College of Medicine and Health Sciences
School of Medicine

PREVALENCE OF TYPE 2 DIABETES MELLITUS IN ADULT PATIENTS WITH HEPATITIS C VIRUS INFECTION AND ASSOCIATED LABORATORY MARKERS. EXPERIENCE AT RWANDA MILITARY HOSPITAL:

A cross sectional descriptive study

Submitted in partial fulfilment of requirements for the Degree of Master of Medicine (M.MED) in Internal Medicine, University of Rwanda (UR).

Principal Investigator: **Dr Anthony BAZATSINDA**, UR Reg. No 213003790

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Supervisor: **Dr Jules KABAHIZI**

Co-supervisor: **Dr Charlotte BAVUMA**

March 2016

DECLARATION

I, Anthony Bazatsinda, hereby declare that this is my original work and has not been presented for the award of a degree in any other university. I also declare that the intellectual content of this thesis is the product of my own work, although I have received invaluable assistance from my supervisors and others which I dully acknowledge.

Dr Anthony Bazatsinda MB ChB. (UR)

Department of Internal Medicine, University of Rwanda.

Signed.....Date.....

This research report has been presented with our full approval as supervisors:

Dr Jules Kabahizi (MB ChB), M.Med (Internal Medicine), Nephrologist , Chief consultant King Faisal Hospital, Head of Internal Medicine department Rwanda Military Hospital, Senior Lecturer, University of Rwanda.

Signed.....Date.....

Dr Charlotte Bavuma (MB ChB, M.Med (Internal Medicine),Endocrinologist, PhD Candidate in Diabetes Mellitus, Senior Lecturer , University of Rwanda.

Signed.....Date.....

DEDICATION

To God the Almighty, who is the provider of everything.

To my late Father, who couldn't live long to witness this work.

To my great loving Mother, my Unique Wife Babrah UWIMBABAZI, beloved sisters and b brothers.

To my M. Med friends for all their support and companionship.

ACKNOWLEDGMENTS

I thank and acknowledge my supervisors, Dr Jules Kabahizi and Dr Charlotte Bavuma for their assistance and guidance in planning and conducting this research.

Thanks are also due to the registrars, nurses in OPD in specialized hepatitis and diabetes mellitus clinics, general medical wards, and Rwanda Military Hospital and Laboratory department staff for their great laboratory work. In sincerely, I would like to thank the consultants in Internal Medicine department for their comments in moving forward the proposal approval and in the editing process.

I deeply acknowledge RMH to have financed this research and to have allowed me to conduct the mentioned research in both OPD Specialized hepatitis and diabetes clinics and general medical wards.

Many thanks to the Rwandan government for having enabled me to do M.Med program and last but not least, this work would not have been feasible without the willingness and cooperation of the patients.

ACRONYMS

UR: University of Rwanda.

RMH: Rwanda Military Hospital.

T2DM: Type 2 Diabetes Mellitus.

HCV: Hepatitis C Virus infection.

ALT: Alanine aminotransferase (formerly SGPT).

AST: Aspartate aminotransferase (formerly SGOT).

GGT: Gamma glutamyl transferase.

ELISA: Enzyme-linked immunosorbent assay

BMI: Body Mass Index

SPSS: Statistical Package for Social Sciences.

WHO: World Health Organization.

OPD: Outpatient department.

M.MED: Master in Medicine.

IDF: International Diabetes Federation

IGT: Impaired Glucose Tolerance.

IFG: Impaired Fasting Glucose.

HDL: High-Density Lipoprotein.

LDL: Low-Density Lipoprotein.

CTGF: Connective Tissue Growth Factor.

NIDDM: Non-Insulin -Dependent Diabetes Mellitus.

KSA: Kingdom of Saudi Arabia

PCR: Polymerase chain reaction.

Th1: T helper lymphocytes.

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ABSTRACT

Background: Type 2 diabetes Mellitus and hepatitis C co-morbidity remains a public healthproblem globally and they are both associated with significant morbidity and mortality. Anecdotally, in Rwanda referral hospitals, HCV infection has been found in different cases of type 2 diabetes mellitus. Hence, the first study to be carried out in Rwanda Military Hospital (RMH) to describe such cases. This study aims at determining the prevalence of diabetes mellitus among adult patients with hepatitis C infection and assessment of the impact of hepatitis C-type 2 diabetes co-morbidity on selected biochemistry and imaging parameters.

Methods: This was a 10 months cross sectional study including consecutive adult patients (18years and above) with hepatitis C Virus infection who presented in Outpatients specialized hepatitis C clinic and internal Medicine admission wards. Participants were considered to have diabetes if they were on diabetic treatment or if they exhibited Fasting blood glucose ≥ 126mg/dl and glycated haemoglobin ≥ 6.5%. All patients were tested for lipid profile and liver function. They underwent also an abdomen ultrasounds. . SPSS version 16.0 was used for data analysis and we compared two groups (those with diabetes and those without diabetes) regarding laboratory and imaging results.

Results: Among 298 participants with hepatitis C, 67 (22.48%) had type 2 diabetes. Mostpatients with type 2 diabetes -hepatitis C co-morbidity showed increased levels of Aspartate aminotransferase (AST) (53.7% of patients with co-morbidity versus 35.5% of those with Hepatitis C alone; P<0.007), increased gamma glutamyltransferase (50.7% of patients with co morbidity versus 30.4% of hepatitis C standalone group; P= 0.002) , reduced levels of serum albumin (18.2% in co-morbid group versus 10% in isolate Hepatitis C group ; P<0.005). High levels of total cholesterol and triglyceride were most prevalent in co-morbid group; respectively 29.9% versus 3% (P<0.001) and 23.90% versus 2.60%, P<0.001). In addition, a greatest number of patients with co affection had fatty liver as per ultrasound (63.4% versus 36.60% HCV; P<0.001).

