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Determinants of Insulin Resistance in Viral Hepatitis C and Hepatic Steatosis Interaction

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ABSTRACT

Background: The Hepatitis C virus, through its proteins, blocks the insulin signaling pathway, thus causing insulin resistance. He also interferes in lipid metabolism leading to hepatic steatosis. The objective of this study was to determine the effects of the interaction of viral Hepatitis C and hepatic steatosis on insulin resistance in non-diabetic patients in Kinshasa.

Methods: It was a cross-sectional analysis carried out between 2021 and 2022 in non-diabetic patients suffering from Hepatitis C at Biamba Marie Mutombo Hospital (HBMM), Masina/Kinshasa.

Results: Of the 120 patients, 64 were women (53%) and 56 were men (47%), the average age was 71 ± 21 years, the majority of patients, i.e. 67.5% (n=81), were characterized by advancing age, compared to a third of patients, i.e. 32.5% (n=39) without advancing age. There was an epidemic magnitude of insulin resistance estimated at 75% among 120 patients with viral Hepatitis C. The proportions of insulin resistance varied statistically unequally in the different interaction groups between Hepatitis C infection and hepatic steatosis (P<0.000 1). Advancing age ≥ 60 years and very urbanized/polluted residence were the independent determinants of insulinoreresistance. SBP and BMI significantly discriminated against viral Hepatitis C.

Conclusion: This study confirmed that Hepatitis C interacts strongly with fatty liver handled with insulinoresistance in people prearranged.

Keywords: Hepatitis C; Insulin resistance; Hepatic steatosis; HBMM, Kinshasa/Democratic Republic of the Congo

INTRODUCTION

Viral Hepatitis C is a public health problem worldwide but especially in SAA both in terms of its morbidity and mortality [1]. Her Severity is variable and can range from a mild form, lasting only a few weeks, to a serious illness that persists for life [1]. In 2016, the World Health Organization (WHO) estimated around 400,000 the number of patients died from complications of Chronic Hepatitis C [1].

Chronic Hepatitis C can lead, in 5% to 20% of cases, to hepatic steatosis, cirrhosis, liver failure or primary liver cancer, which constitute the main complications of HCV (Hepatitis C Virus) infection [1]. These complications occur after more than 20 years of disease progression and are rare in children [1]. But more and more, other extrahepatic complications are described, including insulin resistance [2-8].

The association between HCV and insulin resistance is more significant in patients aged over 40 years [8-10].The significant association with age would suggest that diabetes is the consequence of progressive liver damage and not the effect of the virus itself.

The longitudinal study by Mehta et al., demonstrated that the

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excess risk in the onset of diabetes during follow-up mainly concerns obese patients aged over 65 years, also suggesting that HCV would not be responsible for the development of diabetes, only in patients at risk [10].

HCV can be considered a viral disease, but also a special type of metabolic disease [11]. Indeed, HCV interferes with lipid metabolism leading to hepatic steatosis; disrupts the carbohydrate metabolism, thereby leading to 'IR or the diabetes, but also increases the risk of developing atherosclerosis [11].

The present study set itself the objectives of determining the effects of the interaction of viral Hepatitis C and hepatic steatosis on insulin resistance in non-diabetic patients in Kinshasa and of determining the influence of the components of Metabolic Syndrome/Insulin Resistance on the different types of steatosis in patients suffering from Hepatitis C.

MATERIALS AND METHODS

This was a descriptive and analytical cross-sectional study which took place from April 2021 to April 2022 at the Biamba Marie Mutombo Hospital (HBMM), located in Kinshasa/Masina, Democratic Republic of Congo.

Study population

The study population consisted of patients suffering from chronic viral Hepatitis C who had developed hepatic steatosis and/or insulin resistance. All patients over 20 years old, non-diabetic, carrying anti-HCV antibodies and who consented were included in this study. has participate in the study, while patients under 20 years of age, who did not carry anti-HCV antibodies and who did not consent to participate in the study were excluded.

