean levels of alkaline phosphatase, GGT, ALT, FBG, BMI, and waist circumference. However, lipid-related markers (total cholesterol, triglycerides, HDL, and LDL) were not associated with the occurrence of NAFLD. Green tea consumption was not associated with the presence or severity of NAFLD (OR = 1.02; 95% CI [0.80; 1.3]; p = 0.82). After adjustment for NAFLD risk factors and factors associated with coffee consumption, we reported that coffee consumption assessed as the number of cups/day was still associated with a decreased risk of NAFLD (OR = 0.62; CI 95% [0.43; 0.88]; p = 0.04) (Figure 1).

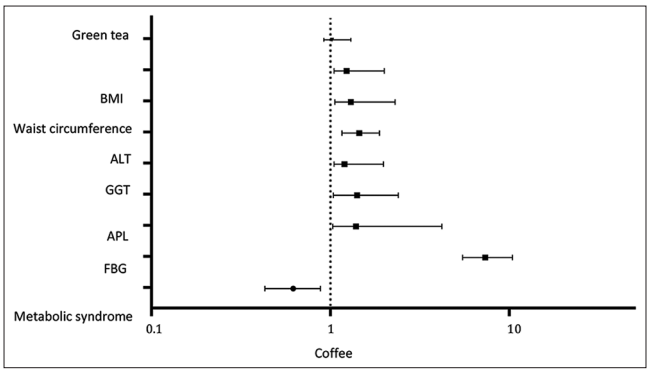

Figure 1: OR to the NAFLD occurrence. OR: Odds ratio, Note: NAFLD: Nonalcoholic fatty liver disease; BMI: Body mass index; ALT: Aspartate alanine transferase; GGT: Gamma-glutamyl transferase; FBG: Fasting blood glucose

Discussion

In this case–control study, we noticed a significant decrease in the prevalence and severity of steatosis in coffee consumers.

Several studies have examined the effects of coffee on NAFLD, with different approaches and equivocal results. In 2014, Catalano *et al*. proposed a protective role of coffee against the onset and progression of NAFLD through an observational study. In this study, steatosis was assessed using a BLS score [11]. This result agrees with our data.

The study by Zelber-Sagi *et al*. was the first prospective study to investigate the association between coffee and NAFLD using blood tests (Steatotest and Fibrotest) in addition to liver ultrasound. In contrast to our study, this work showed the lack of a significant association between coffee consumption and the prevalence of NAFLD, but showed a 51% reduction in fibrosis risk in those who consumed three or more cups of coffee (OR = 0.49 [0.25; 0.97] p = 0. 041). This inverse association was only significant in the univariate analysis, adjustment for other factors such as smoking, sugar consumption, and physical activity rendered the result insignificant, which can be explained by the relatively poorer health lifestyle of the coffee consumers, characterized by smoking and a sedentary lifestyle [12].

In a large French cohort of obese patients who had undergone bariatric surgery, it was reported that consuming regular coffee rather than espresso would play a protective role against hepatic fibrosis during NAFLD. The strength of this study was the use of liver biopsy to diagnose NAFLD and fibrosis, but its main limitation was its selectivity for obese patients, so this finding cannot be generalized [13].

In another study, which also used histology to enroll steatotic patients and assess their inflammatory stage and hepatic fibrosis, the authors concluded that while there is an inversely significant association between coffee consumption and hepatic fibrosis, coffee does not influence the occurrence of benign steatosis [14].

In a study by the North American NASH Research Network [15], coffee consumption was associated with a reduced risk of advanced histological fibrosis in patients with NAFLD and absent or mild insulin resistance, according to this result, the authors hypothesized that coffee would play its preventive role against fibrosis without necessarily going through metabolic disorders caused by insulin resistance. In our work, the inverse correlation between the number of cups of coffee consumed per day and BMI and waist circumference suggests that coffee's potential protective role is due in part to its role in reducing abdominal obesity through its effect on insulin resistance.

The positive effects of coffee on NAFLD are not unanimously supported by studies, some of which have shown the opposite of our findings. A cross–sectional study of 3000 participants showed that coffee consumption did not affect the presence or severity of NAFLD, however, this study used ultrasound to assess steatosis and the proportion of patients with severe steatosis was small [16]. According to a meta-analysis of 11 studies, coffee consumption was not associated with either the prevalence or the incidence of NAFLD [17].

On the other hand, we had as secondary objectives the assessment of other factors that would influence NAFLD; the following factors were reported as risk factors for NAFLD: BMI, waist circumference, levels of ALT, GGT, alkaline phosphatase, FBJ, and metabolic syndrome. We analyzed tea consumption with more attention because it is the beverage most commonly consumed by Moroccans, and its consumption has not been associated with the occurrence or severity of NAFLD.

The "Rotterdam study" was the first prospective study conducted in a general population to evaluate both coffee and tea consumption and the stiffness of the liver measured by transient elastometry (fibroscan®),

coffee, and tea consumption were inversely related to liver stiffness but not steatosis. In contrast with our study, green tea was associated with steatosis in univariate but not multivariable analysis [17].

At the molecular level, coffee contains more than 100 substances whose role is not yet fully understood. The best studied is caffeine, which plays an important hepatoprotective role by inhibiting steatogenesis and fibrogenesis. Experimental studies have shown that caffeine has an antioxidant capacity that allows the restoration of redox balance, and glutathione peroxidase levels [18], it also prevents hepatic fibrosis by inhibiting the expression of TGF beta and hepatic stellate cells [19], [20]. There are other substances that perform their roles independently of caffeine such as polyphenols, chlorogenic acid, and tocopherol, they have antioxidant, insulin-sensitizing, and inhibiting actions of lipid accumulation in hepatocytes [21], [22], [23].

Our study had some strengths, to the best of our knowledge, this is the first Moroccan study to assess the association between coffee consumption and NAFLD by including a population that has never consumed alcohol. The consensus definition of NAFLD tolerates low alcohol consumption (< 20 g/d in females and < 30 g/d in males), this could affect the interpretation of the results in coffee drinkers, by formally excluding from our study alcohol drinkers, we were able to avoid this powerful confounding factor. Diabetes was the second confounding factor to be excluded from the study.

However, our results must be interpreted with certain limitations. First, we have relied on liver ultrasound to diagnose hepatic steatosis, this test has a variable sensitivity between 60% and 94% depending on several parameters [24]. Second, coffee and tea quantities were rated based on the number of cups consumed per day without specifying the type and the method of preparation, this method remains subjective as the cups used may vary by demographic groups.

Conclusions

In conclusion, the relationship between coffee and steatotic liver disease is not fully understood, and the results of studies are disparate. Our work suggests that coffee drinking in inversely associated with prevalence and severity of NAFLD.

As coffee is an accessible and relatively inexpensive beverage, it could be included in dietary rules for a healthier diet and implemented as a preventative strategy if future studies were to confirm our data. But it's not yet time to comment on its nutraceutical effects. Further prospective studies are needed to establish a cause-effect relationship between coffee and NAFLD.

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