HELICOBACTER PYLORI INFECTION AMONG DIABETIC AND NON-DIABETIC PATIENTS AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA

BY

JANE EVERLYNE AKINYI OWUOR

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DECLARATION

Student's Declaration:

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Jane Everlyne Akinyi Owuor.

SM/PGM/01/18

Signature: …… Date: ……

Declaration by Academic Supervisors

We submit this thesis for marking with our approval as university supervisors.

Dr. Fatuma F. Some.

Specialist Physician & Senior Lecturer,

Department of Medicine, Moi University.

Signature: …… Date: ……

Prof. Abraham M. Siika.

Associate Professor of Medicine,

Department of Medicine, Moi University.

Signature: …… Date: …….

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DEDICATION

I dedicate this work to my family, thanking them for their love and support.

Special dedication to my mother, for the huge support every step of the way.

ABSTRACT

Background: Globally, the burden of Diabetes Mellitus (DM) and Helicobacter pylori (*H. pylori*) infection is vast, both conferring significant morbidity and mortality risks. *H. pylori*, categorized as a class 1 carcinogen by WHO, has been identified as a common pathogen in DM, and has also been linked to altered glucose metabolism, increasing risk of gastric malignancy and DM complications. While it is thought that patients with DM are at increased risk of acquiring *H. pylori*, because of impairment in their humoral and cellular immunity, the results of several studies investigating this association are conflicting. Data on this association is limited in sub–Saharan Africa, including Kenya.

Objectives: To determine the prevalence of *H. pylori* in patients with and without DM, and to describe any association between DM and *H. pylori* infection, in patients attending clinics at Moi Teaching and Referral Hospital (MTRH) Eldoret, Kenya.

Methods: This hospital-based cross-sectional comparative study was conducted at outpatient clinics, MTRH, Eldoret, between December 2020 and April 2021. A total of 470 unmatched participants were enrolled. (232 with DM and 238 without DM). *H pylori* prevalence was compared between those with DM and those without DM using *H. pylori* antibody test. Null hypothesis was that the prevalence of *H. pylori* is similar in both groups. Two sampling techniques were employed: 1) systematic random sampling for the DM group and 2) simple random sampling for the non-DM group. Standardized interviewer administered questionnaires were used to collect demographic, socioeconomic and medical history data. *H. pylori* serum antibody tests were done and recorded for both groups. Categorical data were summarized using frequencies and continuous variables were summarized using means and medians with corresponding SD and IQR respectively. Bivariate analysis was conducted to test for association. Level of significance was set at $p<0.05$. This study was approved by the MTRH/Moi University Institutional Research and Ethics Committee (IREC).

Results: Positive *H. pylori* antibody test was found in 142/470 (30.4%) of the participants. In the DM group, 68/232 (29.3%) had a positive *H. pylori* antibody test while in the non-DM group, 75/238 (31.5%) were positive (p=0.604; 95% CI). In both groups the prevalence of *H. pylori* was not associated with age, gender, level of education, body mass index, alcohol, smoking, increased number in household, presence of pets or domestic animals, type of waste disposal or type of toilet facility. For DM group, there was no difference in the prevalence of *H. pylori* between Type 1 and 2 DM (p=0.088; 95% CI). *H. pylori* seropositivity was not associated with duration of DM in this group.

Conclusion: The prevalence of *H. pylori* infection is not increased in those with DM. There is no association between DM and *H. pylori* infection. This study failed to reject the null hypothesis.

Recommendation: The same *H. pylori* screening guidelines for general population should be used in DM patients. Larger multicentre studies need to be conducted in different settings to corroborate the study findings.

LIST OF ABBREVIATIONS

BMI	Body Mass Index
DM	Diabetes Mellitus
DM2	Diabetes Mellitus Type 2
DOPC	Diabetic Outpatient Clinic
ENT	Ear Nose Throat
H. pylori	Helicobacter pylori
HP	Helicobacter pylori
IgG	Immunoglobulin G
MTRH	Moi Teaching and Referral Hospital
OR	Odds Ratio
PPI	Proton Pump Inhibitors
WHO	World Health Organization
RBS	Random blood sugar
FBS	Fasting blood sugar
HBA1C	Hemoglobin A1c (Glycated hemoglobin)

DEFINITION OF TERMS

Alternate hypothesis	Used in statistics to indicate that there is a significant difference between the specified populations.
Antibody	Protective protein produced in blood in response to foreign substances. They bind to the foreign substances and enhance their clearance from the blood stream.
Biological plausibility	Method of reasoning used to ascertain a cause-and-effect association between a biologic factor and a disease.
Carcinogen	Any substance of that can cause cancer.
Dr	Doctor.
Dysautonomia	Dysfunction of the autonomic nervous system.
Dyspepsia	Abdominal discomfort after meals.
Gastroparesis	Delayed gastric emptying.
Null hypothesis	Used in statistics to indicate that there is no significant difference between specified populations.
Interleukins	Proteins released by white blood cells. They are responsible for regulating immune responses.

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CHAPTER ONE: INTRODUCTION

1.1 Background

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium that colonizes the stomach causing peptic ulcers, chronic gastritis and gastric cancer. *H. pylori* has been identified as the most common cause of peptic ulcer disease globally. In addition, it accounts for the majority, which is estimated to be about 90% of gastric cancers. There is evidence from literature, including several clinical trials that early eradication of *H. pylori* significantly reduces the incidence of, and mortality rates associated with gastric cancer (Moss, 2017). Globally, *H. pylori* is estimated to affect up to 4 billion people (Kato et al., 2019), with the highest prevalence rates in developing countries, especially in Africa, and this has been attributed to low socioeconomic status (Hooi et al., 2017). In Kenya, the prevalence of *H. pylori* is estimated at 55% and 73% in dyspeptic adults, and children respectively (Kimang'a et al., 2010).

H. pylori also has an increased prevalence in developing countries, especially in Africa with a prevalence of about 70%. It has been identified as class 1 carcinogen by WHO. There is increasing risk of gastric cancer especially in the background of gastric epithelial changes that occur as seen in DM. H. pylori has also been associated with altered glucose metabolism, insulin resistance and elevated HbA1c levels, worsening DM complications associated with hyperglycemia. H. pylori has also been associated with immunosuppression secondary to reducing the functions of macrophages, dendritic cells and CD4 T lymphocyte cells (Moyat, 2014).

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to impairment of insulin action, secretion or both. The American Diabetes Association classifies diabetes mellitus (DM) into: Type 1; Type 2; Gestational; and other types of diabetes (Kharroubi & Darwish, 2015). Over the last 4 years, global prevalence of diabetes mellitus has risen rapidly. This is especially in middle- and low-income countries. The World Health Organization (WHO) recommends regular screening and treatment of complications associated with diabetes ("Diabetes", 2018). In Kenya, as per Diabetes statistics, the prevalence is increasing at a distressing rate, and according to WHO reports, there is an anticipated rise to 4.6% by the year 2025 from the current 3.3 %. Kenya was also ranked by International Diabetes Federation as the 31st African country based on documented prevalence of approximately more than 450 cases of DM per 10,000 of population (Katambo, 2021).

The bacterium *H. pylori* has been identified as a common pathogen causing gastrointestinal infection in people with diabetes mellitus. This is especially in cases of inadequate or poor glycemic control. *H. pylori* typically colonizes the gastric antrum, and with the presence of inflammatory cytokines such as interleukins 1, 2 and 8 in the gastric epithelium, inflammation commences, causing damage and structural changes in the gastric epithelium. Chronic inflammation leads to increased risk of abnormal repair with epithelial metaplasia, increasing the risk of gastric cancer (Devrajani, Shah, Soomro and Devrajani, 2010).

Diabetes has been identified as a potential risk factor for acquiring *H. pylori* infection. While there is no clear proof for this, 4 postulates have been advanced to explain the connection:

1) Impaired cellular and humoral immunity characterized by failure to shift to a balanced cytokine response, which indicates optimum mucosal resistance

(Borody, Ren, Pang & Clancy, 2002).

2) Diabetic gastropathy characterized by delayed gastric emptying (Jeon et al., 2012).
3) Altered glucose metabolism (de Luis et al., 1998, He, Yang & Lu, 2014).
4) Exposure to various pathogens in the diabetic population (Gentile, Turco, Oliviero & Torella, 1998, He, Yang & Lu, 2014).

Alluding to the 4 postulates, several studies have examined the association between diabetes mellitus and *H. pylori*, but with conflicting results. In Africa, 2 studies exploring this association have been published, both from Nigeria. One reported a higher prevalence of *H. pylori* in a DM population compared to controls (Ugwu et al., 2008) whereas the other reported no difference in prevalence between the two groups (Oluyemi et al., 2012).

In Kenya, there is no published data on association. Closest to examining an association was a study conducted at Kenyatta National Hospital whose objectives were to look at prevalence of *H. pylori* in dyspeptic patients with diabetes mellitus and in those without diabetes mellitus. Method used for diagnosis was endoscopy with biopsy for histology. The results from the study showed no significant difference in endoscopic lesion findings and *H. pylori* in those with DM and those without DM (Wafula et al., 2002).

This is evident that there is uncertainty regarding the association of DM and *H. pylori*, warranting additional studies that will contribute to some conclusion.

1.2 Problem Statement

Globally, the prevalence of DM is high and increasing. It has currently been identified as a global threat based on the persistence increase in prevalence noted and recorded over the last four decades. It has also been predicted that DM will reach pandemic levels by 2030, and this will mainly affect middle- and low-income countries, including Kenya. In Kenya, apart from the anticipated rise, more than two thirds are unaware of their diabetes status and are undiagnosed (Katambo, 2021). With the increase in the prevalence, and DM having both long term and short-term complications, there is an increased risk of premature morbidity and mortality rates.