For convenience, all patients aged over 20 years who were seen in consultation or in the emergency room during the study period were pre-selected. Only those who had positive HCV antibodies were retained. The sample size was calculated according to the formula following schwartz [12].

$$n \geq \frac{z^2 \times p(1-p)}{d^2}$$

n: sample size

Z: Student's normal distribution, estimated at 1.96 for a 95% confidence interval

p: estimated prevalence of Hepatitis C (3%)

d: margin of error, estimated at 5%

Thus, the calculated sample size was 45. Given the reduced sample size calculated, the option was taken for exhaustive sampling, which is why a sample of 120 patients was retained.

Data collection

A pre-established, pre-coded form was used to collect sociodemographic data, clinical data, biological data (biochemical, serological) and imaging data (ultrasound). Non-modifiable personal attributes were age and gender. The weight, height as well as the address and the degree of environmental pollution of the study subjects constituted the sociodemographic data.

The clinical data included: The notion of smoking, the concept of alcoholism, the concept of taking IV drugs, a sedentary lifestyle, diet, Blood Pressure (BP), Body Mass Index (BMI), waist circumference, hip circumference, jaundice and the hepatomegalia.

The serological marker was characterized by the search for anti-HCV antibodies. Transaminases (GOT, GPT), gamma GT (GGT), glucose, HbA1C, total cholesterol, insulin, Homa score constituted the biochemical markers.

The determination of anti-HCV antibodies and insulin was carried out using the Mindray CL-900 i automated system. (Nanshan, Shenzhen/China). The CL-900i uses the principle of Chemiluminescence Immunoassay (CLIA).The other biochemical parameters were analyzed using the Mindray BS-240 automaton (Nanshan, Shenzhen/China) which uses the principles of spectrophotometry, turbidimetry and potentiometry. Abdominal ultrasound was performed on behalf of medical imaging data.

Operational definitions

The patient who is a chronic carrier of HCV was characterized by the presence of anti-HCV antibodies with normal or slightly elevated levels of transaminases (<3 N) [12].

Metabolic Syndrome was defined by the presence of at least 3 of the following elements (13): BP ≥ 130/85 mmHg, BMI>25 Kg/m2, Waist circumference >94 cm in men and >80 cm in women, Fasting blood sugar >126 mg/dL or >7 mmol/L in two doses spaced at least 'one week or HbA1>7%, Triglycerides>150 mg/dL or >1.7 mmol/L, HDL<40 mg/dL or <1 mmol/L in men and <1.3 mmol/L in women [13].

Insulin resistance was the decreased response to insulin: seither normal biological response requiring a high quantity of insulin (normoglycemia at the cost of hyperinsulinism), or insufficient biological response for insulinemia (glucose intolerance or diabetes with high insulin levels).

Le HOMA (Homeostasis Model Assessment of Insulin Resistance) was the ratio between [14]:

Ins(µUI/mL) × Gly(mmol/L)/22.5. Resistance aI insuline si>25.

Hypoglycemia was defined as blood glucose <3.3mmol/L or <60 mg/dL [15].

Hyperglycemia was defined as blood sugar ≥ 7mmol/l or ≥ 126 mg/dL [15].

Hyperinsulinemia was defined as an insulin value >25 µIU/mL [15].

Hypoinsulinemia was defined as an insulin value <2 µIU/mL [15].

Hepatic steatosis was defined as the presence of a bright liver on ultrasound and/or by the elevation of the ASAT/ALT ratio >1 [16].

Simple steaosis was defined as the presence of a bright liver on ultrasound, without any notion of alcohol intake or metabolic syndrome [16].

Alcoholic steatosis was defined as the presence of a bright liver on ultrasound with the notion of alcohol intake [16].

Non-alcoholic steatosis was defined as the presence of a bright liver on ultrasound associated with the presence of metabolic syndrome [16].

Steatohepatitis/cirrhosis was defined by a cirrhotic liver on ultrasound [16].