Conclusion: Type 2 diabetes mellitus is prevalent in adult patients with hepatitis C atRwanda Military Hospital and its co-existence with hepatitis C would have conjunctive negative impact on liver function as well as on the lipid metabolism. However, there is a need of further deep studies to understand the pathophysiological mechanism.

Chapter I: INTRODUCTION

I.1 Theoretical framework.

Hepatitis C is an enveloped, single-stranded RNA flavivirus[1]. The spread is through blood products, secretions, and sexual intercourse (even if there is little evidence for sexual transmission). Some groups of people such as health workers, haemophiliacs, homosexuals, intravenous drug abusers and patients on haemodialysis .have been reported to be at high risk of hepatitis C infection[1] : Up to 70-85% of the cases progress to chronic hepatitis[2], with elevated risk of hepatocellular carcinoma, and abnormal liver histology even in carriers who are asymptomatic[1] . The worsening of the disease is in patients with concurrent HIV infection and/or alcoholic cirrhosis[1]**.** Usually, screening of hepatitis infection is based on hepatitis viral antibodies testing however these antibodies are detectable within 90 – 180 days and even if detected they could not indicate active infection. To confirm that the patient has active hepatitis C infection viral load is needed[1.]

Diabetes mellitus (DM) is a complex non communicable chronic disease including carbohydrate, lipid and protein metabolism disorders[7]. It is characterized by raised blood glucose due to defects in action of insulin, its secretion following progressive beta cells destruction or both[7]. Diabetes Mellitus is currently classified as type 1 Diabetes Mellitus, type2 Diabetes Mellitus, gestational Diabetes Mellitus and other secondary diabetes Mellitus [7]. The World Health Organization (WHO) and National Diabetes Data Group have set criteria for diabetic mellitus diagnosis [8-10]. According to WHO, 2 of the following criteria are required to diagnose diabetes: diabetes mellitus symptoms plus random plasma glucose equal or greater than 200md/dl (11.1 mmol/l), fasting plasma glucose equal or greater than 126 mg/dl (7.0 mmol/l), 2 hours plasma glucose equal or greater than 200 mg/dl (11.1 mmol/l) during oral glucose tolerance test and glycated heamoglobin equal or greater than 6.5%..

Diabetes mellitus may be diagnosed following classic symptoms like frequent urination, thirst, weight loss or symptoms of complication, however many individuals diabetes do not present with symptoms, and their disease remains undiagnosed for many years, especially patients with type 2 diabetes[11] . There is evidence that at the time of diagnosis, the patient with type 2 diabetes has had the disease for at least 4 to 7 years[11]. Furthermore, they might have complications of

diabetes: 25% would have diabetic retinopathy; 9%, diabetic neuropathy; and 8%, diabetic nephropathy. Therefore, patients at high risk of type 2 diabetes should be identified and screened regularly to avoid late diagnosis with complication. As hepatitis C infection might be a predisposing factor to type 2 diabetes, screening of diabetes in patients with hepatitis C and evaluation of the magnitude of this co-morbidity would be important for evidence based decision making and clinical care,

I.2 Background

At present, there are approximately 170 million HCV chronic carriers around the world and most of them are in the developing countries[3-4] as reported in April 1998 by the World Health Organization. Hepatitis C infection is not a new issue. Jaundice was recognized as a sign of HCV many centuries before Christ[4-5]. The first recognition of Hepatitis C as a separate disease entity was in 1975 when the transfusion related hepatitis was very prevalent and found not to be caused by only Hepatitis B virus and Hepatitis A viruses[4-5]. At that time it was called "non-A non-B Hepatitis[4-5].

The prevalence of viral hepatitis C is increasing tremendously over the past 3 decades However, in developed countries cases of hepatitis C infection are reported to decrease[3-4]. Transmission of Hepatitis C Virus through blood transfusions in United States of America (USA) reduced from 3-5% in 1992 to 0.001% per transfusion[6]. Even though the overall prevalence is decreasing, there is increasing complications burden[6]. Hepatitis C virus infection

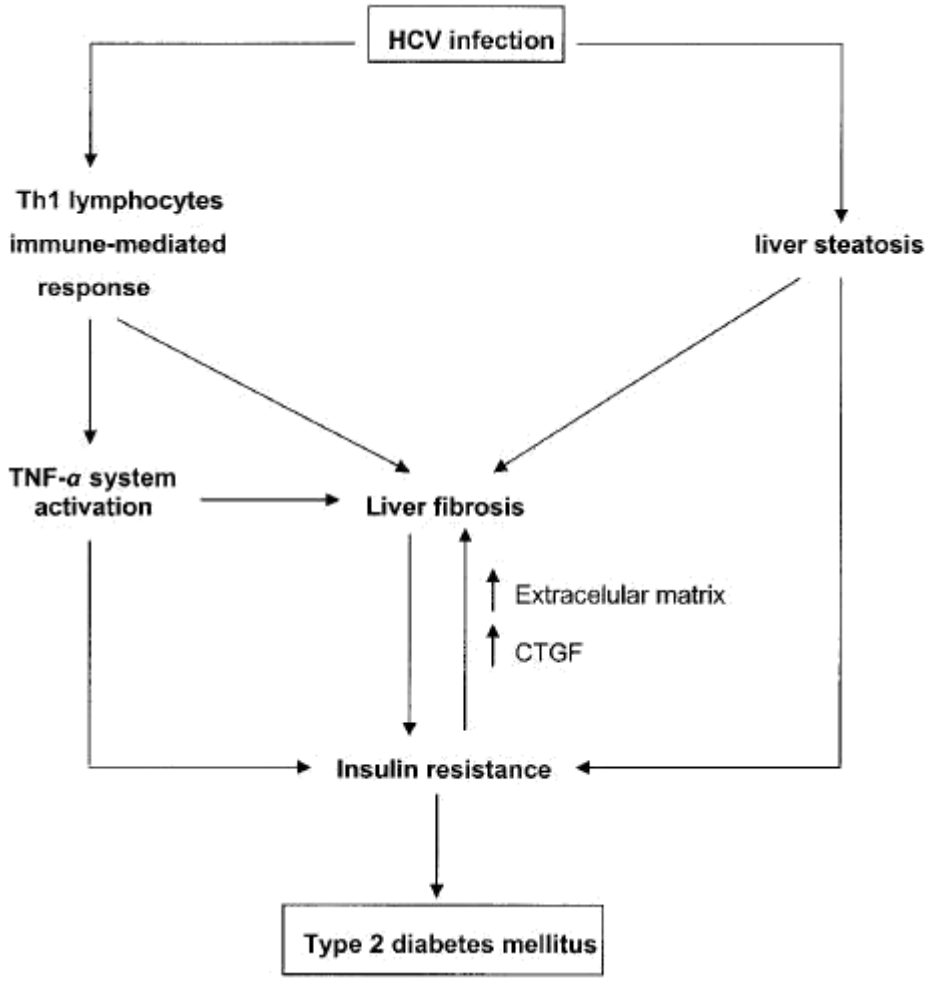
is a leading cause for cirrhosis, liver transplantation and Hepatocellular Carcinoma[6.] The estimated related deaths in USA per year is 12,000. Furthermore, in Japan, Southern Europe, and North America. Hepatitis C Virus has been reported to play an important negative role in causing chronic liver disease (CLD), and has become a major cause of liver cirrhosis and primary liver cell carcinoma (PLCC) [6].