Both DM and *H. pylori* infection are now common in developing countries, and in Kenya to be precise. Both are known to have short- and long-term complications that increase morbidity and mortality rates. DM with *H. pylori* co infection portends even a greater risk for complications associated with hyperglycemia, with increased morbidity and mortality associated with immunosuppression secondary to *H. pylori* co infection. How this happens: *H. pylori* has been identified as a common pathogen in DM population, and this can be supported by the study conducted at KNH where all lesions, both cancerous and non-cancerous were associated with *H. pylori.* Furthermore, *H. pylori* has been associated with insulin resistance, altered glucose metabolism, and elevated HbA1c levels. Failure to eradicate *H. pylori* in the setting of DM may lead to treatment failure in DM patients with an increased risk of complications associated with hyperglycemia, worsening of immunosuppression with possibility of recurrent infections and increased risk of gastric cancer as a late complication.

Both DM and *H. pylori* cause chronic gastritis, causing pain and discomfort to the patient. Misdiagnosis of the cause of such gastritis will prolong the patient's agony and expenditure due to prolonged ineffective treatment.

1.3 Justification and Significance of the Study

At present, there is paucity of data. The subject on association between DM and *H. pylori* is still controversial. Several studies have been done in different parts of the world, but with conflicting results. In addition, there is very little data on the topic, especially in sub-Saharan population, including Kenya. No data has been published in Kenya looking at an association between DM and *H. pylori*, yet both are common in Kenya with risks of premature morbidity and mortality.

At the moment, based on the conflicting results, biological plausibility is still questionable. It is still a matter of conjecture how DM is a predisposing factor to acquisition of *H. pylori* infection, and whether there is an association between the two medical conditions. In addition, the prevalence of *H. pylori* among people with DM in Uasin Gishu area and Eldoret town, Kenya, is unknown.

H. pylori infection has been associated with high HbA1c levels, altered glucose metabolism and insulin resistance. Failure to eradicate early leads to poor glycemic control and increased risk of DM complications associated with hyperglycemia. Early screening and eradication also prevent treatment failure. Once DM complications such as gastropathy set in, it becomes difficult to eradicate *H. pylori* due to poor antibiotic absorption through the gastrointestinal system.

The study would objectively inform on the burden of *H. pylori* among DM and non-DM population with possible development of screening and treatment protocols, with increased health benefits if a cause-and-effect relationship is ascertained. The study

would also determine whether there is any association between DM and *H. pylori*, and whether DM is a risk factor for acquisition of *H. pylori* infection.

There is also plethora of evidence regarding reduction of incidence of gastric cancer by almost half with early *H. pylori* eradication, which is also applicable to the DM population. This study will help in creation of awareness, putting in place timely eradication measures of *H. pylori* in diabetes mellitus and prevention of gastric cancer, hence, decrease in mortality rates if indeed there is found to be an association between DM and *H. pylori*. According to data published by WHO in 2018 on cancer burden, Kenya has been ranked as the 48th country in the world based on rate of death from gastric cancer.

1.4 Research Question

Is the prevalence of *H. pylori* infection increased in those with DM compared to those without DM?

1.5 Objectives

1.5.1 Broad Objective

To determine whether the prevalence of *H. pylori* infection is increased in patients with DM compared to those without, at Moi Teaching and Referral Hospital (MTRH) Eldoret, Kenya.

1.5.2 Specific Objectives

1. To determine the prevalence of *H. pylori* in DM and in non-DM patients and whether there is an association between DM and *H. pylori*.
2. To describe the association of *H. pylori* with potential risk factors.

1.6 Hypothesis

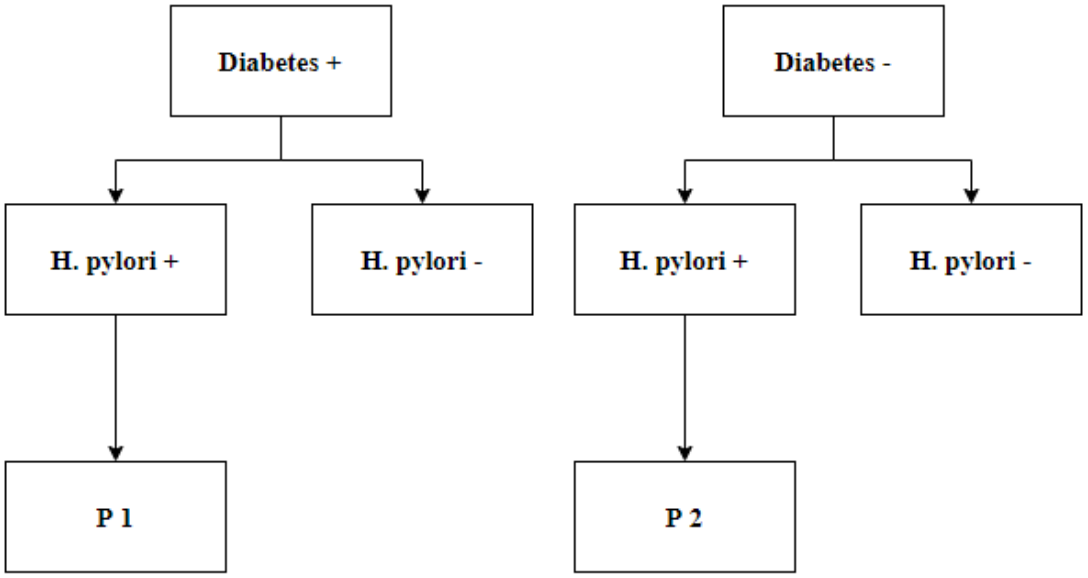

Figure 1: Study flowchart

Figure 1 is a summarized flowchart on how the study was conducted. The proportion of participants in the DM population who tested positive for *H. pylori* were designated as P1 while the proportion of participants in the non-DM population who tested positive for *H. pylori* were designated as P2. Therefore, the null and alternate hypothesis was as follows:

Null hypothesis: The prevalence of *H. Pylori* in people with DM is the same as in those without DM (P1 = P2)

Alternate hypothesis: The prevalence of ~~*H.*~~ *H. pylori* in people with DM is greater than in those without DM (P1≠P2). Based on a previous study in Nigeria, it was anticipated that the difference in the prevalence would be 7% (Ugwu et al., 2008).

CHAPTER TWO: LITERATURE REVIEW

2.1 Helicobacter pylori

Helicobacter pylori is a gram negative, spiral microaerophilic bacterium that was discovered in 1982 by Barry Marshall and Robin Warren as the main causative agent of peptic ulcer disease and gastritis. Prior to the discovery, it was believed that the human stomach was a sterile area (Khalifa et al., 2010). Presently, *H. pylori* is recognized as the most common cause of peptic ulcer disease, gastritis, and gastric cancer globally (Akushe et al., 2015). In 1994, *H. pylori* was ranked as a Class 1 carcinogen by WHO (Ahn & Lee, 2015), accounting for approximately 90% of gastric cancers (Moss, 2017). It has also been ranked as one of the top carcinogens worldwide. Early eradication, as proven by several large, randomized trials, decreases the risk and incidence of gastric cancer by half (Ford et al., 2015; Lee et al., 2016; Moss, 2017).

The global prevalence of *H. pylori* in 2015 was approximated at 4.4 billion (Hooi et al., 2017). A systematic review and meta-analysis on global prevalence of *H. pylori* done in 2017 showed that USA and Australia had the lowest prevalence at 35.6% and 24.6% respectively. The highest prevalence regions were Africa (70.1%), South America (69.4%) and Western Asia (66.6%). In Africa, Nigeria had the highest prevalence (87.7%). In East Africa, the seroprevalence of *H. pylori* is between 55 and 75%, whereas in Kenya it is estimated to be at 55% in dyspeptic adults, and 73% in children (Jaka et al., 2018; Kimang'a et al., 2010). Locally, at MTRH, Sang, (2013) found the prevalence of *H. pylori* to be at 52.3 % in adult patients with dyspepsia.

According to the latest data published by WHO in 2018, the rate of death from gastric cancers in Kenya was at 0.65% (1,647) of the total deaths. The reported age adjusted rate was 9.65 per 100,000 of population, ranking Kenya as the 48th country in the world (Stomach Cancer in Kenya, 2021). In Kenya, the third leading cause of death after infectious diseases and cardiovascular diseases is cancer (Macharia et al., 2019). It is estimated that almost 30% of the absolute cancer burden in the sub- Saharan region of Africa is due to infections, precisely *H. pylori*, HPV (human papilloma virus), HBV (hepatitis B virus), and HCV (hepatitis C virus), which contribute greatly to cancer burden globally. In totality, they account for approximately 92% of all cancers secondary to infections worldwide. *H. pylori* leads at 35.4%, followed by HPV at 29.5%, HBV at 19.2% and HCV at 7.8% (Plummer et al., 2016).

H. pylori has been associated with extra gastrointestinal conditions. Examples include:

1. Immunological – Immune thrombocytopenic purpura and vasculitis.
2. Vascular – Atherosclerosis and Ischemic Heart disease.
3. Liver and biliary disorders – Nonalcoholic fatty liver disease, gall bladder malignancy, hepatocellular carcinoma and transaminitis.
4. Autoimmune – Autoimmune thyroiditis.
5. Hematological – Iron deficiency anemia and Vitamin B12 deficiency anemia.

(He, 2014; Shi et al., 2013; Zare et al., 2012; El-Eshmawy et al.,2011; Gravina et al., 2020).

2.2 *H. pylori* transmission

Modes of transmission of *H. pylori* are still unclear (Blanchard & Czinn, 2001; Stone, 1999) but proposed modes of transmission are many. Natural reservoirs of *H. pylori* are humans, other vectors include animals, water and food (Mehtar, 2018).

The bacterium has been identified in drinking water suggesting that it can be passed through ingestion of contaminated water (Stone, 1999). There is also evidence regarding transmission through contaminated food, especially uncooked vegetables (Hopkins et al., 1993). Faecal oral route of transmission has been identified as the most common route especially in developing countries with low socioeconomic status (Blanchard & Czinn, 2001), poor sanitation and drainage systems (Awuku et al., 2017; Etukudo et al., 2012). Frequently used markers for socioeconomic status are occupation, education, wealth and household income. These indicators give information on the ability of an individual to access both social and economic resources (Duncan et al., 2002).