Statistical analyzes

The data was encoded using Excel 2010 software, after cleaning and verification of their consistency and their quality. They were exported to SPSS 21.0 for analyses.

Descriptive statistics consisted of calculating the mean and standard deviation for continuous and normally distributed data, the median for non-Gaussian data, and the proportions (%) for categorical data.

The chi-square test made it possible to compare the proportions that of Student's t and Man Withney's U made it possible to compare the means and medians. Predictive factors for the occurrence of insulin resistance in the study group have been researched using the logistic regression test in analysis univariate and multivariate. The calculation of the odds ratio and its confidence interval made it possible to evaluate the strength of association between the independent variables (anti-HCV viral markers, age, sex, BMI and degree of pollution) and the dependent variable (insulin resistance). For all tests used, the value of P<0.05 was the threshold for statistical significance.

RESULTS

There was an epidemic scale of insulin resistance with 90 patients among the study population: rate of ¾ of insulinoreresistance (Figure 1). Among the entire study population (n=120), 46.7% (n=56) patients were men compared to 53.33% (n=64) women (Figure 2). The majority of patients, i.e. 67.5% (n=81), were characterized by advancing age, compared to a third of patients, i.e. 32.5% (n=39) without advancing age (Figure 3).

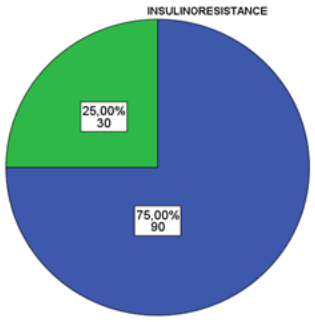

Figure 1: Proportion of insulin resistance in the study population. **Note:** (■): OUI, (■): NON

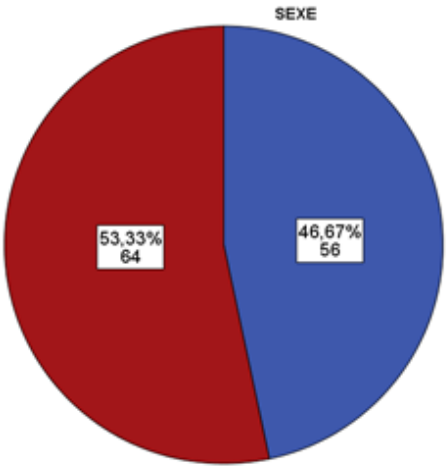

Figure 2: Distribution of the study population by sex. **Note:** (■): HOMME, (■): NON: FEMME

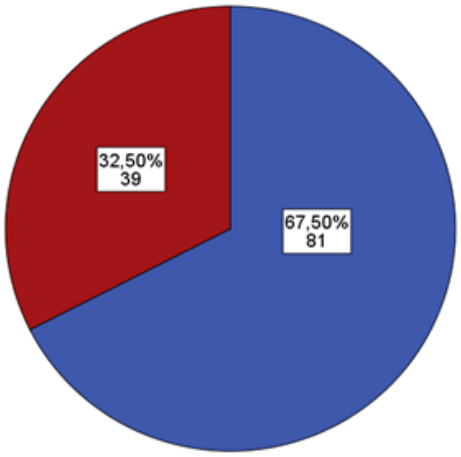

Figure 3: Distribution of patients according to age progression. **Note:** (■): OUI ≥ 60 ans, (■): NON<60 ans

The proportions of the HCV (+) group with alcoholic steatosis were higher than those of the HCV (+) groups with steatohepatitis/ Cirrhosis, CVH (+) with non-alcoholic steatosis and CVH with simple steatosis (Figure 4) (Table 1).