Hepatitis C virus has various genotypes Worldwide. Genotype 1 was the most frequent and accounting for 46 percent of all infections, followed by genotypes 3 at 22 %, and genotypes 2 and 4 (13% each)[7] . Subtype 1b accounts for 22% of all infections globally[7]. There are variations which are significant across the world with genotype 1 dominating in Europe, North America, Latin America, Australia, Europe, Latin America and North America (53-71% of all cases) and Genotype 3 accounting for 40 percent of all infections in Asia. Genotype 4 was most frequent (71 %) in Middle East and North Africa, but when Egypt was not included, genotype

4 accounted for 34 percent while genotype 1 accounted for 46 percent of infections across the same region[7]. Egypt has a very high prevalence of genotype 4. To our knowledge, the prevalence of Hepatitis C virus and its genotypes has not been evaluated in Rwanda population, however, based on case findings in clinical practice, it might be high.

Type 2 Diabetes Mellitus accounts for more than 90% of all Diabetic Mellitus cases[13]. More than 100 million people globally have diabetes and there are still many who are undiagnosed[12]. The overall approximate prevalence among adult diabetes in the USA is 5.8% -12.9 % (median 8.4 %) [14]. This is in sharp contrast to other countries. For instance, there was a Nigerian survey on the prevalence of type 2 diabetes mellitus and discovered it to be 2.7% among all Nigerians[15]. Globally, the diabetes mellitus prevalence has tremendously increased for the past two decades, and in 1985 there was an approximation of about 30 million patients and in 2010 it was around 285 million[16]. And based on this tremendous increase, according to the International Diabetes Federation, by 2030 the diabetes mellitus is projected to be 438 million individuals worldwide[43]. It is true that the prevalence of type 1 and type 2 DM is globally rising. Yet, the type 2 Diabetes Mellitus prevalence is vigorously increasing even faster than type 1 diabetes mellitus, due to decreased activity as many countries are becoming more and more modernized and industrialized, leading to increasing obesity and population aging[16].

Diabetes is particularly increasing in Low and Middle income countries (LMIC). Approximated[43] prevalence of diabetes mellitus in South Africa, Uganda, Kenya, and Tanzania are 8.39%, 4.42%, 3.6%, and 7.95%, % respectively[17]. In Rwanda, according to recent Non communicable disease (NCD) risk factors step by step survey whose results are not yet published but announced in NCD synergy conference in 2013, the prevalence of diabetes was estimated to be 3%. In LMIC increasing prevalence of diabetes has been associated to lifestyle modification such as physical inactivity, unhealthy diet and ageing [43], however the impact of some potential risk factors for diabetes such as hepatitis C virus has not deeply assessed in these countries particularly in Rwanda. However there some evidence on Diabetes and hepatitis C co-morbidity in non-African ethnic population. The chart below show the hypothetic pathophysiology of hepatitis C and diabetes association.



Role of HCV in type 2 diabetes mellitus *18-19*

Hepatitis C directly may cause liver fat deposition. These 3 events which include: Th1 lymphocytes immune-mediated response, TNF-Alpha system stimulation and liver steatosis can be risk factors for liver fibrosis. The insulin resistance and type 2 diabetes mellitus occurrence or development are associated with above 3 events. Alternatively, increased levels of insulin in the blood affects the liver fibrosis course by stellate cells proliferation, hence enabling the extracellular matrix production, and connective tissue growth factors expression. Type 2 diabetes mellitus is the major etiology of nonalcoholic fatty liver disease[18] and as a result, it leads to liver fibrosis [19]. Therefore, having these two co-existent diseases can exacerbate chronic hepatitis C and lead to advanced liver disease like cirrhosis and hepatocellular carcinoma

Diabetes may have also an impact on hepatitis C infection outcome, Diabetes mellitus leads to accelerated liver fibrosis progression and hepatocellular carcinoma development in chronic hepatitis C. However, the effect of diabetes mellitus on the long-term outcome and the synergistic interactions of many diabetic host factors on the liver fibrosis progression is idiopathic[20]. Diabetes mellitus has a significant effect on the long term outcome or prognosis on hepatitis C by decreasing the time of hepatocellular carcinoma occurrence due to hepatitis following transfusion (PTH) and death related to the liver. The existence of both obesity (BMI ≥25 kg/m (2) or hypertriglyceridemia (≥150 mg/dl) with diabetes mellitus has a synergistic impact on the progression of liver fibrosis in patients with chronic hepatitis C. Hence, the treatment of hypertriglyceridemia, obesity, and diabetes are keys to improve the chronic hepatitis C prognosis[20].