Person to person route of transmission has also been reported (Blanchard & Czinn, 2001) via oral route. *H. pylori* has been cultured from the oral cavity with isolates from saliva and dental plaques (van Duynhoven & de Jonge, 2001). Based on isolation of *H. pylori* from saliva, it is also postulated that *H. pylori* can be transmitted via other sexual activities (Eslick, 2000). Person to person transmission mostly occurs in overcrowded houses especially between siblings (Kivi & Tindberg, 2006) and mothers to children (Weyermann et al., 2006).

Another mode of transmission is iatrogenic, associated with medical procedures involving unsterilized endoscopes and probes shared amongst patients (Favero & Pugliese, 1996). The complexity of medical instruments and scopes making

disinfection and sterilization a bit difficult, poses as a major contributing factor to iatrogenic transmission (Fantry et al., 1995). In developed countries, the mode of transmission via upper gastrointestinal endoscopes is curbed, due to the use of single use forceps for biopsy and follow up of reprocessing of the endoscopes. Since *H. pylori* is highly susceptible to most commonly used disinfectants, appropriate reprocessing prevents inoculation of the scopes by the bacterium (Mehtar, 2018).

In hospital setting, there have been reports on patient to staff member transmission and staff to staff transmission (Lin et al., 1994; Peters et al., 2011). A systematic review looking at work-related risk of *H. pylori*, specifically the prevalence of *H. pylori* in specific occupational groups in comparison to general population, determined that healthcare professionals had a higher prevalence compared to the general population (Kheyre et al., 2018). Occupational modes of transmission from staff to patient and vice versa could be through contact with infected body fluids (De Schryver et al., 2004) including gastric juice, saliva, urine and feces (Makristathis et al., 1998; Vaira & Vakil, 2001). Up to 13 studies as identified from a meta-analysis, documented a higher prevalence of *H. pylori* among healthcare workers in comparison to the general population (Kheyre et al., 2018).

Recently, studies have been published on the possibility of mother to child transmission. An example is a prospective study that was conducted in Japan, with a 5 year follow up. The aim of the study was to determine the prevalence of *H. pylori* in children born to *H. pylori* positive mothers. Results showed that transmission from mother to child is possible (Konno et al., 2005). *H. pylori* IgG antibodies have also been reported to cross the placental barrier causing mother to child transmission (Blecker et al., 1994).

H. pylori has also been identified and isolated in saliva and gastric tissues of some domestic animals including cows and sheep, thereby proposing the possibility of transmission from animals as reservoirs through food contamination (Zamani et al., 2017). *H. pylori* DNA has also been detected and isolated from animal dairy products. The organism has been isolated from milk from sheep and cows (Momtaz et al., 2014).

After transmission, *H. pylori* infection is usually asymptomatic. Symptoms are usually present after development of complications such as peptic ulcer disease, gastritis, or duodenal inflammation These symptoms; abdominal pains, nausea, vomiting, and dyspepsia are non-specific and could be due to other gastrointestinal conditions or diseases (Abbas et al., 2018). Only about 3 to 15% develop complications such as peptic ulcers, otherwise majority are asymptomatic (Mehtar, 2018).

H. pylori infection commonly manifests as chronic gastritis. The bacterium causes gastritis characterized by reduced levels of gastric acid (hypochlorhydria). This form of acute gastritis slowly evolves into a chronic form, which is active and can affect different parts of the stomach; either the corpus, the antrum of the stomach or both. Infection of the corpus is characterized by gastric atrophy and achlorhydria (absence of hydrochloric acid secretion) whereas infection of the antrum (lowest portion close to the intestines) is characterized by duodenal ulcers and increased acid secretion (Diaconu et al., 2017).

An article published by American Academy of Family Physicians indicated that about 90% of people infected with *H. pylori* will be asymptomatic (Meurer and Bower, 2002). Asymptomatic *H. pylori* infection has been reported mainly in developing

communities (Figueiredo, 2002). Because *H. pylori* is usually asymptomatic, timely selection of patients for diagnosis and management is essential to minimize complications associated with the infection (Ansari & Yamaoka, 2018). Asymptomatic or not, according to a global consensus report by Kyoto on *H. pylori* gastritis, *H. pylori* has been identified as an infectious disease requiring eradication (Sugano et al., 2015).

2.3 Risk factors and *H. pylori*

H. pylori is mostly transmitted through the faeco-oral route. Therefore, the findings of a high prevalence of the infection in sub-Saharan Africa is likely to be related to the region's poor socio-economic and sanitation status (Awuku et al., 2017). Overcrowding in households, use of other sources of water except borehole and piped water, and open- air defecation versus latrine and water closets increase the prevalence of *H. pylori*, as documented in cross-sectional studies conducted in rural communities in Africa (Khalifa et al., 2010; Etukudo et al., 2012; Awuku et al., 2017). Overcrowding in households in addition to sharing of beds increase the risk of acquiring and transmitting *H. pylori* as there have been reports on isolation of the same strain of *H. pylori* in spouses living in the same house (Moayyedi et al., 2002).

A cross sectional survey in rural China revealed that increased prevalence of *H. pylori* was associated with low levels of education, poor hygiene practices such as irregular handwashing, overcrowding in households with sharing of utensils, and use of water from shallow wells (Brown et al., 2002). With education, the more an individual is educated, the more likely they are to engage in self health enhancing practices and activities (Duncan et al., 2002), reducing the risk of *H. pylori* infection and transmission.

Poor sanitation is listed as one of the major risk factors for acquiring *H. pylori* infection, and sanitation and, drainage systems in Kenya vary depending on location. According to a report made by water.org (2021), rural areas and urban slums in Kenya are the most affected areas with poor sanitation because of lack of connection to piped water infrastructure. The same report indicated that, with a population of around 50 million, 24 million have no access to improved sanitation and 16 million have no access to safe water. In addition, around 48% are deprived of basic sanitation solutions and 32% depend on unimproved sources of water such as rivers, wells, and ponds. Unfortunately, not all areas in urban and semi-urban areas with connections to piped water have constant water supply, thereby depending on other solutions such as rainwater harvesting tanks and boreholes ("Kenya's Water Crisis - Kenya's Water In 2020 | Water.org", 2021). Another report made by UNICEF stated that only about 59% people in Kenya have access to safe drinking water, and only 29% have access to improved sanitation. About 9.9 million Kenyans drink from contaminated water sources ("Water, Sanitation and Hygiene", 2021).

Pets and domestic animals have also been identified as sources of *H. pylori* infection. Cats and sheep also harbor *H. pylori* and have been identified as reservoirs and risk factors for human infection (Feldman et al., 1998). While both animals are prevalent in well to do and poor communities, those in the latter are at greater risk of getting the infection from their animals presumably because of poorer hygiene standards compared to developed countries.

Educational status has been used both as a proxy marker and an important determinant of socioeconomic status (Rosenstock et al., 1996; Awuku et al., 2017). Again, the levels of education are higher in developed countries, and this might

explain the reduced prevalence of the infection. According to a report by United Nations in 2018 on education in Africa, it was documented that training programs and education in Africa suffer from low quality learning and teachings. In addition, the report stated that there is inequality and exclusions at all levels of education in Africa (Musau, 2018).

H. pylori infection causes chronic inflammation and is linked to changes in BMI, insulin resistance and metabolic syndrome (Chen et al., 2018). There have been reports on a positive *H. pylori* association with obesity and increased BMI, based on results of a study conducted in Chinese population (Xu et al., 2019). This has also been supported by other studies conducted in other regions (Arslan et al., 2009). A cohort study conducted in Israel reported a higher prevalence of *H. pylori* in patients with increased BMI compared to those with normal weights regardless of the socioeconomic status (Suki et al., 2018). On the contrary, in developed countries, there are studies that have reported a negative association between *H. pylori* and obesity (Lender et al., 2014).

Alcohol consumption has been identified as a protective factor, decreasing the risk of acquiring *H. pylori* infection. This has been attributed to the fact that alcohol consumption increases gastric acid production hence creating an environment that is unfavorable and harsh for *H. pylori* colonization and subsequent infection (Brenner et al., 1999). The inverse relationship between alcohol consumption and *H. pylori* infection has also been supported by other studies conducted globally: in Germany (Kuepper-Nybelen et al., 2005) and Italy (Luzza et al., 1998). A meta-analysis looking at the association concluded that the risk of *H. pylori* infection is lower in alcohol consumers compared to non-consumers, with mixed types of alcohol and wine

reporting better outcomes compared to beer (Du et al., 2021). On the contrary, some studies have reported no major or significant association (Moayyedi et al., 2002; Rosenstock et al., 2000; Ito et al., 2001).

Association between *H. pylori* and cigarette smoking has also been examined, but with conflicting results. It has been argued that nicotine present in cigarettes can and may promote colonization of the gut by *H. pylori*, possibly secondary to alteration of blood flow to the gastric mucosa and secretion of mucus which is a protective factor (Zhang et al., 2009). Maintenance of both gastric and duodenal mucosa integrity is by balance between protective and aggressive factors of both endogenous and exogenous origin (Abdel-Salam et al., 2001). Aggressive factors of endogenous origin include, hydrochloric acid, gastric enzymes like pepsin, bile acid and stomach contents. Exogenous aggressive factors include medications such as non-steroidal anti-inflammatory drugs (NSAIDS), toxins, alcohol and cigarette (Richardson, 1985; Abdel-Salam et al., 2001). Protective factors maintain gastric mucosa integrity despite irritation by endogenous and exogenous aggressive factors. Protective factors include constant blood flow supplying nutrients and oxygen, mucus, prostaglandins and peptide growth factors (Tarnawski et al., 2012; Laine et al., 2008). Some studies found a positive relationship between smoking and *H. pylori* (Woodward et al., 2000; Murray et al., 1997), whereas others reported no association (Moayyedi et al., 2002; Rosenstock et al., 2000; Zhang et al., 2009).