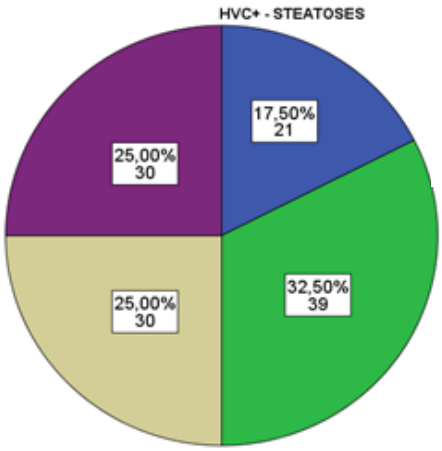

Figure 4: Proportions of HCV and steatosis interaction groups in the study population. **Note:** (■): HVC+ avec Steatose simple, (■): HVC+ avec Steatose Non Alcoolique, (■): , (■): HVC+ avec Steatoshepatite/ Cirrhose

Table 1: Interaction between Hepatitis C infection and Steatoses

Variables	Effective (n=120)	Percentage (%)
HCV (+) with simple steatosis	21	17.5
HCV(+) with alcoholic steatosis	39	32.5
HCV(+) with non-alcoholic steatosis	30	25
HCV(+) with steatohepatitis/ cirrhosis	30	25

Considering the degree of urbanization-pollution and human mobility, insulinoreresistance was significant (P for trend<0.000 1) in multi-ethnic sites tres urbanises with pollution and strong migration (90.9%, n=30/33) only in semi-urbanized Bantu siteses, chaotic-polluted with rural exodus (84.3%, n=43/51), and in Bantu-rural-non-migrant sites without pollution (47.2%, n=17/36) (Figure 5).

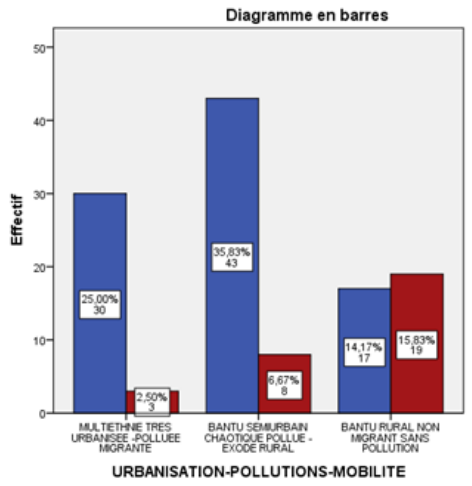

Figure 5: Distribution of proportions of insulin resistance across sites of degree of urbanization-pollution-human mobility. **Note:** (■): OUI, (■): NON

Insulin or proportions resistance varied statistically unequally in the different interaction groups between Hepatitis C infection and fatty liver disease (P<0.000 1) (Figure 6). So there were:

- 23.8% (n=5/21) insulinoreresistance in the HCV+ group with simple steatosis;
- 64.1% (n=25/39) insulinoreresistance in the HCV+ group with alcoholic steatosis;
- 100% (n=30/30) insulinoreresistance in the HCV+ group with non-alcoholic steatosis;
- 100% (n=30/30) insulinoreresistance in the HCV+ group with steatohepatitis/cirrhosis.

There was an uneven but very significant variation in mean values (SBP, DBP, waist circumference, hip circumference, blood glucose, total cholesterol, gamma GT, SGOT, SGPT) between steatosis types.

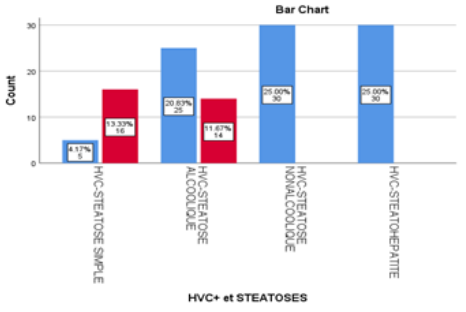

Figure 6: Proportions of insulin resistance in the interaction between HCV infection and steatosis. **Note:** (■): OUI, (■): NON

An exponential curve between PAS, THE Waist circumference, hip circumference, blood sugar, insulinemia, Homa score, Gamma GT, SGOT, SGPT and types of steatosis (the highest average values were observed in steatohepatitis/cirrhosis; intermediate values in alcoholic and non-alcoholic steatosis, while the lowest values were observed in simple steatosis) against a quadratic function with curves in U or in J between PAD, cholestetotal rol, BMI and types of steatosis (the lowest mean values were observed in the alcoholic steatosis group, while the highest values were observed in the steatohpatitis/cirrhosis groups; stenonalcoholic atosis and simple steatosis) (Figures 7-18) [17-23].