I.3 Rationale

In our Rwandan population, there is no study showing the prevalence of type 2 diabetes mellitus in HCV patients. However, the literature does support the association of type 2 Diabetes Mellitus and hepatitis C. It is of medical importance to know the existing correlation of DM and HCV infection in Rwanda where there are no studies about the association. Information on type 2 diabetes and hepatitis C co-morbidity would provide guidance to clinicians and policy makers for implementation of evidence-based practices.

The study outcome will be evidence based towards our clinical practices. The prevalence of Type 2 DM in HCV patients will create awareness of the existing correlation of DM and HCV. Some of the laboratory markers for DM and HCV will be visited and used as a guide for the overall treatment modalities of the disease. The study findings would be the basis for planning the screening of Diabetes Mellitus in HCV Patients.

I.4. Hypothesis and objectives

There is a significant association of Type 2 diabetes Mellitus in our Hepatitis C population.

I.4.1. Main objective

To assess the burden of type 2 diabetes mellitus and Hepatitis C co morbidity in adult people at Rwanda Military Hospital.

I.4.2. Specific objectives:

1. To determine the prevalence of type 2 diabetes mellitus among adults with hepatitis C at RMH.

2. To compare the laboratory markers in T2DM /HCV versus with HCV alone .The focus would be on comparison of Liver function tests (AST, ALT, GGT, INR, albumin and bilirubin) and Lipid profiles (Total cholesterol, LDL, HDL, TRIGLYCERIDES).

3. To compare the abdominal ultrasound findings in Type 2 Diabetes Mellitus and HCV group and in HCV alone.

Chapter II: METHODOLOGY

II.1 Study design

This is a cross sectional, descriptive study.

II.2 The study site

The study was conducted in Rwanda Military hospital in the specialized hepatitis clinic, as well as patients with hepatitis C admitted to the general medical wards.

II.3 Study population

All Patients who are at least 18 years old or older, who were found positive for hepatitis C and attended the hepatitis specialized clinic, and those who has been admitted to the general medical wards in Rwanda Military Hospital were potential participants in the study. Patients who declined to sign the consent form were excluded.

II.4 Inclusion criteria

All Patients aged 18 or greater with HCV infection who attended the hepatitis clinic, with or without the presence of liver cirrhosis, and those who were found to have type 2 diabetes mellitus among HCV.

II.5 Exclusion Criteria

All patients under age 18, with hepatitis B and/or HIV co-infection with HCV, or who declined to consent were excluded.

II.6 Sample size

All HCV patients who attended specialized hepatitis clinic, as well as those admitted to the general medical wards were consecutively screened for type 2 diabetes mellitus and HCV in Rwanda Military Hospital during the study period of 10 months from April 2015 to January 2016.

Sample size was calculated using the simple formula (Daniel, 1999) and the aim of this is to determine enough sample size to estimate the population prevalence with good precision[41]

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

n= minimal sample size required for the study.

z= 1.96 (normal deviate corresponding to 95% confidence interval)

d= 0.05 (degree of precision around the mean)

P= 24% (represents prevalence of type 2 diabetes mellitus among hepatitis C patients in Egypt[22])

$$\text{Thus } n = \frac{1.96^2 \times 0.24 \times 0.76}{0.05^2}$$

The minimum sample size was n=280.This was achieved in this study with 298 participants.

II.7. Recruitment procedure, data collection and sampling technique

Data were collected during the 10 months study period (from April 2015 to January 2016). The investigator visited the specialized hepatitis clinics were all patients with hepatitis C (confirmed by a positive, detectable viral load) were included in our study and seen in their respective days of consultations and those who were admitted in general medical wards at RMH. Among these hepatitis C patients, we screened for type 2 diabetes mellitus using fasting plasma glucose or random glycemia and also glycosylated haemoglobin. During the study period, a focal person for data collection helped in the recruitment of the study participants. Informed consent was obtained from the patient or caretaker after detailed explanations of the

study content. After the study participant consent signature was obtained, the hospital phlebotomists then collected the blood samples and sent them to the RMH Laboratory. ELISA technique was used to test HCV antibodies using Cobas e 411machine. The following laboratory parameters were also investigated: fasting plasma glucose and random glycemia was done using Cobas c 311 /Cobas c 6000, glycosylated hemoglobin using Cobas c 311, and lipid profile, transaminases, liver function tests except INR using Cobas c 311/6000, HCV viral load using Cobas Ampliprep-0514 and INR using Diagnostica STAGO or Sysmex CA 1500. Genotype were not tested due to lack of reagents. The abdominal ultrasound was done using MINDRAY Africhem machine to see the aspect of the liver for every participant who was enrolled in the study.

II.8. Data management

The study data were collected using a worksheet (see appendix) and then entered into personal computer for analysis using SPSS. The results of the research were kept in a confidential, password protected electronic file accessible only by the investigator. Each study participant was informed about his/her results individually.

II.9. Data analysis

Data was entered into the Epidata sheet for database creation and then exported to SPSS version 16.0 statistical package for analysis. Frequencies, means and proportions were calculated. To compare the means, student t-test were used or its non-parametric equivalent if data was not normally distributed. Statistical significance was taken at the level $p< 0.05$ and results were presented in the form of frequency tables, bar graphs, linear graphs or charts as appropriate.

II.10. Dissemination of results

The results of the study will be strictly disseminated for educational purposes. Copies of the study findings will be submitted to the University of Rwanda library and faculty of medicine. The study will also be presented at scientific conferences.