In adults, male gender has been associated with an increased risk of acquiring *H. pylori* infection in various countries. This has been documented from results of a large population-based meta-analysis (de Martel and Parsonnet, 2006), and cross-sectional studies conducted in Israel using urea breath test (Moshkowitz et al., 2012) and in

Douala Cameroon (Kouitcheu Mabeku et al., 2018). The high prevalence of *H. pylori* in male gender as supported by studies, could also explain the dominance of *H. pylori* related disorders such as peptic ulcers and adenocarcinomas in the same gender (Moshkowitz et al., 2012).

2.4 Diagnosis of *H. pylori* infection

Diagnostic preferences for *H. pylori* infection depend on the prevalence and the incidence of age-related gastric cancer in different regions (Ansari & Yamaoka, 2018). Preference of non-invasive methods of diagnosis is where the incidence of gastric cancer is low, and endoscopy is used where the incidence of gastric cancer is high, or in individuals at risk of gastric cancer, e.g., those who are above the age of 60 years and or those with a positive family history of gastric cancer (Asaka et al., 2010).

As shown in Table 1, diagnosis of *H. pylori* can either be invasive or non-invasive (Talebi Bezmin Abadi, 2018).

The invasive methods, which are the most accurate and considered gold standard, involve the use of endoscopy, biopsy for histology, and culture. Although accurate, these methods are rarely used because they are costly and cumbersome (Shimoyama et al., 2009). Other disadvantages of invasive methods of diagnosis include possible transmission of infections such as Human Immunodeficiency Virus (HIV) and Hepatitis through contaminated instruments and medical devices (Kovaleva, 2016) and the fact that patients would require some time in order to be prepared for the procedure (Talebi Bezmin Abadi, 2018). Although considered gold standard, endoscopy with biopsy has its shortcomings. It is difficult to detect *H. pylori* using only one biopsy specimen, this is due to the bacterium's nature of patchy distribution in the stomach (Kusters et al., 2006). Therefore, reliable diagnosis requires obtaining

multiple biopsy specimens, but gastroenterologists are only limited to a maximum of five biopsies (Megraud & Lehours, 2007). In addition, it is difficult and challenging to perform endoscopy in certain groups of people, such as children, pregnant women and the elderly (Ricci et al., 2007). In pregnancy, there are concerns regarding both fetal and maternal safety (O'Mahony, 2007). Associated risks in pregnancy include radiation exposure, trauma, teratogenic effects and premature labor (Shergill et al., 2012). Another challenge with endoscopy and biopsy involves transportation of the specimen which should be done with extra caution, without exposure to room air or oxygen and within four hours after collection (Talebi Bezmin Abadi, 2018). Endoscopy associated adverse effects or events are infections, perforation, bleeding and anesthesia or sedation related physiological changes (Lightdale et al., 2019). Due to these complications, a preoperative check list is used to assess patients and potentially alleviate risks (Ragsdale, 2011).

Based on the serious complications that may arise during endoscopy, some guidelines, i.e., Canadian association of Gastroenterology and American College of Gastroenterology, recommend performing endoscopy in patients who are 60 years of age or older, are symptomatic for *H. pylori* or come from a region with a high incidence of gastric cancer, or have a positive family history of gastric cancer (Moayyedi et al., 2017). On the contrary, European guidelines recommend endoscopy in patients who are equal to or more than 45 years of age with a high risk of gastric cancer (Smith et al., 2017).

Histology is considered the gold standard and most accurate for detection of active *H. pylori* infection. However, there are a few factors that influence diagnostic accuracy of this method. These limiting factors include, the site of biopsy, the size per biopsy,

number of biopsies taken, type of staining method used, prior antibiotic use (before procedure), use of proton pump inhibitors (before procedure) and the pathologists experience. Proton pump inhibitors may alter histology findings; therefore, recommendation is made to stop these medications at least two weeks before the test is performed (Malfertheiner et al., 2012). Staining is also plays a major role as part of diagnosis. Commonly used stains for diagnosis are Immunohistochemical stain, Hematoxylin and eosin stain, Giemsa stain and Ancillary stain (Batts et al., 2013). Giemsa satin is highly sensitive, simple and relatively cheap (Rotimi et al., 2000). There is an exclusive method named PNA-FISH (Peptide nucleic acid fluorescent *in situ* hybridization) used on histological preparations. This method has a sensitivity of 97% and specificity of 100% in detection of *H. pylori*. This method can detect coccoid forms of the bacterium which is usually not picked up by routine histological methods (Cerqueira et al., 2013).

Rapid urease test is invasive and is done on biopsy specimens. It is quite expensive and necessitates mass spectrometric analysis. This is unavailable in resource limited regions and centers (Kato et al., 2004). Another limitation of this test is that a minimum of 10,000 bacteria is required for a positive test (Wang et al., 2015). Depending on the manufacturers, different commercially produced rapid urease tests have different turnaround time for results. Reading results earlier give false negative results (Vaira et al., 2009). Antibiotics and proton pump inhibitors can also affect test results; therefore, it is recommended to be off antibiotics for at least four weeks and proton pump inhibitors for at least 2 weeks before conducting the test (Gisbert & Abraira, 2006).

Non-invasive methods are the urea breath test method, which is considered the most accurate; stool antigen test; and serology for *H. pylori* antibodies; (Douraghi et al., 2013). Majority of physicians, who also take part in making guidelines recommend the use of non-invasive test methods as the initial step to testing and screening for *H. pylori* infection (Zagari et al., 2015). For detection of an active infection, with the intention to treat, stool antigen test is considered most accurate, effective and cost efficient (Malfertheiner et al., 2012). Non-invasive methods are easy to perform and are mostly recommended in primary care setting areas (Ricci et al., 2007). Serology testing on the other hand is useful in mass surveys and epidemiological studies (Douraghi et al., 2013; Raj et al., 2017).

Urea breath test can be used for diagnosis of an active infection, monitoring after eradication therapy and epidemiological research. Due to exposure to some degree of radiation, this test is contraindicated in pregnant women and children (Ferwana, 2015). *H. pylori* produces an enzyme called urease, that can degrade urea.To perform this test, patient ingests either non-encapsulated or encapsulated form of urea, and after about 15 minutes, marked carbon dioxide is measured in the exhaled air after degradation of urea by *H. pylori* in the stomach (Pathak et al., 2013; Ferwana, 2015). Proton pump inhibitors can affect the results of a urea breath test; therefore, it is recommended that the medication be stopped 4 weeks to the procedure (Graham et al., 2003) and repeat test after eradication therapy should be done from 4 to 8 weeks after treatment (McColl, 2010).

Polymerase chain reaction (PCR) has also been used broadly for *H. pylori* infection diagnosis. PCR is performed on specimens like saliva, gastric juice, stool and biopsy samples. This test has a sensitivity and specificity of more than 95% and can detect

H. pylori in the presence of active bleeding, unlike other tests such as urea breath test. PCR is also faster, does not require any special processing, and can detect fewer bacteria in the sample (Momtaz et al., 2012; Saez et al., 2012). PCR method can also detect genetic variations in virulent factors of *H. pylori*, thus giving more information on different strains of *H. pylori* (Almeida et al., 2014; Siddique et al., 2014). Another advantage of PCR method is ability to identify *H. pylori* in samples such as water, which is useful for epidemiological studies (Amirhooshang et al., 2013). The bacterium has also been detected in salads and vegetables using PCR method (Atapoor et al., 2014).

Stool antigen test detects the presence of *H. pylori* antigens in stool. It can be used as ICA (immunochromatographic assay) or EIA (enzyme immunoassay) (Tonkic et al., 2018). Monoclonal or polyclonal antibodies can be used, but from literature, monoclonal based tests appear to be more accurate than polyclonal based tests (Gisbert et al., 2006). Stool antigen test can be used for both diagnosis of an active infection and monitoring of eradication after treatment. Repeat test after eradication therapy should be done 4 weeks after completion of treatment (Vaira et al., 2002). Recent antacids use, especially proton pump inhibitors, antibiotics and low bacteria load may give a false negative result (Manes et al., 2001). Results of stool antigen test may also be altered or affected when the stool is watery, because of dilution of *H. pylori* specific antigens, and when there is prolongation of intervals between sample collection and testing (Shimoyama, 2013). Stool antigen test is also the most preferred method of diagnosing *H. pylori* infection in children (Prell et al., 2009).

Serology testing establishes a diagnosis by detecting the titers of IgG anti *H. pylori* antibodies in serum. Examples of this test which are readily available commercially

include ELISA (enzyme linked immunosorbent assays) or ICA (immunochromatographic assays) (Tonkic et al., 2018). The ELISA test is considered to be more accurate compared to ICA (Burucoa et al., 2013). Results of serology testing do not seem to be affected by history of medication use, including antibiotics and antacids such as proton pump inhibitors (Malfertheiner et al., 2016), unlike other tests. Apart from inability to detect an active infection, another disadvantage of serology testing is that accuracy majorly depends on the antigenic composition of *H. pylori* strain affecting a population and the kinds of antigens in the manufactured commercial kit used for testing (McNulty et al., 2011), that is why local validation of the test kit is recommended (Feldman et al., 1995).

Diagnosis of *H. pylori* infection may also pose as a concern, causing variation in prevalence results. Serology testing detects exposure to *H. pylori* without ability to distinguish between and active and previous infection (Smith et al., 2001). Although not recommended for diagnosis, serology tests are recommended for epidemiological studies (Raj et al., 2017). Stool antigen testing has been argued to be a good and almost accurate method in detection of active *H. pylori* infection (Oluyemi et al., 2012).

Table 1: Overview of *H. pylori* diagnosis with invasive and non-invasive methods.

