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Changes in High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL) and Cholesterol Concentration in Heavy Cannabis Users: A Single-Centre Study in Cusco, Peru

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Abstract: Background: The effect of cannabis on cholesterol and lipid balance has been reported for decades. However, there are conflicting reports on the reduction of low-density lipoprotein (LDL-C) and total cholesterol. The purpose of this study was to determine the immediate changes of *Cannabis* spp. consumption by pyrolytic route in heavy users. Methods: A cross-sectional study on 20 Peruvian heavy cannabis users (mean age: 31 ± 9.5 years). The inclusion criteria were males with an average weight of 50–70 kg, normal BMI, and having used cannabis, without association with other drugs, for at least one year with a high frequency per week (use: 4–7 days/week). High-density lipoprotein (HDL-C), LDL-C, and total cholesterol were evaluated 30 and 120 min after the administration of *Cannabis* spp. (~0.2 g by inhalation). Results: Of the total 12 (60%), 10 (50%), and 11 (55%) had desirable total cholesterol, fairly good HDL-C (40–60 mg/dL) and fairly good LDL-C (100–129 mg/dL) values, respectively. The mean basal concentration of total cholesterol, HDL-cholesterol, and LDL-cholesterol was 193.37 ± 20.18 mg/dL, 60.05 ± 6.36 mg/dL, and 129.65 ± 14.50 mg/dL, respectively. HDL-cholesterol showed progressive increases in participants with desirable HDL-C > 60 mg/dL at 30 min (10 vs. 14 participants, $p < 0.001$) and at 120 min (10 vs. 16 participants, $p < 0.001$), while LDL-C peaked in participants with concentrations <100 mg/dL at 30 min (desirable cholesterol: 0 vs. 2, $p = 0.001$). HDL-C concentration showed differences after cannabis consumption, showing increases at 30 (63.25 ± 7.68 mg/dL) and 120 min (69.15 ± 18.67 mg/dL) and total cholesterol concentration changed to 180.95 ± 19.3 mg/dL (95%CI 172.5 to 189.4) at 120 min ($p = 0.007$). Conclusions: HDL-C cholesterol increased 30 and 120 min after *Cannabis* spp. ingestion, while LDL-C and total cholesterol showed partial reductions in heavy-users from Cusco, Peru.

Keywords: cannabis; high density lipoproteins; low-density lipoprotein; cholesterol; Peru

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1. Introduction

Lipoproteins are a set of proteins responsible for the regulation of cholesterol in the human body. Alterations in these macromolecules lead to the development of dyslipidaemias, a set of lipid disorders that favour the mis-storage of lipids in cells and are important risk factors for the development of chronic diseases such as metabolic syndrome and cerebrovascular diseases [1,2].

The effect of cannabis on cholesterol and lipid balance has been reported for decades [3]. The activity of cannabis on cholesterol fractions, such as high-density lipoprotein (HDL-C) or low-density lipoprotein (LDL-C), by reducing their concentrations, has been proposed [4–6]. On the other hand, the increased risk of lipoprotein-related cardiovascular diseases in cannabis users has been described [7,8].

Reduced reverse cholesterol transport (RCT) and smaller HDL-C size have been found in heavy cannabis users, which may affect the homeostasis of cholesterol [9]. It has recently been described that Δ9-tetrahydrocannabinol (Δ9-THC) has caused inflammation, vascular dysfunction, and oxidative stress in cell cultures and rats due to the activity of cannabinoid receptor 1 (CB1/CNR1), causing an increased risk for cardiovascular diseases such as atherosclerosis [10]. However, it has also been shown that a common CB1/CNR1 haplotype prevents HDL-C lowering and that α,α'-dihydro-3′,4,5′-trihydroxy-4′-methoxy-3-isopentenylstilbene (HM1), a new stilbenoid isolated from *Cannabis sativa* L. allows a better RCT-related protein expression by regulating cholesterol-based processes [11,12].