II.11. Ethical consideration

An approval to carry out the study was obtained from the department of Internal Medicine, University of Rwanda Ethical Review Committee. Rwanda Military Hospital Ethical Committee has also approved to do the study.

Chapter III: RESULTS

III.1. Baseline patient demographics (Ref Table 1)

Two hundred and ninety-eight (298) patients met eligibility criteria and were enrolled in our study from April 1, 2015 to January 31, 2016. No patients were lost to follow up. Therefore all the patients were included in the study analyses. The majority of study participants were above 40 years of age (77.5%), compared to 22.5% aged 18-40 years (Table 1). Among participants in our study, males were almost similar to females (51.01% and 48.99%) respectively. 54.03% of our study participants were residing in the urban areas (Gasabo: 20.81%, Kicukiro: 20.47%, Nyarugenge: 12.7%) compared to 45.97% of our study participants were residing in the rural areas (with the most significant numbers in the districts of Bugesera 4.36% and Kirehe 3.36%). In our study, the majority of participants were married 81.54%. In our study population, the predominant Body Mass Index (BMI) was normal at 58.05% versus overweight at 40.60%. A family history of type 2 diabetes mellitus among our study participants was 10.74%, which was confounded by the fact that 32.21% did not know about the family history of type 2 diabetes mellitus. The remaining 57.05% had no family history of type 2 diabetes mellitus.

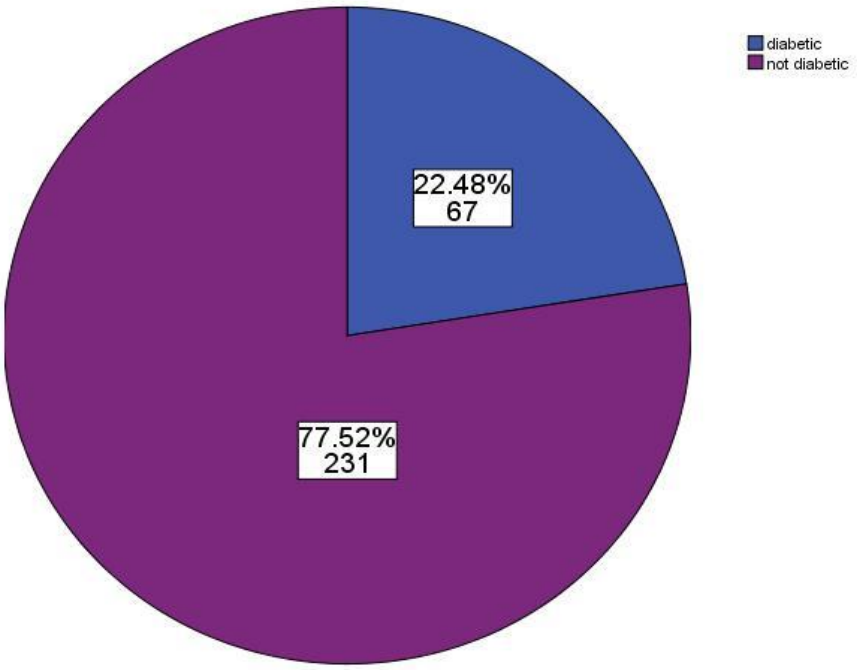
Table 1: Baseline Patient Demographics

Variables	N	%
Age		
18-40 years	67	22.5
>40 years	231	77.5
Sex		
Male	152	51.01
Female	146	48.99
Locality		
Urban	161	54.03
Rural	137	45.97
Marital status		
Single	26	8.72
Married	243	81.54
Widow	28	9.4
Co-inhabitant	1	0.34
BMI		
<18	4	1.35
18-24.9	173	58.05
25-29.9	121	40.6
Family history of diabetes		
Yes	32	10.74
No	170	57.05
Unknown	96	32.21
Family history of HCV		
Yes	19	6.38
No	230	77.18
Unknown	49	16.44
Jaundice		
Yes	9	3.02
No	289	96.98
Abdominal distension		
Yes	37	12.42
No	261	87.58
District distribution		
Nyarugenge	38	12.75
Kicukiro	61	20.47
Gasabo	62	20.81
Rural districts	137	45.97

III.2. Prevalence of type 2 diabetes mellitus in HCV patients.

The total number of type 2 diabetes mellitus in our study was 67 out of 298 hepatitis C patients, thus the prevalence of type 2 diabetes mellitus was **22.48%.**

Figure 1: Prevalence of diabetes in HCV patients.



III.3. Laboratory markers and ultrasonography results (Ref Table 2)

Among our study participants, there was increased levels of aspartate aminotransferase (AST) in combined type 2 Diabetes Mellitus and Hepatitis C by **53.7%** compared to **35.5%** in Hepatitis C alone (P=0.007).

Among 67 patients with type 2 diabetes mellitus-HCV infection co-morbidity 33 (30.3%) had increased Alanine aminotransferase (ALT) levels versus 76 among 231 patients with HCV infection alone (69.7%) with P=0.014.

The gamma glutamyltransferase (GGT) was increased in patients with co-morbidity rather than in patients with hepatitis C alone (50.70% in patients with co-morbidity versus 30.40% Hepatitis C alone with P=0.002).

There was reduced levels of albumin among Type 2 Diabetes Mellitus and HCV compared HCV alone 18.20% and 10.00%, respectively with statistically significant P=0.005.

The total bilirubin was increased by 46.30% in those with both Type 2 Diabetes Mellitus and HCV versus 20.80% with hepatitis C alone with P<0.001.

Comparing the levels of direct bilirubin in our study participants of two groups, HCV infection with type 2 Diabetes Mellitus and hepatitis C alone was increased by 49.30% and 31.20% respectively with P=0.001.

In combined hepatitis C with type 2 diabetes mellitus, there was increased total cholesterol by 29.90%, compared to 3.00% in HCV alone (P<0.001).