Derived and modified from Talebi Bezmin Abadi, 2018

Name	Type	Characteristics	Advantages	Disadvantages
Urea breath test	Non invasive	Sensitivity: >95% Specificity: >95%	High specificity and sensitivity Useful to confirm H. pylori eradication Relatively cheap, simple and safe Gold standard only for asymptomatic patients No sampling errors, good for epidemiology studies practically useful for children ~100% sensitivity	Rarely false positive results refer to urease positive organisms Radiation in the case of application of 14C-UBT
Serology	Non invasive	Sensitivity: >96% Specificity: 60–90%	Has no false negative result Cheap, simple and safe Highly recommended for initial H. pylori screening	No data about antibiotic resistance Failure to distinguish between active and past infection No application in clinical practice and hospitals
Stool Antigen Test	Non invasive	Sensitivity: >95% Specificity: >95%	High specificity and sensitivity Relatively fast and simple Easy modification to produce better results (v) No need to skilled staffs	No data about antibiotic resistance The false positive result in the case of PPI and antibiotics Variation in specificity and sensitivity over the different clinical circumstances
Rapid urease test	Invasive	Sensitivity: 95% Specificity: 80–90%	Rapid, simple and cheap method High specificity (~99%), but low sensitivity (~80%) The most handful test in a clinical setting	No data about antibiotic resistance Decreased sensitivity in patients with gastric bleeding Increased false negative results in the case of antibiotics & PPI consumption and achlorhydria Not useful for screening the eradication in epidemiologic studies
Histology	Invasive	Sensitivity: 60–90% Specificity: >95%	The gold standard for direct H. pylori detection Almost cheap method for using in the universal scale Simple method	Contradictory results following the PPI consumption Need extra biopsy sample and facing with ethical limitations Fluorescent microscope required method (limiting wide-spread usage) The relatively high rate of false negative reports

2.5 *H. pylori* antibody sero-reversion after infection

Majority of *H. pylori* infections are acquired during childhood, with prevalence rates of up to 90% (Aitila et al., 2019). The risk of acquiring *H. pylori* rapidly declines after childhood (Salih, 2009). Adult acquisition of *H. pylori* occurs at a slower rate and the major mode of transmission is based on geographical area, family, and socioeconomic status (Feldman et al.,1998). The isolation of the bacterium from faeces is rare in adults compared to younger children (van Duynhoven & de Jonge, 2001).

Some have argued that once acquired during childhood, *H. pylori* antibodies stay positive for years, even lifetime (Liker, 2003; Malfertheiner et al., 2012; Wang et al., 2015). However, there is evidence to dispute this. In a cross-sectional study where sera collected from a particular group in the 1960's was compared to sera collected from the same group 20 years later, results obtained showed a reduction in the prevalence of *H. pylori* from the initial sera, an indication of existence of sero-reversion. This decrease was noted to occur after a year onwards. In another cohort study of 141 adults with serum stored in 1969 and 1990, the prevalence of *H. pylori* was found to be 39% and 34.8% respectively (Feldman et al., 1998). Similarly, results from a cohort of Swedish children aged 6 months monitored to 11 years, showed a decrease in the prevalence of *H. pylori* over the years. About 14% were infected between ages 18 and 24 months, but by age 11 years, only 3% were seropositive (Granström et al., 1997).

Prospective studies done in different populations reported that sero-reversion of *H. pylori* with declines in serum IgG antibodies start at around 1 year after successful eradication with antibiotics (Cutler and Prasad, 1996; Wang et al., 1994). Mean

reduction in IgG titers reported at around 40% by the 6th month post therapy (Marchildon et al., 1999), although other studies looking at quantitative reduction of antibody titers reported reduction in IgG titers as early as 2 months post eradication therapy (Gisbert et al., 2000). Quantitative IgG titers or serology tests can be used for monitoring or confirming eradication of *H. pylori*. However, this requires follow up for up to or more than 6months as titers decline (Cutler and Prasad, 1996: Gisbert et al., 2000).

Rates of spontaneous sero-reversion without *H. pylori* eradication therapy was reported to be 24% annually. This spontaneous sero-reversion rate was noted to increase with increase in age in a Korean population (Jung et al., 2013). Spontaneous disappearance of *H. pylori* has also been documented after diagnosis confirmation via endoscopy (Freeman, 1997). In a study conducted in Italy, *H. pylori* infection was described as extremely dynamic with spontaneous clearance (Luzza et al., 2014). The spontaneous clearance of *H. pylori* may be influenced by presence of duodenal ulcers and alcohol intake, possibly secondary to intensified acid secretion (Kikuchi et al., 2004).

There are studies indicating that recurrence of *H. pylori* infection decreases gradually but with a rapid decline after the first-year post infection and treatment (Gisbert, 2005). Reinfection rates of *H. pylori* infection have been reported to be as low as 3.5% annually in adults (Kim et al., 2012). Reinfection can occur post eradication with antibiotics (Gisbert et al., 2000) or without any form of treatment administered (Freeman, 1997). In a Korean retrospective study, reinfection rate was documented at 2.79% annually, with being married and living with *H. pylori* positive family members identified as the main risk factors (Jung et al., 2013).

Two main mechanisms are involved in recurrence of *H. pylori*, i.e., recrudescence and reinfection (Moya & Crissinger, 2012). Recurrence of the original or same strain of *H. pylori* is called recrudescence. In this case, there was a temporary suppression of the strain after treatment with no capability of detection. Reinfection on the other hand, is recurrence with a different strain of *H. pylori* after eradication successfully (Zhang et al., 2009). Recurrence is more common in developing countries, compared to developed countries (Niv, 2008).

2.6 Complications and Extra gastric manifestations of *H. pylori* Infection

After infection or acquisition, complications of *H. pylori* infection range from acute and chronic gastritis to gastric lymphoma and cancer (FitzGerald and Smith, 2021). Chronic *H. pylori* infection has been identified as a potential risk factor for gastric cancer, secondary to changes in the gastric epithelium induced by *H. pylori* bacterium. This is supported by prospective studies conducted in different groups (Kuipers et al., 1995; Uemura et al., 2001).

Gastric cancer is ranked at fifth place, as the most diagnosed cancer globally, and in addition, has been identified as the third leading cause of death from cancer globally (Bray et al., 2018).

Apart from the popular gastrointestinal manifestations and complications of *H. pylori*, this bacterium has also been known to cause extra gastrointestinal complications.

H. pylori has been associated with coronary artery disease via atherosclerotic pathogenetic mechanisms which is unclear (Dadashi et al., 2021). The most common manifestation of coronary artery disease is myocardial infarction, which is also one of the leading causes of death in patients with diabetes mellitus, with very high case

fatality rates (Stevens et al., 2004). One of the studies evaluating the relationship between *H. pylori* infection and coronary artery disease concluded that elimination of *H. pylori* infection greatly reduces the risk of decrease in coronary artery lumen size in patients with coronary artery disease after percutaneous transluminal coronary angioplasty. This is thought to be due to eradication of chronic inflammatory state with reduction in release of proinflammatory cytokines (Kowalski, 2001).

Eradication of *H. pylori* has been proven to increase the serum levels of ferritin and hemoglobin levels in patients with iron deficiency anemia (Kato et al., 2017). Clinical benefit has also been shown with eradication in patients with idiopathic thrombocytopenic purpura. These clinical benefits of eradication in iron deficiency anemia and idiopathic thrombocytopenic purpura are both in children and adults (Malfertheiner and Selgrad, 2010). There are various mechanisms by which *H. pylori* causes iron deficiency anemia. It can be through upper gastrointestinal bleeding, which is a common presenting complain in patients with gastritis, secondly, *H. pylori* disrupts absorption of iron the gut via upregulation of hepcidin (Mendoza et al., 2019), a hormone produced by the liver, whose action is to prevent absorption of iron in the small intestines, and promotes iron degradation (Collins et al., 2008). Vitamin B12 deficiency anemia has also been linked to *H. pylori* infection. After successful eradication of *H. pylori* in patients with low levels of vitamin B 12, these levels, plus the level of its metabolite, homocysteine, return to normal (Malfertheiner et al., 2016). Pathogenetic mechanism behind development of vitamin B 12 deficiency in *H. pylori* infection is thought to arise from impaired absorption of vitamin B 12 caused by damage to parietal cells by *H. pylori* infection. Parietal cells produce intrinsic factor that aid in absorption of vitamin B 12 (Lahner et al., 2012). Vitamin B12 deficiency can lead to anemia and neuropathy (Kumar, 2014). Neuropathy is a

common manifestation and presentation in patients with diabetes mellitus. Vitamin B 12 deficiency manifests with neurological signs and symptoms including dementia, delirium and neuropathy (Alvarez et al., 2019).

Ophthalmologic complications of *H. pylori* infection include central serous chorioretinopathy which is characterized by detachment of retina, and open angle glaucoma. Both lead to vision changes and loss (Cotticelli et al., 2006; Zeng et al., 2015).

Dermatologic conditions have also been linked to *H. pylori* infection. An increased prevalence of *H. pylori* has been demonstrated in patients with Rosacea, with resolution of skin lesions after successful eradication of *H. pylori* (Gravina et al., 2015). Other reported dermatological presentations include chronic urticaria, bullous disease of autoimmune origin and alopecia aerate (Magen, 2014).

Metabolic disorders associated with *H. pylori* infection include metabolic syndrome and diabetes mellitus. Although the association between diabetes mellitus is still controversial, some studies demonstrated better glycemic control with eradication of *H. pylori* in patients with diabetes mellitus (Bégué et al., 2002). *H. pylori* interferes with glucose homeostasis through induction of insulin resistance and through this mechanism, a higher prevalence of metabolic syndrome has been documented in case control studies (Chen et al., 2015) including documentation of increased levels of triglycerides and total cholesterol in a Finnish population (Niemela et al., 1996).