Although the health benefits of cannabis have been described more frequently in the last decade [13], the effects of cannabis use on lipoproteins, glucose and triglycerides are not fully elucidated or available for all medicinal and recreational cannabis-using communities [14]. During the last 20 years, Latin America has undergone an economic, political, and social change regarding the use of cannabis at all levels, increasing not only the market for the acquisition and sale of cannabis, but also the number of users due to progress in decriminalization and legalization of some marijuana products [15]. With the change in legislation on the medicinal use of cannabis in Peru [16,17], there is a new population that would be accessing this therapeutic resource. Therefore, it is necessary to understand the effects of cannabis consumption on lipoproteins, as the health characteristics of the user population are not fully understood.

Furthermore, when describing the physiological alterations of metabolites linked to the endocannabinoid system and the processes derived from this system, the effects of immediate consumption of cannabis via the pyrolytic route are not yet fully clarified; this is primarily due to the difficulty of accessing experimental trials in recreational or medicinal cannabis users in countries with strict regulations or where cannabis use has been decriminalized.

In this study, we determined the immediate changes of *Cannabis* spp. consumption by pyrolytic route in heavy-users in Cusco, Peru. The hypothesis of the study included (a) that cannabis consumption produces an increase in HDL-C and (b) that total cholesterol and LDL-C could vary according to the time of control after cannabis smoking. Given that no study in Peru, to our knowledge, has examined these human lipoprotein changes, it is certainly important to assess these effects of Cannabis.

2. Materials and Methods

2.1. Study Design, Subjects, and Samples

We designed a cross-sectional study of 20 volunteer heavy cannabis users (mean age: 31 $\pm$ 9.5 years). Although there is no single definition of heavy cannabis use, in this study we considered a pattern of weekly or more frequent use of any form of cannabis (i.e., smoking, vaporizing) for at least 12 months. Demographic data are shown in Table 1. Participants were asked to participate in the study using social networks, and those who did so satisfied the following inclusion criteria: males aged 20–45, of Peruvian nationality, with an average weight of 50–70 kg and having used cannabis for at least one year with a high frequency per week (daily or inter-daily use).

Table 1. Baseline characteristics of cannabis users (n = 20). * significant $p < 0.05$.

Variable	Categories	f	%	p-Value *
Age (year)				
	<25	3	15	
	25–35	12	60	0.088
	36–45	5	25	
Body Mass Index				
	Underweight	1	5	
	Normal	18	90	0.071
	Overweight	1	5	
Self-reported Cannabis use				
	Inter-daily	3	15	0.201
	Daily	17	85	

2.2. Assessment of Cannabis Use, Determination of Lipoproteins and Cannabinoids in Urine

Selected participants underwent a survey on patterns of substance use and abuse to choose participants with primary cannabis use without association with other drugs (cocaine, tobacco, ecstasy, and alcohol) (data not shown). Participants with a history of chronic diseases (such as dyslipidaemia, diabetes, hypertension, etc.) and female participants were excluded. (Figure 1). After screening, participants signed an informed consent form and received an orientation to the study.