In study participants, there was decreased High Density Lipoprotein (HDL) in Hepatitis C with Type 2 Diabetes Mellitus by 32.80% versus 8.70% of HCV alone (P<0.001).

Also there was increased levels of Low Density Lipoprotein in hepatitis C with type 2 diabetes mellitus by 22.40% as compared to 1.30% in hepatitis C alone (P<0.001).

In the Type 2 Diabetes Mellitus and Hepatitis C co-mobidity cohort, triglycerides was increased by 23.90% compared to 2.60% in the Hepatitis C alone cohort (P<0.001) .

Among the participants having both type 2 Diabetes Mellitus and Hepatitis C, the ultrasound finding of fatty liver was present in 63.40% versus 36.60% of Hepatitis C alone (P<0.001).

Table 2: laboratory markers and ultrasonography findings

	HCV/Diabetes n (%)	Hepatitis C alone n (%)	P value
Laboratory markers			
Increased AST (> 40 IU/L)	36 (53.7)	82 (35.5)	0.007
Increased ALT (> 41 U/L)	33 (30.3)	76 (69.7)	0.014
Increased GGT (>60 U/L)	34 (50.7)	70 (30.4)	0.002
Increased Total bilirubin (>17.1µmol/L)	31 (46.3)	48 (20.8)	<0.001
Low Albumin (< 3.97gms/dl)	12 (18.2)	23 (10.0)	0.005
Increased Direct bilirubin (>3.4 µmol/l)	33 (49.3)	72 (31.2)	0.001
Increased Total cholesterol (>5.2 mmol/l)	20 (29.9)	7 (3.0)	<0.001
Low HDL (<0.9 mmol/l)	22 (32.8)	20 (8.7)	<0.001
Increased LDL (>4.12mmol/l)	15 (22.4)	3 (1.3	<0.001
Increased Triglyceride (>2.26mmol/l)	16 (23.9)	6 (2.6)	<0.001
Abdomen Ultrasound result			
Ascitis	34 (82.9)	7(17.1)	<0.001
Fatty liver	26 (63.4)	15(36.6)	<0.001
Cirrhosis	13 (81.2)	3(18.3)	<0.001

Chapter IV: DISCUSSION

IV.1 Results discussion

In our study, the prevalence of type 2 diabetes mellitus was high; 22.48%. Most patients with type 2 diabetes mellitus-hepatitis C co-morbidity showed liver enzymes and bilirubin disturbance with low albumin, and impaired lipid profile than those with hepatitis C alone. Furthermore, fatty liver and features of cirrhosis were most observed in co-morbid group.

The prevalence of type 2 diabetes mellitus in patients with hepatitis C was 22.5% in our study population. It was relatively high. This could be due to the fact that most of our patients were above 40 years, and age is a known risk factor for diabetes[34]. Moreover, most of our patients were from urban districts, which could have contributed to the patients' high prevalence of diabetes mellitus, being overweight (40.6 % of our population study). However this is higher than the prevalence of diabetes in general Rwanda population (3% according to step by step NCD risk factors survey's preliminary results).Even though diabetes screening methods were not similar, the prevalence of diabetes in hepatitis C patients is extremely higher (7 times) than in general population.

This study outcome is similar to different other studies done in different places of the world. The Mason et al: Multicenter study done in New Orleans showed that 21% of patients with hepatitis C had type 2 diabetes[23]. They also found that most of their participants who had co morbidity had deranged liver functions tests[23]. Raouf et al published a similar prevalence of type 2 diabetes (24%) in the cohort Hepatitis C patients[25]. In the Middle East and Europe, the prevalence of type 2 diabetes in hepatitis patients oscillated from 24% to 26%[26-28]. It was noted, as per the study done by Caronia et al that the prevalence of type 2 diabetes mellitus in Hepatitis C related cirrhosis was 23.6%[40]. The studies conducted by Akbar DH, Siddique AM, and Ahmed MM in the Kingdom of Saudi Arabia reported similar prevalence of type 2 diabetes mellitus in HCV patients (22%)[30]. Zein CO, Mason AL, and Lecube A reported a range of 14-40% patients with HCV related liver disease with concurrent type 2 diabetes mellitus[31-33].

Others reports showed higher prevalence of type 2 diabetes mellitus than ours probably due to different demographic and lifestyle characteristics. For example Muhammad Sadik Memon et al showed a prevalence of 31.5% of type 2 diabetes mellitus in hepatitis C seropositive patients[34] and Samir Rouabhia et al done in Algeria showed also a higher prevalence of 39.1%[35]

compared to our study results. Obesity and physical inactivity which are common risk factors for diabetes were more prevalent in their study population as compared to ours. This could raise their type 2 diabetes prevalence.

Prevalence of type 2 diabetes mellitus in patients with hepatitis C infection is various due to screening methodology and characteristics of population studies. However, it is found to be sensibly high and suggests that hepatitis C infection may contribute to the rising burden of diabetes on public health worldwide. Prevention of hepatitis C infection may contribute to prevent type 2 diabetes mellitus.

There are also several studies examining the prevalence of liver function tests findings among co affected diabetes/HCV cohort. In our study, we observed raised transaminases in the patients with type 2 diabetes mellitus and hepatitis C. Samir Rouabhia et al found an increased level of alanine aminotransferase in 51% of co-morbid patients as compared to our findings (30.3%)[35]. According to Bashir et al, the ALT levels were more elevated in patients with Hepatitis C and type 2 diabetes co affection than Hepatitis C alone[37]. A similar study done by Tolman and associates came up with elevated liver enzymes ALT in 24% of patients with type 2 diabetes mellitus and hepatitis C[38].