Association between *H. pylori* and insulin resistance has been studied. *H. pylori* has been identified as a risk factor for development of insulin resistance (Polyzos et al., 2011; Eshraghian et al., 2008). Insulin is defined as a state in which insulin fails to trigger disposal of glucose into muscles or suppress production of glucose in the liver

(Dinneen et al., 1992). The mechanism by which H. pylori causes insulin resistance is unclear, but it thought to arise from the chronic inflammatory state caused by H. pylori infection triggering cytokine release and generalized inflammatory response (Gunji et al., 2008). Insulin resistance can develop either in the background of chronic inflammation (Moss et al., 1992) or because of alterations and changes in the counter regulatory hormones which affect insulin (Shinohara et al., 2002). In H. pylori infection, there is low levels of fasting leptin hormone in serum, and high levels of tumor necrosis factor (TNF) alpha, which is an inflammatory cytokine (Roper et al., 2008). Leptin is a peptide hormone whose function is to regulate intake of food, body weight and also plays a major role in the body's proinflammatory immune response (Obradovic et al., 2021). This imbalance has been proposed as one of the mechanisms by which insulin resistance develops (Hotamisligil et al., 1993; Shoelson et al., 2007). A study conducted in Japan in 2005, with recruitment of asymptomatic patients, who did not have any cardiac, renal, liver disorders and were not hypertensives, showed that H. pylori independently and significantly contributed to insulin resistance (Gunji et al., 2009). Similar results were reported from a community-based cohort study conducted in Taiwan, which recruited participants aged 50 years and below (Chen et al., 2015), and a systematic review, which was irrespective of some confounders (Polyzos et al., 2011).

Insulin resistance, obesity (via metabolic syndrome) and abnormal serum cholesterol levels, all of which are complications and extra gastric manifestations of H. pylori infection, play a major role in augmenting cardiovascular diseases and events (Ormazabal et al., 2018). Insulin resistance has also been proven to promote atherosclerosis and atherosclerotic plaque rupture and in addition, causes cell dysfunction, with decreased nitric oxide production, and release of pro coagulant

factors causing platelet aggregation in the blood vessels (Wu & Meininger, 2009; Wang et al., 2003).

Some neurological disorders have been associated with *H. pylori*, even though results are controversial. These disorders include ischemic stroke, Guillain-Barre syndrome, Parkinson's disease and Alzheimer's disease (Gravina et al., 2020). Infection with Cag A strains of *H. pylori* increase the risk of ischemic stroke (Wang et al., 2012), possibly through inflammatory response leading to activation of coagulation cascade and platelets (Álvarez-Arellano, 2014). Eradication of *H. pylori* in patients with Alzheimer's disease, led to improvement of symptoms related to Alzheimer's disease. Mechanism could be through increased prevalence of *H. pylori* in people with polymorphism of apolipoprotein E, which is the main risk factor for Alzheimer's disease (Kountouras et al., 2015). *H. pylori* antibody IgG has been isolated in cerebrospinal fluid of patients with Alzheimer's (Kountouras et al., 2009). Association with Guillain-Barre syndrome is through molecular mimicry between the peripheral nerve gangliosides and *H. pylori* (Kountouras et al., 2005). There are several routes by which *H. pylori* can access the central nervous system. One is through oral nasal olfactory pathway, consequently leading to neurodegeneration. Secondly, through interrupted blood brain barrier via *H. pylori* infected monocytes. Thirdly, from the gastrointestinal tract, via retrograde neural pathway, also leading to neurodegeneration (Gravina et al., 2018).

The bacterium has also been associated with liver diseases, with a role in pathogenesis of chronic liver diseases, including cirrhosis and hepatocellular carcinoma (Pellicano et al., 2000). Possible pathogenetic mechanism is via retrograde neural pathway from the duodenum to the liver (Queiroz and Santos, 2001).

The role of *H. pylori* in development of respiratory disorders has also been studied. *H. pylori* could possibly have a role in occurrence or development of bronchiectasis, chronic bronchitis, tuberculosis, asthma and lung cancer (Wang et al., 2012). A meta-analysis looking at *H. pylori* and lung cancer relationship revealed that the risk of lung cancer in *H. pylori* infection was up to 3.24-fold in comparison to controls. The conclusion from the meta-analysis was that *H. pylori* infection was a risk factor for lung cancer (Zhuo et al., 2009). From literature, it is known that majority of patients with peptic ulcer diseases have increased rates and incidences of chronic respiratory disorders such as chronic bronchitis and lung cancer, compared to those who do not have peptic ulcer disease (Moller & Toftgaard, 1991; Caygill et al., 1991). Previous epidemiological studies conducted in the years 1960s and 1980s looking at chronic bronchitis and peptic ulcer disease showed that the prevalence of chronic bronchitis was higher in cases with peptic ulcers, up to three times, compared to controls, who did not have peptic ulcers (Arora et al., 1968; Kellow et al., 1986). A prospective study conducted in Denmark revealed that the leading cause of death in patients with peptic ulcers was chronic bronchitis (Bonnevie, 1977). Mechanisms behind the development of respiratory infections or disorders in the background of *H. pylori* infection involve the fact that *H. pylori* induces a chronic systemic inflammatory state with release of cytokines causing either local or distant infections (Kanbay et al., 2007). Regarding the relationship between *H. pylori* infection and asthma, there is paucity of data, with recommendations that further studies be conducted to corroborate findings negating an association (Tsang et al., 2000; Wang et al., 2012).

2.7 Diabetes mellitus

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia and arises as a result of defects in insulin secretion, action or both (Deshpande et al., 2008).

Diabetes mellitus can be classified into: Type 1 and 2, which are the most common; Gestational diabetes which is typically diagnosed in pregnancy; A hereditary type known as maturity onset diabetes of the young (MODY), which is secondary to a single gene mutation ("Diabetes Symptoms, Causes, & Treatment | ADA", 2022). Other types include; neonatal diabetes which is rare and is usually diagnosed in neonates less than 6 months old, caused by a gene mutation, Type 3 diabetes mellitus found in Alzheimer's disease, linked to insulin resistance caused by Alzheimer's and, diabetes mellitus secondary to medications such as steroids (Sapra and Bhandari, 2022).

Some risk factors for type 1 diabetes mellitus include positive family history, genetics, African American race, and recurrent viral infections in childhood. For type 2 diabetes mellitus, risk factors are categorized into modifiable and non-modifiable risk factors (Deshpande et al., 2008).

Recognized non modifiable risk factors for type 2 diabetes mellitus comprise of positive family history, age and gender. Modifiable risk factors include high body mass index with obesity, behaviors such as alcohol intake and cigarette smoking, poor nutrition and physical inactivity (Gudjinu and Sarfo, 2017).

The pathophysiology of diabetes mellitus depends on the type. Type 1 diabetes mellitus is autoimmune mediated with destruction of beta cells in the pancreas, leading to insulin deficiency. Type 2 is due to insulin action resistance with the body underproducing insulin to counteract the resistance. Gestational is secondary to development of glucose intolerance in pregnancy (Deshpande et al., 2008).

Diabetes mellitus has been classified as a non-communicable disease. In the world, there are more than 400 million people living with diabetes mellitus. It is estimated that by 2045, this figure will rise to more than 600 million (Toniolo et al., 2019).

The global prevalence of diabetes mellitus is increasing especially in middle- and low- income countries. Global prevalence rose from 4.7% in 1980 to 8.5 % in 2014 ("Diabetes", 2018). Diabetes is currently considered a global threat, mainly because of its persistent increase in global prevalence noted with concern over the last four decades (Bommer et al., 2018). It is predicted that by 2030, DM will reach pandemic levels, with an estimated increase to 360 million from 170 million documented in 2000. Developing countries will have the highest number, anticipated to reach approximately 230 million from 80 million (Hossain et al., 2007).

2.8 Diagnosis of Diabetes Mellitus

Clinical diagnosis of diabetes mellitus begins with typical history supported by other laboratory tests.

Type 1 diabetes mellitus can be of sudden onset with symptoms as polyphagia, polyuria, polydipsia, weight loss (Kharroubi & Darwish, 2015). In patients with type 2 diabetes mellitus, the classical features include middle aged onset of hyperglycemia in a patient who is obese (Genuth et al., 2018).

Diabetes mellitus can be diagnosed via several methods: use of fasting plasma glucose level of equal to or more than 7 mmol/l, a random blood glucose level of equal to or more than 11.1 mmol/l in the presence of symptoms, an elevated glycated hemoglobin (HbA1c) of more than 6.5% or an impaired oral glucose tolerance test of more than 11.1 mmol/l (Pippitt et al., 2016).

A random blood glucose level of less than 7.7 mmol/l is considered normal. The diagnosis of prediabetes is an impaired OGTT of between 7 – 11 mmol/l or a fasting blood glucose level of between 5.5-6.9 mmol/l. Patients with prediabetes may be asymptomatic ("Diagnosis | ADA", 2022).

An OGTT (oral glucose tolerance test) is a test that measures blood glucose levels before and after intake of any liquid with glucose. This is done after fasting overnight or for at least 8 hours, but not to exceed 16 hours. After intake of a drink containing glucose, measurement of blood glucose level is done after 2 to 3 hours and compared with the initial reading. A diagnosis of prediabetes or diabetes mellitus is made after the second measurement which is done after 2 to 3 hours ("Diagnosis | ADA", 2022).

Using plasma glucose levels for diagnosis of diabetes mellitus has shortcomings. Blood glucose levels tend to fluctuate throughout the day, with the lowest levels detected in fasted state or before a meal, hence the possibility of misdiagnosis. Therefore, it is recommended to take measurements in the morning (Gurung & Jiala, 2022). In addition to fluctuation, there can be a difference in blood glucose measurements depending on blood processing methods. For example, in whole blood, with normal hematocrit levels, the level of plasma glucose is about 11 % higher, whereas in comparison to venous blood, postprandial capillary blood glucose level is about 20% higher (Sacks et al., 2011; Kim, 2016).

Glycated hemoglobin (glucose bound hemoglobin) (HbA1c) measures average blood glucose levels over a period of two to three months ("Diabetes Tests", 2021). Apart from the use in diagnosing diabetes mellitus, it is also used in monitoring treatment or glycemic control (Higgins, 2012). The two to three months is estimated to be the half-life of circulating red blood cells (RBCs) (Sherwani et al., 2016). Though considered gold standard, a retrospective study in Saudi male patients demonstrated that a HbA1c cut off of 6.5 % was associated with almost 4 % false negative predictions (Khan et al., 2013). Glycated hemoglobin test is convenient in that it is not affected by the time of day when the test is conducted (Juarez et al., 2014).