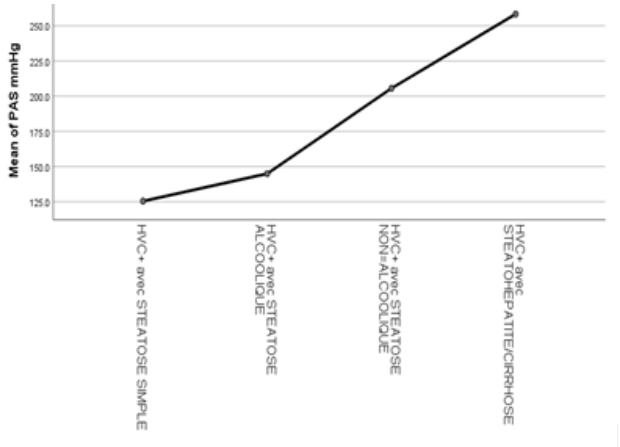

Figure 7: HCV/Steatosis and PAS interactions.

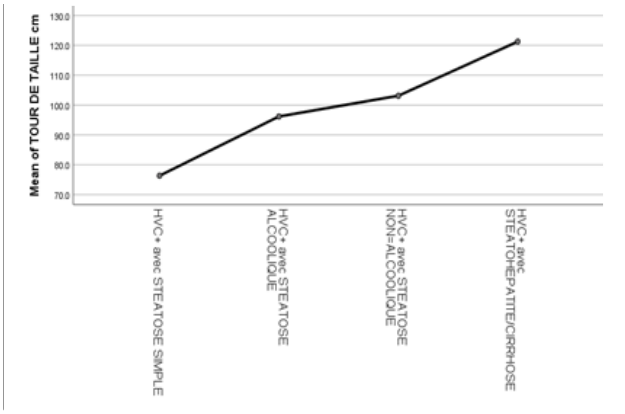

Figure 8: HCV/Steatosis and Waist Circumference Interactions.

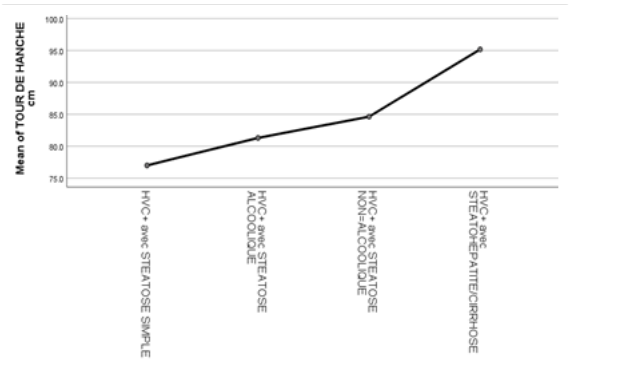

Figure 9: HCV/Steatosis and hip size interactions.

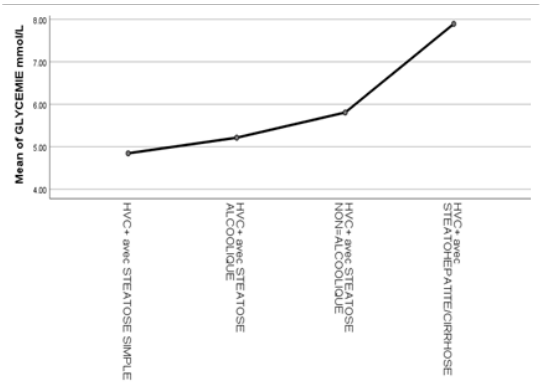

Figure 10: HCV/steatosis and blood glucose interactions.