In our study participants, we observed lipids disorders in combined type 2 diabetes mellitus and hepatitis C. In Bashir et al, HCV with type 2 diabetes mellitus showed a marked increase in serum cholesterol and triglyceride level[37]. However this may be due to the fact that diabetes itself is a risk factor for dyslipidaemia but the combination of diabetes and dyslipidaemia in patients with hepatitis C increase cardiovascular risk in this latter group. Furthermore, fatty liver was most found in co-affected participants. In Wang et al, fatty liver was observed in less number than we did however still high (35.7%) patients with both type 2 diabetes mellitus and hepatitis C[39]. This is in accordance with the literature as diabetes causes Nonalcoholic fatty liver disease (NAFLD) [42].The co-existence of type 2 diabetes and hepatitis C may increase liver deterioration and cardiovascular risk factors in patients with hepatitis C. The addition of type 2 diabetes mellitus on hepatitis C can synergistically cause liver fibrosis through the mechanism of insulin resistance[18-19] .This should be taken into consideration while managing hepatitis C patients.

IV.2 Study limitations

There are certain limitations of this study. The most important are small sample size, single-Centered-hospital-based study and short period of 10 months which was unable to reflect the actual incidence of type 2 diabetes mellitus in HCV Patients.

In our study ,it was not possible to know in terms of hepatitis C infection and type 2 diabetes mellitus which came first to help in the causality and risk factors from each other.

Also in our study, we were not able to do liver biopsy for cirrhotic patients, ultrasonographically diagnosed.

IV.3 Local relevance and generalizability

Based on our study results and despite its limitations, it is important therefore for every patient with hepatitis C virus infection to also be screened for type 2 diabetes mellitus and vice versa. Patients with hepatitis C infection found by early detection would help us to stop the progression of the disease as nowadays we have proper treatment for infection for six months (Ribavurin and sofosbivir) and Harvoni for three months. Thus preventing the co-existence of type 2 diabetes mellitus induced by hepatitis C is essential. This can prevent the activation of the immune system by Th1 lymphocytes to induce diabetes. Furthermore, our study creates a significant local awareness of the association between type 2 diabetes mellitus and hepatitis C infection. This is a great preventative approach for patients. There is also needs to be simultaneous awareness among policy makers to put preventive measures on hepatitis C and type 2 diabetes mellitus.

Also these results will guard clinicians to educate patients about lifestyle modifications and diet as it has a significant impact on these two diseases.

Chapter V. CONCLUSSION AND RECOMMENDATION

Type 2 diabetes mellitus is prevalent in adult patients with hepatitis C at Rwanda Military Hospital and its co-existence with hepatitis C would have compounded negative impact on liver function as well as on lipid metabolism. There is a need for further in-depth studies to understand the pathophysiological mechanisms and causality.

As there was positive association between type 2 diabetes mellitus and HCV, it is necessary to screen and control earlier in life for the presence of type 2 diabetes mellitus in HCV-infected patients. It is also advisable to rule out HCV infection among the diabetic population.

To train all health care providers, particularly those working in the accident and emergency department as well as in internal medicine, to better recognize hepatitis C and diabetes mellitus as a co-morbidity.

To provide sufficient laboratory equipment to hospitals to be able to do HCV viral load for early detection of the hepatitis C virus infection, which would be useful in the management and prognostication of hepatitis patients.

To continue and support further studies on hepatitis C and type 2 diabetes mellitus comorbidity in larger sample sizes, consider multicentre, for further generalizability and guidance in the management of HCV and type 2 diabetes mellitus and look for further correlations on the mechanism and causality.

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APPENDICES

Consent form

I, **Dr Anthony BAZATSINDA** postgraduate in college of medicine and health sciences, school of medicine, internal medicine Department University of Rwanda, I hereby conducting a study entitled **prevalence of type 2 diabetes mellitus in adult patients with hepatitis c virus infection and associated laboratory markers. Experience at Rwanda Military Hospital.**

I hereby asking patient/caretaker…….. Permission of conducting or participating him/herself in our study entitled as above for the interest of Rwandans after completion of data collection and analysis of the results. There will be no identification of patient's names in this study so as he/she fears to be involved in the study and I will keep confidentiality of every patient and I will put the data in office and rock. No one else will be in contact with these data except me and investigator assistant. Thereafter the results will be communicated to the patient later. In case of any emergency to my patient during the study, always the patient is priority.

The study is about to see the relationship between HCV and diabetes mellitus, its prevalence and associated laboratory markers. Results will help us in national protocol, guidelines on treatment so as to improve management.

I ……..hereby confirm that i understand the content of this document and the nature of this research project, i consent to participate in this research project. I understand that I have the liberty to withdraw from the project at any time I desire.

We thank you to have accepted to participate in research project.

Name and Signature of the Participant

Investigator:

Dr Anthony BAZATSINDA

URUHUSHYA RWO GUKORERWAHO UBUSHAKASHATSI.

Njyewe, Muganga **Anthony BAZATSINDA** , umunyeshuri muri kaminuza y'u Rwanda , mu kicikiro cya gatatu, mw'ishami ry'ubuvuzi , mu rwego rwo kurangiza icyo kiciro ,ndimo gukora ubushakashatsi .

None ndagusaba uburenganzira bwokugukoreraho ubushakashatsi kubijyanye n'indwara y'isukari (Diabetes mellitus),twasanga uy'ifite tukaba twanagupima n'indwara y'umwijima (Hepatitis C) ibi ni mu rwego rwo kumenya niba hari ihuriro izo ndwara zombi zifitanye, kandi tugusanganye ubwo burwayi , tuzagufasha kubona ubuvuzi.

Ibizava mur'ubushakashatsi bizafasha urwego rw'igihugu rushizwe kwita kubarwayi bizo ndwara zavuzwe hejuru

Ibi bikorwa mw'ibanga risesuye hagati yanjye na we gusa.

Tubashimiye uburyo mwakiriye icy'ikifuzo.