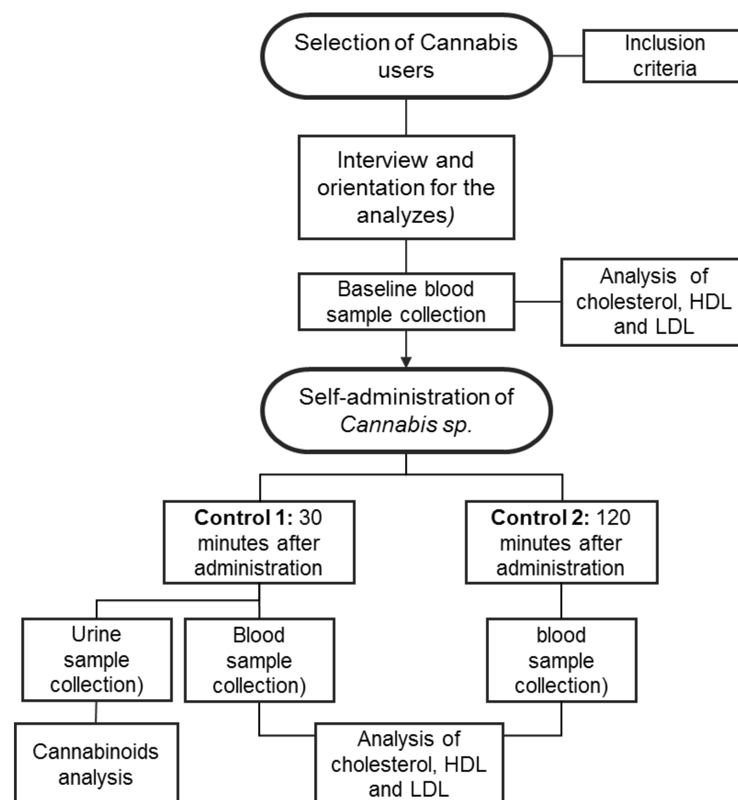

Figure 1. Study flowchart of cannabis effects on cholesterol in Peruvian heavy-users.

Patients were assigned a particular hour in the morning for the realization of the project. As part of this workflow (Figure 1), blood samples were collected in Vacutainer tubes with a clot activator and gel (yellow cap) 30 min before self-administration of the test substance. Sample collection followed the sample collection quality criteria described in

the CLSI H18-A4 guideline [18]. Samples were immediately processed to determine total cholesterol, HDL-C, and LDL-C.

In the next step, volunteers were free to self-administer *Cannabis* spp. (approximately 0.2 g) by inhalation (pyrolytic). Then, urine samples were collected for cannabinoid determination (by thin-layer chromatography). Blood was collected 30 min and 120 min after cannabis administration according to the protocol previously described. The HDL-C, LDL-C, and total cholesterol were immediately determined using the Cobas c111 automated system (Roche, Basel).

For the qualitative analysis of cannabinoids [Δ-9-THC and cannabidiol (CBD)] in urine, 20 mL per participant was collected, and cannabinoids were determined by thin-layer chromatography (cut off: 20 ng/m) [19]. The protocol of alkaline hydrolysis (with KOH), and extraction with cyclohexane and chloroform was used following a previously described protocol [20].

2.3. Data Analysis

We used IBM SPSS v22.0 software (Armork, New York, NY, USA) for Windows (Redmond, Washington, CA, USA). Continuous variables were presented as means with standard deviation and categorical variables as frequencies. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP II) classification was used to estimate threshold concentrations of HDL (males: normal >50 mg/dL, desirable: >60 mg/dL), LDL (normal range: 70 a 130 mg/dL, desirable <100 mg/dL), and total cholesterol (normal range: 125 a 200 mg/dL) [21]. The paired *t*-test and one-way ANOVA with Bonferroni post-hoc test were used to estimate differences in each lipoprotein measurement, considering a double-tailed *p*-value of 0.05 and a 95% confidence interval as statistically significant.

3. Results

3.1. Baseline Cholesterol Concentration

A total of 180 assays were performed, 60 for each lipid marker. Of the total 12 (60%), 10 (50%), and 11(55%) had desirable total cholesterol, fairly good HDL-C (40–60 mg/dL) and fairly good LDL-C (100–129 mg/dL) values, respectively (Table 2). The mean basal concentration of total cholesterol, HDL-C and LDL-C, was 193.37 ± 20.18 mg/dL (95%CI 184.5 to 202.2), 60.05 ± 6.36 mg/dL (95%CI 57.3 to 62.8), and 129.65 ± 14.50 mg/dL (95%CI 123.3 to 136), respectively. The ranges of total cholesterol, HDL-C and LDL-C were 153 to 225 mg/dL, 48 to 69 mg/dL, and 53 to 144 mg/dL, respectively.

Table 2. Lipoprotein distribution profile in heavy cannabis users. Changes in cholesterol concentration were evident for HDL at 30 and 120 min, for LDL at 30 min, and for total cholesterol at 120 min. Lipid profile results were interpreted according to NCEP ATP II. Data in N (%).