2.9 Complications of Diabetes Mellitus

Diabetes mellitus is known to have both acute and chronic complications. Acute metabolic complications of diabetes mellitus include diabetic ketoacidosis, hyperosmolar hyperglycemic state, hypoglycemia and lactic acidosis ("Diagnosis and Classification of Diabetes Mellitus", 2009).

With chronic hyperglycemia, there is increased risk of developing long term damage, failure and dysfunction of the eyes, kidneys, heart, nerves, and blood vessels. Chronic hyperglycemia causes non enzymatic type of glycation of lipids and proteins. Glycation causes damage of blood vessels in the eyes, kidneys and nerves, with higher glucose levels hastening the process (Sapra and Bhandari, 2022).

Regardless of the type, chronic complications can be divided mainly into microvascular (damage to small blood vessels) and macrovascular (damage to large blood vessels, mainly arteries) (Yamazaki et al., 2018).

Microvascular complications affect the eyes, kidneys and nerves. These are termed retinopathy, nephropathy and neuropathy respectively. Main macrovascular events affect the heart presenting as myocardial infarction and brain presenting as strokes (Forbes and Cooper, 2013).

Cardiovascular disease is a common occurrence in diabetes mellitus, and almost 70 percent of deaths in diabetes mellitus is due to cardiovascular events. Increased morbidity rates in diabetes mellitus are also due to stroke and ischemic heart diseases (Booth et al., 2006). Risk factors for mortality and predictors of cardiovascular disease mortality in diabetes mellitus include being of male gender with cardiovascular disease, high cholesterol levels, cigarette smoking and high blood pressures (Stamler et al., 1993). In the background of diabetes mellitus, life expectancy is lowered by almost 20 years due to increased morbidity and mortality related to abnormalities in the vessels. In addition, these patients' cardiovascular diseases are up to eightfold compared to the general population (Martín-Timón et al., 2014).

Risk factors for diabetic kidney disease include hypertension, obesity, chronic and recurrent infections, poor glucose control, metabolic syndrome, elevated cholesterol levels and insulin resistance (Thomas et al., 2015). Diabetic kidney disease is defined as marked impairment of kidney function plus or minus presence of elevated levels of albumin in urine (Dwyer et al., 2011). Reactive oxygen species produced as a result of chronic hyperglycemia promote inflammation leading to kidney disease (Sulaiman, 2019).

Diabetic neuropathy is common and affects up to 50% of patients with diabetes mellitus (Candrilli et al., 2007). Main risk factor is hyperglycemia; however, other independent risk factors are hypertension, age, obesity, being tall, cigarette smoking and alcohol consumption, high triglycerides and duration of disease (Tesfaye et al., 2005). Diabetic neuropathy manifests as loss of sensation, muscle aches and muscle weakness. There is also a feeling of burning sensation and numbness especially on the feet (Vinik et al., 2000; Slyk, 2000). Vitamin B12 deficiency has been reported in patients with diabetic neuropathy, especially in patients taking oral agent, metformin for glucose control (Alvarez et al., 2019). This result has also been reported from a cross sectional study that was conducted in India (Singh et al., 2013). Metformin possibly caused vitamin B12 deficiency by altering the motility of the small intestines leading to overgrowth of bacteria. This inhibits absorption of vitamin B12 intrinsic factor complex, subsequently, vitamin B12 deficiency (Ko et al., 2014; Kibirige & Mwebaze, 2013). Since vitamin B12 deficiency can present with neurological symptoms as in diabetic neuropathy, these neurological manifestations could be interpreted erroneously as the result of diabetic neuropathy instead of the metformin use (Ghosh et al., 2016; Rodríguez-Gutiérrez et al., 2017).

Diabetic retinopathy is a common microvascular complication in diabetes mellitus. It is slow in progression but can start as early as 7 years before the diagnosis of type 2 diabetes mellitus (Harris & Leininger, 1993). The prevalence of retinopathy increases with age, and duration of disease is a significant predictor of visual loss and impairment (Deshpande et al., 2008). Pathogenetic mechanisms include hyperglycemia, inflammation, neurodegeneration of the retina (Wang & Lo, 2018).

Another common complication of diabetes mellitus in both type 1 and type 2 DM is diabetic gastroparesis, estimated to affect about 50 percent of patients diagnosed with DM (Ju Huang et al., 2017). This is characterized by delayed gastric emptying as a result of the dysfunction of the autonomic nervous system secondary to poor glycemic control. The manifestations of diabetic autonomic neuropathy of the gastrointestinal tract are majorly divided into three groups: 1) Gastroparesis 2) Esophageal dysmotility 3) Diabetic enteropathies – diabetic diarrhea, fecal incontinence, and small intestines dysmotility syndromes (Krishnasamy and Abell, 2018).

There is an increased prevalence of gastrointestinal symptoms in diabetes mellitus. This has been attributed to several factors including *H. pylori* infection, age, gender, BMI, and psychological comorbidities (Hammer et al., 2003).

Gastrointestinal manifestations and symptoms negatively affect the quality of life in people living with diabetes mellitus. In addition, tolerability of medications is also affected greatly by functional gastrointestinal disorders such as functional dyspepsia, potentiating non-adherence to medication (Florez et al., 2010) and treatment failure.

Iron deficiency anemia is also a complication of diabetes mellitus. It can occur even in the absence of erythropoietin deficiency seen in diabetic kidney disease (Praveen et al., 2020). This type of anemia has a poor outcome on quality of life, worsens disease progression and promotes occurrence of comorbidities (Ueda et al., 2003; Meroño et al., 2017). Anemia in diabetes mellitus determines heart failure outcomes and organ damage due to hypoxic state (Thomas et al., 2005).

2.10 Postulates on association between DM and *H. pylori*

H. pylori has been recognized as a common chronic infection in DM, but data is limited and conflicting. Even though data is limited and conflicting, association between DM with *H. pylori* has been based on four main postulates.

First, an individual's susceptibility and sensitivity to *H. pylori* infection is increased in diabetes mellitus, due to diabetes-induced impairment of both humoral and cellular immunity (Geerlings & Hoepelman, 1999; Borody et al., 2002). In DM, there is suppression of interleukins, especially 6, which plays a major role in defense against pathogen invasion. There is also decrease in cytokine production, impairment in phagocytosis, defects in function of immune cells leading to failure of eradication of pathogens and microbes (Moutschen et al., 1992; Berbudi et al., 2020). Cells affected include diabetic monocytes, polymorphonuclear cells and macrophages, causing a delayed type of hypersensitivity reaction and impaired function of the complement system (Plouffe et al., 1978). The complement system plays a major role in regulation of innate immunity. It mainly eliminates self-antigens that have undergone modification, also, identify and eliminate harmful microorganisms (Ghebrehiwet, 2016).

Secondly, decreased acid secretion and gastrointestinal motility, commonly seen in diabetes mellitus, promotes bacterial growth, colonization, and subsequent infection of the gut (Jeon et al., 2012). Gastrointestinal complications of DM include diarrhea, incontinence, and bacterial overgrowth in the small intestines due to delayed emptying, and more than 70% of patients with DM will have gastrointestinal symptoms (Krishnasamy and Abell, 2018). Diabetic gastroparesis, an element of autonomic neuropathy, is a term that has been used to define delayed gastric

emptying which is a complication seen in diabetes mellitus without any mechanical or physical obstruction (Hasler, 2012). Diabetic gastroparesis is due to prolonged poor glycemic control of types 1 and 2 diabetes mellitus and majorly promotes bacterial overgrowth (Vanormelingen et al., 2013; Krishnasamy & Abell, 2018). Retention of gastric contents has also been associated with decreased acidity attributed to vagal neural defects and atrophic gastritis developed as a result of autoimmune factors, for example development of anti-parietal cell antibodies causing a decrease in acid production (De Block et al., 2002; Hasler et al., 2008). Mechanisms of diabetic gastroparesis include autonomic neuropathy, which is the most common, followed by enteric neuropathy affecting inhibitory and excitatory nerves, and lastly, loss interstitial cells of Cajal (ICC) whose main function is to promote peristalsis (ördög, 2007). Other documented mechanisms include variations in blood glucose levels, medications for post prandial glucose control, which are incretin based, and psychosomatic factors through several autoimmune mechanisms (Krishnasamy & Abell, 2018).

Thirdly, with altered glucose metabolism, there is a possibility of production of compounds with subsequent changes that may affect the gastric mucosa, hence paving way for *H. pylori* colonization and infection (de Luis et al., 1998; He et al., 2014). With inadequate metabolic control in DM, *H. pylori* is a common infection because of cytokines production inducing changes in the gastric epithelium thus promoting epithelial damage and inflammation increasing risk of epithelial cell metaplasia (Devrajani et al., 2010)., is also associated with *H. pylori* infection. Chronic DM with poor glycemic control and increased levels of HbA1C has been associated with increased incidence of *H. pylori* infection, as examined in several studies (He, 2014; Sarita Bajaj et al., 2014). High Hemoglobin A1c (HbA1C) level, is

a marker for monitoring blood sugar level control over 2 to 3 months (Sherwani et al., 2016). Hyperglycemic state in DM predisposes to infection by *H. pylori* or reactivation of a latent *H. pylori* infection via several mechanisms: inhibition of leukocyte recruitment, pathogen recognition defects, neutrophils, natural killer cells and macrophages dysfunction and impaired complement effector activation (Devrajani et al., 2010; Berbudi et al., 2020).

The fourth mechanism has been linked to patients with diabetes mellitus attending hospitals more frequently for follow ups and routine checkups than the healthy individuals, giving them exposure to different strains of pathogens, including *H. pylori* (Gentile et al., 1998; He et al., 2014). Because of impaired immune system, this increases susceptibility to infections by various pathogens, including viruses, bacteria, and parasites (Toniolo et al., 2019).

2.11 Evidence for and against the association

Several studies conducted in different populations have examined the association between DM and *H. pylori*, but with conflicting results. Countries with data include USA, Italy, Japan, Iran, Pakistan, and Nigeria in Africa.