Njyewe. . . . . nyuma y'ibisobanuro mpawe k'ur'ubushakashatsi bugiye gukorwa, nemeye kuba nabukorerwaho

Amazina Umukono w'ukoreweho Umuganga

Ubushakashatsi . **Anthony BAZATSINDA**

Approved by:

Institutional review board

University of Rwanda

School of medicine and pharmacy

PREVALENCE OF TYPE 2 DIABETES MELLITUS IN ADULT PATIENTS WITH HEPATITIS C VIRUS INFECTION AND ASSOCIATED LABORATORY MARKERS. EXPERIENCE AT RWANDA MILITARY HOSPITAL.

Work sheet on T2DM/HCV.

Demographic data

1. Age in year a. 18-40

   b. > 40

2. Gender a. male

   b. female

3. Residence a. urban

   b. rural

4. Marital status a. Single

   b. Married

   c. Separated

   d. Divorced

   e. Widow

5. Weight (Kg)

6. Height (m)

7. BMI (Kg/m^2)

   a.18

   B.18-24.9

   C.25-29.9

   D.30-34.9

E.35-39.9

f. >40

8. Family history of diabetes

a. Yes

b. No

c. Don't know

9. He/she is T2DM

a. Yes

b. No

c. Don't know

10. He/she is HCV +

a. Yes

b. No

11. Family history of HCV

a. Yes

b. No

c. Don't know

12. Any colour change to jaundice

a. Yes
b. No

13. Abdominal distension

a. Yes

b. No

14. Ultrasonography findings

a. Normal

b. Ascites

c. Fatty liver

d. Fibrosis

e. Cirrhosis

f. Fatty liver and ascites

15. Risk factors

a. Previous blood transfusion

b. Previous surgical procedure

c. Tattooing

d. Multiple sexual partners

e. Illicit self-injection

f. Exposure to office or household contact of jaundice

g. Dental extraction

h. Scarification

i. Ear piecing

j. Circumcision

k. Uvulectomy by doctors native

. Laboratory markers

a. LFT's - ALT a. Normal (1-41 U/L) b) Increased c) Decreased

- AST a) Normal (1-40 IU/L) b) Increased c) Decreased

- Albumin a) Normal (2.9-3.97 gms/dl) b) Increased c) Decreased

- INR a) Normal 0.8-1.2) b) Increased c) Decreased

- Total bilirubin a) Normal (0-17.1µmol/l) b) Increased c) Decreased

b. **Lipid profile** - Total cholesterol a) Normal (3.9-5.2mmol/l) b) Increased c) Decreased

- HDL a) Normal (0.9-1.68 mmol/l) b) Increased c) Decreased

- Triglyceride a) Normal (0.35-2.26 mmol/l) b) Increased c) Decreased

- LDL Normal (2.59-4.12) b) Increased c) Decreased

C. Hba1c a. <7

B.7.1-10

c. >10

d. HCV genotype

a. 1

b. 2

c. 3

d. 4

e. combination

e. HCV viral load according to National Genetics Institute assay

a. Negative (undetectable) <100 copies/ml

b. Low (>100-1,000,000)

c. Medium (1,000,000-5,000,000)

d. High (5,000,000-25,000,000)

e. Very high (>25,000,000)

Time frame.

The following was a proposed time-frame of the study process:

Number	Activity	Estimated Time
1	Proposal Development and Presentation	November 2014 to 5th- Jan 2015
2	Proposal Submission to the department for marking	January 2015
3	Submission of proposal for ethical approval	February 2015
4	Pretesting	March 2015
5	Data Collection	April 2015 to January 2016
6	Data Analysis	January 2016
7	Thesis writing	January 2016
8	Thesis submission for correction	February 2016
9	Thesis Final Submission	March 2016

Total sample size is 298 participants. The Study was done a period in 10 months because of the patient turnover in the

OPD specialized hepatitis and diabetes clinics and general medical ward.

Study budget.

Category	**Remarks**	**Units**	**Unit Cost (Rwf)**	**Total (Rwf)**
Proposal Development	Printing drafts	1000 pages	100	100000
	Proposal Copies	8copies	4500	36,000
	Literature review via internet (40 hours)			50,000
Laboratory Investigations.	Transport		100000	100,000
	Viral load	298	75000	22,350,000
	Lipid profile – LDL - TRIGLICERIDE - Total cholesterol - HDL	298	15,000	4,470,000
	Genotype of HCV	298	**NO REAGENTS**	**NOT DONE**
Data Collection	Stationery (pens, papers, etc).			50000
	Research assistant 1 for 10 months	1 Assistant	100,000 each month	1,000,000

Data Analysis	Statistician	1	200,000	200,000
Thesis Write Up	Printing drafts	1000 pages	250,000	250,000
	Printing Thesis	10 copies	25000	250,000
Contingencies 5%				**144280**
Grand total				**29,000,280**

Ethical clearance

UNIVERSITY OF RWANDA

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 3rd /11/2015

Dr BAZATSINDA Anthony
Principal Investigator
School of Medicine and Pharmacy, CMH, UR

Ethical Approval Notice: No 334/CMHS IRB/2015

Re: Your research project entitled *"The Prevalence Of Type II Diabetes Mellitus In Hepatitis C Patients Associated With Laboratory Markers In Specialized Hepatitis Clinics In Rwanda Military Hospital"*

After reviewing your protocol by full review board procedure of 4th July 2015 and revisions made on the advice of the RNEC submitted on 30 th August 2015, we are pleased to inform you that **your ethical clearance has been approved** by the CMHS IRB.

Please note that approval of the protocol and consent form is valid for 12 months.
Date of Approval: 3rd November 2015
Expiry date: 3rd November, 2016

You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval
5. Failure to submit a continuing review application will result in termination of the study
6. Notify the IRB committee once the study is finished

Professor Kato J. NJUNWA
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Cc:
- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate studies, UR

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