Lipidic Biomarkers		Profile	Baseline	30 min	120 min	*p*-Value
Total Cholesterol (mg/dL)	<200	Desirable	12 (60)	11 (55)	17 (85)	0.001
	200–239	Borderline	8 (40)	8 (40)	3 (15)	
	>240	High risk	0 (0)	1 (5)	0 (0)	
HDL-C (mg/dL)	<40	At risk	0 (0)	0 (0)	0 (0)	<0.001
	40–60	Fairly good	10 (50)	6 (30)	4 (20)	
	>60	Desirable	10 (50)	14 (70)	16 (80)	
LDL-C (mg/dL)	<100	Desirable	0 (0)	2 (10)	1 (5)	0.001
	100–129	Fairly good	11 (55)	5 (25)	13 (65)	
	130–159	Borderline high	9 (45)	12 (60)	5 (25)	
	160–189	High risk	0 (0)	1 (5)	1 (5)	

Abbreviations: HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol.

3.2. Changes in Lipoproteins Due to Cannabis Use

One hundred and twenty minutes after cannabis ingestion, the number of participants with cholesterol < 200 mg/dL increased (desirable cholesterol: 12 vs. 17 participants, $p = 0.001$). HDL-cholesterol showed progressive increases in participants with desirable HDL > 60 mg/dL at 30 min (10 vs. 14 participants, $p < 0.001$) and at 120 min (10 vs. 16 participants, $p < 0.001$), while LDL-cholesterol peaked in participants with concentrations <100 mg/dL at 30 min (desirable cholesterol: 0 vs. 2, $p = 0.001$). The outcomes of changes in lipoprotein concentration after cannabis use appear in Figure 2.