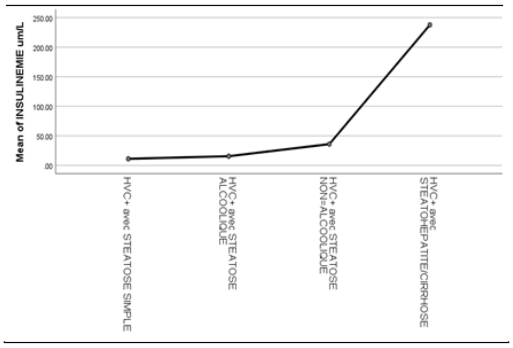

Figure 11: HCV/steatosis and insulinemia interactions.

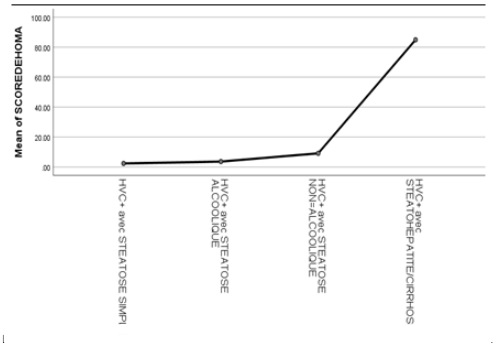

Figure 12: HCV/steatosis and insulin resistance interactions.

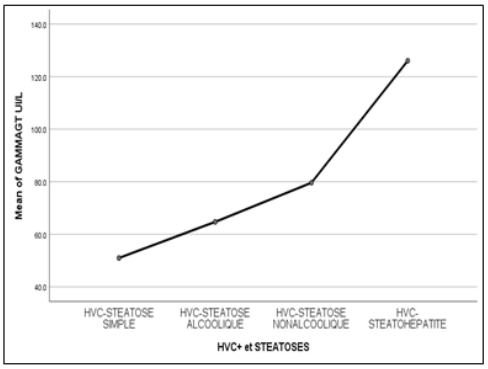

Figure 13: HCV/steatosis and Gamma GT interactions.

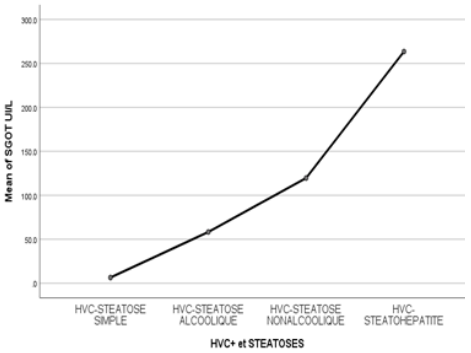

Figure 14: HCV/steatosis and SGOT interactions.

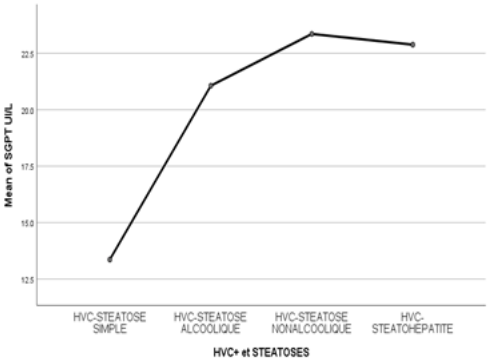

Figure 15: HCV/Steatosis and SGPT interactions.

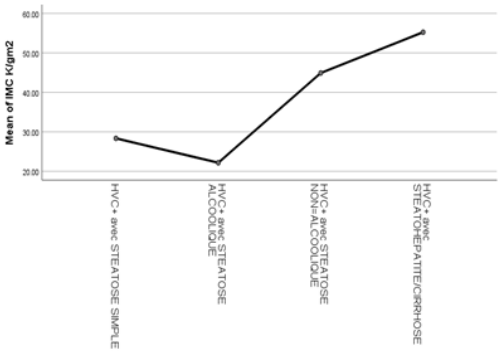

Figure 16: HCV/steatosis and BMI interactions.