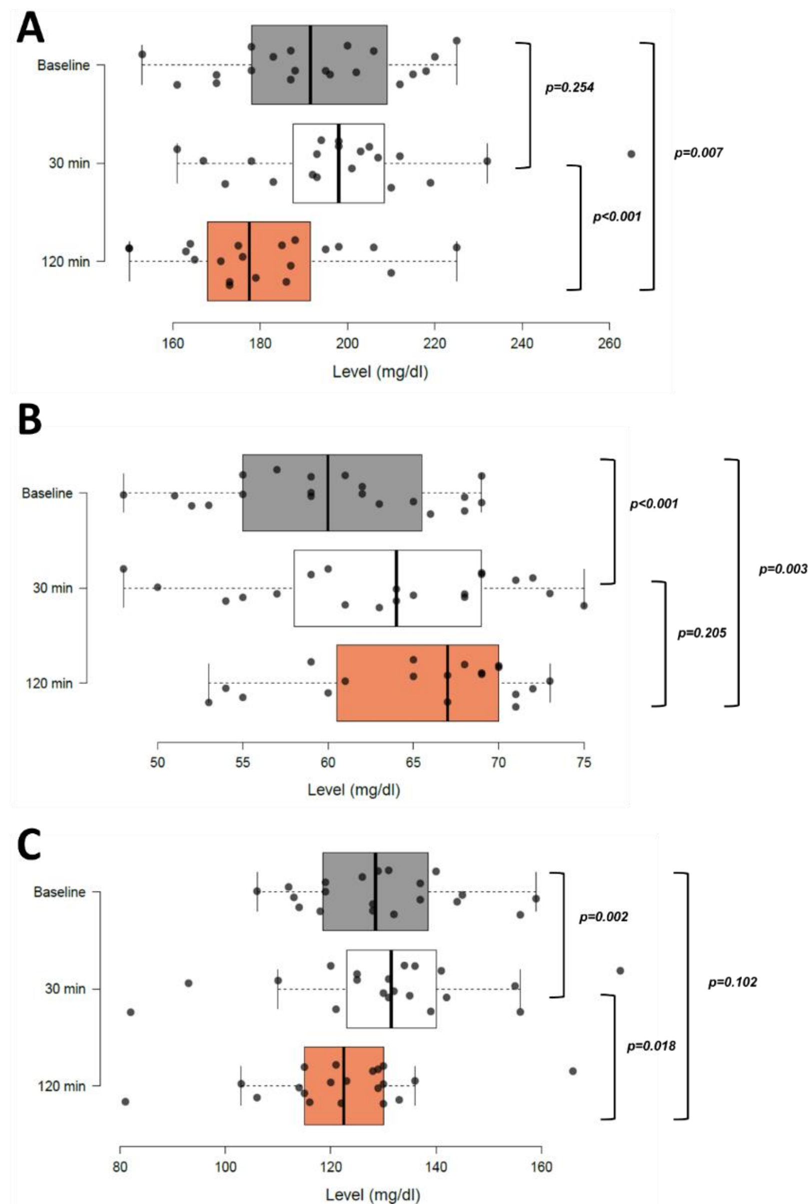

Figure 2. Changes in lipoprotein concentration after cannabis use. (**A**) Cholesterol concentration was significantly reduced 120 min after cannabis intake. (**B**) HDL-C cholesterol showed significant increases at 30 and 120 min of cannabis use. (**C**) LDL-C showed a significant increase 30 min after cannabis use followed by a decrease which was not significant relative to baseline.

After cannabis use, total cholesterol concentration changed to 199.15 ± 23.3 mg/dL (95%CI 188.9 to 209.3) at 30 min and 180.95 ± 19.3 mg/dL (95%CI 172.5 to 189.4) at 120 min. Although we did not demonstrate differences between baseline and 30-min total cholesterol concentrations ($p = 0.254$), we did observe differences in baseline and 120-min

concentrations after cannabis use (p = 0.007). HDL-C concentration also showed differences after cannabis consumption ($p < 0.05$) showing increases at 30 (63.25 ± 7.68 mg/dL, 95%CI 59.8 to 66.6) and 120 min (69.15 ± 18.67 mg/dL, 95%CI 60.9 to 77.3). Analysis of LDL-C only showed changes in its concentration 30 min after consumption (p = 0.002). The results are shown in Table 3.

Table 3. Descriptive statistics on the concentration of lipoproteins in in the three measurements of the study in human serum of cannabis users.

Lipidic Biomarkers	Measures	Mean	SD	Range		IC95%	
Total Cholesterol (mg/dL)	Baseline	193.4	20.2	153	to 225	184.52	to 202.21
	30 min	199.2	23.3	161	to 265	188.95	to 209.35
	120 min	181	19.3	150	to 225	172.48	to 189.42
HDL-C (mg/dL)	Baseline	60.1	6.4	48	to 69	57.26	to 62.83
	30 min	63.3	7.7	48	to 75	59.89	to 66.61
	120 min	69.2	18.7	53	to 144	60.97	to 77.33
LDL-C (mg/dL)	Baseline	129.7	14.5	106	to 159	123.30	to 136
	30 min	130.7	20.6	82	to 175	121.63	to 139.67
	120 min	122.4	16.3	81	to 166	115.18	to 129.51

Abbreviations: HDL: high-density lipoprotein, LDL: low-density lipoprotein, SD: Standard deviation.

Qualitative urine results showed standard concentrations of Δ-9-THC and cannabidiol in all urine samples by thin-layer chromatography. These urine results were independent of age and sex and did not show significant differences ($p > 0.05$).

4. Discussion

This is the first Peruvian study in heavy cannabis users that has demonstrated changes in lipoprotein concentrations after smoked cannabis consumption. HDL-C cholesterol increased 30 and 120 min after cannabis ingestion, while LDL-C and total cholesterol showed partial reductions.

Several studies have shown in heavy cannabis users that cannabis use was associated with unfavourable changes in lipid, glucose, and cholesterol metabolism [9,10,14,22,23]. A recent review has placed the role of cannabis in lipoprotein metabolism as inconclusive [24]. However, the effect of cannabis use on lipoprotein regulation and thus a relevant role in the balance of chronic diseases based on cholesterol alterations have also been highlighted [5,25].

Our findings showed a significant increase in HDL-C after two hours of cannabis consumption. These HDL-C results (69.15 ± 18.67 mg/dL) do not agree with a previous study in a US cohort [23] where cannabis smokers had lower plasma HDL-C cholesterol (49 ± 14 mg/dL, p = 0.02). One explanation for these differences may be due to the timing of HDL measurement, as our study focused on determining pharmacokinetic changes two hours after cannabis, whereas the Muniyappa et al. study [23] estimated HDL-C concentration at any time point.

Another explanation could be due to cannabis use of three and 30 joints per day, four times per week between 6 and 38 years, whereas our population reported ~4/7 days of use in at least one year of use. These differences in use may be crucial to the effect of cannabis on metabolic balance, as previous reports have found an increase in HDL-C in populations with less intense use (more than five uses per month) [5]. Further studies are required for advanced understanding of this relationship.

The importance of increasing HDL-C in health is the control of cardiovascular diseases. Alterations in lipoprotein balance led to a range of diseases such as metabolic syndrome and atherosclerosis [21]. Therefore, the effects of cannabis on lipid regulation are key due to the increase in cannabis use between 2010 and 2020 worldwide [26]. The main chemicals in cannabis are Δ9-THC and CBD which bind to the CB1/CNR1 and CB2 receptors in the body [27]. It has been reported that CB1/CNR1 binding may contribute to an increase

in HDL-cholesterol in treated adults [28]. CBD consumption of 20 mg/kg/day for 8 months in rats has also been reported to have an impact on neuroinflammation and cholesterol concentration [29]. These studies support the conclusions of this study, highlighting the significance of an increase in HDL-C following cannabis use.

The reduction of total cholesterol and LDL levels is also an important part of the prevention of metabolic diseases. Some stilbenoids isolated from *Cannabis sativa* L., such as HM1, may have important effects on cholesterol receptors such as LDL receptor and SR-BI, allowing to improve their metabolism [12]. Our results have shown a partial reduction of LDL-C after cannabis use in agreement with two previous cohort studies [23,30] but differ from a case-control study in an African cannabis-using population [31]. The main differences could be due to the frequency of use, the route of administration, and the products/derivatives used, as these characteristics were not reported in the previous study. A favourable impact of cannabis on triglyceride and cholesterol metabolism has been found to reduce the risk of metabolic syndrome [30], non-alcoholic fatty liver disease [32], and atherosclerosis in patients with Systemic Lupus Erythematosus [33]. However, cannabis abuse may lead to increased cardiovascular risk [7].

While all of these studies strongly support the benefits of cannabis on cholesterol homeostasis, there are also studies that support the opposite. Δ9-THC has been reported to affect RCTs, leading to cholesterol accumulation in blood vessels, thereby increasing the risk of cardiovascular disease [9,10]. CB1/CNR1 has been elucidated as a major cellular component contributing to the pathology of cardiovascular disease [34], although haplotype variations may play distinct roles in cholesterol metabolism independent of BMI [11,35]. These detrimental effects may be due to the components of cannabis products, so the increased recreational use of synthetic cannabinoids may influence the development of cardiovascular disease [26,34]. This outlook leads to the development of future studies that allow the rapid and efficient characterization of the concentration of cannabinoids in medicinal, free-sale and in-house products, mainly in countries with changes in regulation in favour of increased use of cannabis.

Limitations

The limitations of this study are entirely sample-based. The population selected in Cusco was voluntarily invited, fulfilled a set of criteria to avoid analysis bias, and was as small as in previous studies [23,31]. However, the sample size should be expanded in future studies to better understand the effect of cannabis on lipoprotein metabolism. Second, not evaluating the CB1/CNR1 receptor haplotypes may be an important limitation, since this genetic variability may influence the final outcomes of increased or decreased lipoproteins [11,35]. Finally, we do not include an exhaustive concentration analysis of cannabinoids using analytical chromatographic methods (i.e., high-performance liquid chromatography or gas chromatography). Cannabinoids need to be quantified not only in urine, but also in blood during future lipid/cannabis trials.

5. Conclusions

In light of these findings, our results suggest a progressive increase in HDL-C and an immediate reduction in LDL-C cholesterol at 120, after consumption of *Cannabis* spp. in heavy-users in Cusco, Peru. The reduction in LDL-C cholesterol was not significant, but the increase in HDL in the users was significant after 120 min of smoking cannabis. The highlight of this study is also to shed light on the possible physiological effects of cannabis in Peru, where interest in recreational and medicinal cannabis is beginning to grow. Further studies in Peruvian communities are required to determine the kind of cannabis used, the entire lipid profile, and the relationship between changes in subject concentration and anthropometric, demographic, and cannabis intake factors (i.e., route and time of consumption).

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data will be disclosed upon request to the authors.

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