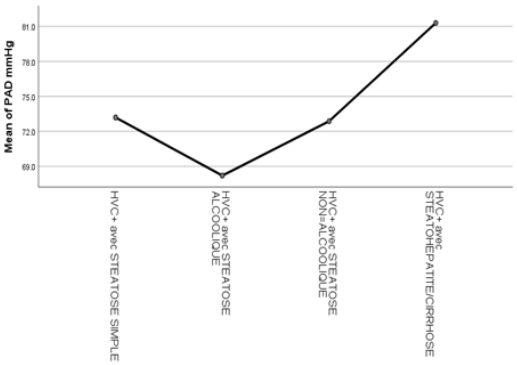

Figure 17: HCV/Steatosis and PAD interactions.

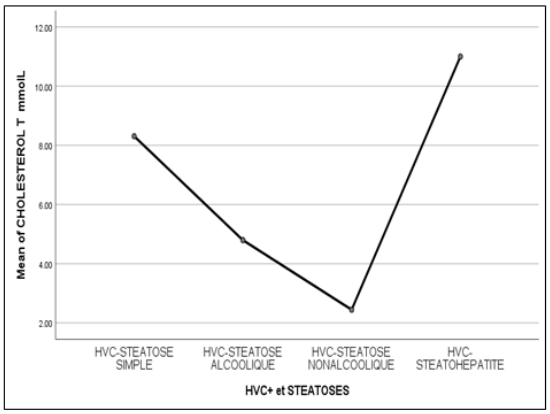

Figure 18: HCV/Steatosis and total cholesterol interactions.

By introducing all covariates into the multivariate binary logistic regression analysis as univariate associated factors of insulinoreresistance and after adjustment for sex (confounding variable), the rest of the covariates (urbanization-pollution-human mobility), the model was considered very valid and reliable according to the Hosmer and Lemeshow test (chi square=0.549).

Using Wilk's Lambda equality group tests, the canonical discriminant functions and the coefficients of the classification functions were presented in Figure 19. Therefore, some confounding factors were excluded from the equation after adjustment according to discriminant analysis [23-27].

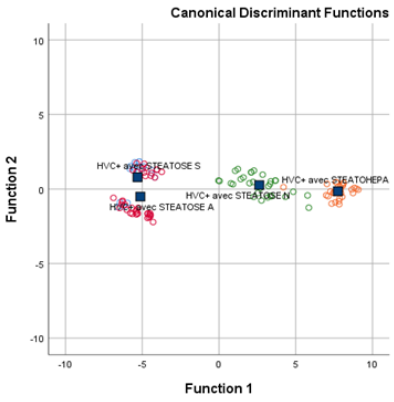

Figure 19: Types of steatosis in multivariate discriminant analyzes. **Note:** (○): HVC+ avec Steatose S, (○): HVC+ avec Steatose A, (○): HVC+ avec Steatose N, (○): HVC+ avec steatophep A.

DISCUSSION

This is the first study has Kinshasa/DRC has determine the effects of the interaction of viral Hepatitis C and hepatic steatosis on insulinoreresistance in non-diabetic patients [27-29].

Hepatitis C and insulin resistance

The present study reinforced the results of other researchers around the world who demonstrated an association between Hepatitis C and insulin resistance [2].

The present work showed an epidemic scale of insulin resistance estimated at 75% among 120 patients suffering from viral Hepatitis C, while Moucari et al., found an insulin resistance rate of 32.4%. The demographic, epidemiological, economic and nutritional transition could be the basis of these significant rates [30].

Insulinoreresistance and interaction between Hepatitis C and Steatosis

The present study revealed a statistically significant link between the interaction of Hepatitis C surmounted by steatosis with insulin resistance: An exponential function of the rate of insulin resistance starting from the group of HCV+ with simple steatosis of the order of 23.8%; tripled for the HCV+ group with alcoholic steatosis of around 64.1% towards an insulin resistance rate of around 100% for the HCV+ groups with severe and non-severe non-alcoholic steatosis. Which demonstrates that on its own, HCV is capable of causing insulin resistance to more or less 24%, while when there is the influence of alcohol and metabolic syndrome, insulin resistance is tripled and even quadrupled, thus supporting the studies of Mehta and Moucari [10,30].

Components of metabolic syndrome and types of steatosis

The univariate and multivariate analyzes of the present study confirmed the work in the literature relating to metabolic syndrome/disorders of carbohydrate and lipid metabolisms, oxidative stress, insulin resistance and fibrosis hepatient [20-23].

However, total hypercholesterolemia, not specific for metabolic syndrome [24], was not associated with the severity of insulin resistance in interactions between HCV and fatty liver disease [25-27].

Circulating biomarkers including glucose, insulin, transaminases and anthropometric parameters including waist circumference, hip circumference and BMI varied in parallel with gamma GT disturbances (marker of oxidative stress) [28] across the different types of steatosis in the present study.

Independent determinants of insulin resistance

The discriminant analysis applied by the present study instead identified increased systolic blood pressure and increased BMI/inflammation as the only independent determinants capable of classifying the different types of steatosis. This demonstrates that hepatic steatosis due to HCV could follow in the footsteps of systolic hypertension and obesity/inflammation in the occurrence of type 2 diabetes mellitus and atherosclerosis [25,26,29].

In the present study, multivariate analysis of binary logistic regression type excluded sex, anthropometric parameters, biomarkers of cardiometabolic risk-oxidative stress from the equation while keeping age advancement ≥ 60 years and urbanization-human pollution-mobility as independent determinants of insulin resistance in patients with HCV and steatosis interaction [31-33].

This association supports the advancement in age and the increase in Gamma GT linked to oxidative stress, as well as the metabolic toxicity also linked to pollution in the city of Kinshasa supporting certain cancers [15].

Implications

The most important results of the present study will have an implication in the plans of research, personalized-precision medicine and Clinical Biology to prevent, screen, diagnose and treat Hepatitis C contributing to insulin resistance and steatoses hepatic.

The same results will be used in continuing education for understanding the pathophysiology of insulin resistance resulting

from the interaction between Hepatitis C and fatty liver disease.

CONCLUSION

This work made it possible to confirm, on the basis of a very significant association, the involvement of the viral Hepatitis C-steatosis interaction on the occurrence of insulin resistance as has been proven in the literature. Advancing age, obesity and systolic blood pressure were predisposing factors for insulin resistance in non-diabetic patients suffering from Hepatitis C, thus confirming the data in the literature. This research validated the strong interaction between Hepatitis C and fatty liver in individuals predisposed to insulin resistance.

ETHICS

The study protocol was submitted for analysis to the National Ethics Committee, and a favourable opinion was granted under number n°407/CNES/BN/PMMF/2021 of 03/04/2021.

AUTHOR CONTRIBUTIONS

Longo Mbenza Benjamin, Nganga Nkanga Mireille and Mpiana Mutombo Baby were responsible for the conception, interpretation and writing. Mpiana Mutombo Baby, Kuyangisa Boloko Bienvenu, Bikaula Ngwidiyo Jacques, Salaboni Mungenzi Vandersal Alain, Matondo Grace Patricia, Bakemo Bombile Eddy participated in the data collection. Longo Mbenza Benjamin analyzed the data. Mpiana Mutombo Baby, Nganga Nkanga Mireille, Kisoka Lusunsi Christian, Mawalala Malengela Heritier wrote the article. Mpiana Mutombo Baby, Nganga Nkanga Mireille, Tshimpi Wola Yaba Antoine supervised the writing of the article. All authors made intellectual contributions to the draft of the manuscript and approved the final version of the manuscript for submission.

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