In Yaounde Cameroon, a case control study comparing the prevalence of *H. pylori* in DM and non-DM group found a statistically significant difference. The study used serology testing using Immunoglobulin G and pepsinogen levels. Results showed a higher prevalence of H. pylori antibodies in DM compared to non-DM group (88.2% in DM vs 67.7% in non-DM, P = 0.015, (Ebule et al., 2017).

Other studies that found an increased prevalence of *H. pylori* among diabetes mellitus patients include two prospective cohort studies conducted in Italy in 2001 and California, USA in 2012, plus a case control study conducted in Pakistan in 2010.

These studies used different testing methods for *H. pylori*, rapid urease test with histology from endoscopy, serology testing and stool antigen test respectively (Marrollo, M. et al., 2001; Devrajani et al., 2010; Jeon et al., 2012).

On the contrary, there are other studies that found no relationship between DM and *H. pylori*. Two studies conducted in Nigeria had similar results. Both were case control studies but used different testing methods, one used serology testing whereas the other used stool antigen test. Results from the serology testing showed no difference in the prevalence rate of *H. pylori* among patients with diabetes mellitus, 35% versus 28% in non-diabetes mellitus (p=0.432). Results from stool antigen test in the second Nigerian study showed no statistically significant difference between the two groups with regards to prevalence of *H. pylori*, 18% in diabetes mellitus vs 13% in non-diabetes mellitus (p=0.52) (Ugwu et al., 2008; Oluyemi et al., 2012). In addition to the Nigerian studies, three cross sectional studies conducted in Iran, Japan and USA using serology testing, urine antibody and serology testing at baseline then follow up for 2.6 years, respectively, showed no association between DM and *H. pylori* (Jafarzadeh et al., 2013; Tamura et al., 2015, Alzahrani et al., 2017).

Table 2: Published studies in support of an association between DM and *H. pylori*

Author	**Type of Study**	**Location**	**Testing Method**	**Result**
Marrollo, M. et al., 2001	Prospective cohort study	Italy	Rapid urease test and histology from endoscopy biopsy	Prevalence higher in dyspeptic DM 65% than in dyspeptic controls 48% OR 2.5
Ebule et al., 2017	Case control study	Cameroon	Serology biomarkers IgG, Pepsinogen II	Increased prevalence in diabetics (88.2%) than in the non-diabetic control group (67.7%), (P = 0.015)
Devrajani et al., 2010	Case control	Pakistan	Stool antigen test	Increased prevalence in dyspeptic DM2 73% vs dyspeptic controls 51.4% (P = 0.0001)

Table 3: Published studies that do not support an association between DM and *H. pylori*

Author	Type of Study	Location	Testing Method	Result
Oluyemi et al., 2012	Hospital based Cross sectional survey	Nigeria	Stool antigen test	No statistical significance 18% in DM2 13% in controls. (p = 0.52)
Jafarzadeh et al., 2013	Cross-sectional study	Iran	Serum IgG using ELISA	Seroprevalence of anti-*H. pylori* IgG antibodies in DM2 (76%) was similar to controls (75%).
Tamura et al., 2015	Cross-sectional study	Japan	Antibody kit for urine (made in Japan) Se 89.6 and Sp 93.8 %	No association between DM and HP
Alzahrani et al., 2017	Case control study	USA	Serology testing at baseline. Follow up for 2.6 years	No association OR 1.04

Varied results in prevalence of *H. pylori* infection between those with diabetes mellitus and those without diabetes mellitus can be influenced greatly by the study population, testing method and the geographical area. Comparing community based and hospital-based studies may not be appropriate as there are several factors that may

affect the results, especially in hospital-based studies. And these factors may not easily be adjusted for during analysis of data. Frequent hospital visitation may lead to exposure to same antibiotics used in treatment of *H. pylori* infection (de Luis et al., 1998), hence show false negative results.

2.12 Significance of an association between DM and *H. pylori*

Both DM and *H. pylori* have been identified as common conditions especially in developing countries ("Diabetes", 2018; He, 2014), with both short-term and long-term complications (Vafaeimanesh et al., 2014). The complications of these two conditions often lead to increased morbidity and mortality (Moss, 2017; He, 2014).

Both DM and *H. pylori* can present with similar complains, symptoms and clinical findings. As previously alluded to, both can present with dyspepsia, neuropathy, cardiovascular events, iron deficiency anemia, and this could possibly lead to misdiagnosis.

Dyspepsia, which is essentially difficulty in digestion, comprises of a number of symptoms in the epigastric region. These include such as discomfort, fullness, early satiation, heartburn, bloating, nausea and vomiting, belching, or abdominal pain (Oustamanolakis & Tack, 2012). Clinical definition of dyspepsia is presenting with one or more symptoms of epigastric pain, burning in nature, early satiety or postprandial fullness (Tack et al., 2006). Bloating and nausea have been excluded from the definition of dyspepsia since they are nonspecific. Heartburn has also been excluded since it mostly signifies esophageal disorder like reflux disease (Talley et al., 1993). Dyspepsia can be classified into either be functional or organic. Different mechanisms causing functional dyspepsia include dysfunction of the autonomic nervous system (as seen in diabetes mellitus), distorted gastric electrical system and

antroduodenojejunal peristalsis and motility, delayed gastric emptying, gastric distention hypersensitivity, impaired sensitivity to acids and lipids in the duodenum and reduced gastric accommodation to meals. *H. pylori* infection, inflammatory state, genetic predisposition and psychosocial factors also cause functional dyspepsia. For organic causes of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease, biliary and pancreatic disorders, cancer of the esophagus, gastric cancer, systemic diseases and infections are all known causes (Oustamanolakis & Tack, 2012). Diagnosis involves detailed history taking, clinical evaluation and endoscopic evaluation (Bowrey et al., 2006; Hammer et al., 2004), especially in patients who are above the age of 50 and are presenting with new onset dyspepsia (Tack et al., 2006).

Dyspepsia is a common symptom in diabetes mellitus due to gastropathy and dysautonomia, secondary to dysfunction of the autonomic nervous system, is also a diagnostic symptom of *H. pylori* infection (Devrajani et al., 2010). Dyspepsia has a great impact on reduction of quality of life. It affects almost 50% of the general population, with peptic ulcers secondary to *H. pylori* as a common cause (Ford & Moayyedi, 2013). DM patients presenting with dyspepsia would perhaps be thought to have DM complications and not *H. pylori* infection. Misdiagnosis of diseases or conditions lead to delayed treatment or recovery resulting in higher costs of treatment and care. Misdiagnosis also leads to an increased risk of developing irreversible complications and treatment failure associated with both conditions, increasing morbidity and mortality.

As previously alluded to, patients with diabetes mellitus are at increased risk of thrombo-occlusive and cardiovascular events, and there has been evidence that there is a positive association between *H. pylori* and cerebrovascular and cardiovascular

events. Presence of *H. pylori* infection in the background of diabetes mellitus intensifies this risk of cardiovascular and cerebrovascular events. Therefore, it is important to determine whether there is a positive association between diabetes mellitus and *H. pylori*.

Anemia is up to three times common in patients with diabetes mellitus compared to the general population or people without diabetes mellitus (Thomas et al., 2003). In diabetes mellitus, anemia is secondary to nutritional deficiencies, chronic inflammation and infections, medication, kidney disease (Cawood et al., 2006), reduced life span of red blood cells, reduced erythropoietin levels (Loutradis et al., 2016; Kuo et al., 2016). Medications such as angiotensin receptor blockers and angiotensin converting enzyme inhibitors tamper with erythropoiesis hence promoting development of anemia (Albitar, 1998). *H. pylori* infection also has a positive association with iron deficiency and Vitamin B12 deficiency anemia, as previously alluded to. Early diagnosis and treatment of anemia in patients with diabetes mellitus improve quality of life and decrease incidence of morbidity and mortality (Baisakhiya et al., 2017).

H. pylori infection may accompany diabetes mellitus. With chronic inflammation and insulin resistant state induced by *H. pylori*, this leads to worsening of diabetes mellitus and challenges in management or glycemic control (He, 2014). A clinical trial in Iran demonstrated that eradication of *H. pylori* improves metabolic abnormalities in patients with diabetes mellitus (Zojaji et al., 2013). Another prospective study demonstrated benefits of eradication on lipid abnormalities, atherosclerosis, and insulin resistance, suggesting that eradication of *H. pylori* prevents coronary artery disease (Gen et al., 2010).

Determining whether there is an association between DM and *H. pylori* is of significance to the patient, population, and doctors. To the patient, it promotes general wellness, preventing recurrent expenditure on treatment hence decreasing morbidity and mortality rates associated with DM, *H. pylori*, and complications of the two. The population, on the other hand would benefit from creation of awareness with emphasis on possible coexistence of the two conditions, requiring regular screening. For doctors and other medical professionals, it would enable early diagnosis and treatment, thus preventing progression to gastric cancer and malpractice lawsuits associated with misdiagnoses. Research opportunities would also be created.

2.13 Conclusion

There is limited data on association between diabetes mellitus and *H. pylori*, especially in Africa. In Kenya, the data is also limited, with no published study looking directly at an association between diabetes mellitus and *H. pylori*.

Closest to examining an association was a study was done at Kenyatta National Hospital in 2002, to determine prevalence of *H. pylori* in dyspeptic patients with diabetes mellitus with associated upper gastrointestinal endoscopy lesions. The study showed no significant difference in endoscopic lesion findings and *H. pylori* in patients with diabetes mellitus and in patients without diabetes mellitus, i.e. (Wafula et al.,2002). Documented lesions from the study were gastritis, duodenitis, esophageal candidiasis, bile reflux, reflux esophagitis, ulcers (duodenal and gastric) and gastric cancer. The study conducted at Kenyatta National Hospital used an invasive method (endoscopy with biopsy) and urea breath test to diagnose and determine the prevalence of *H. pylori*. The population recruited for the study was patients diagnosed with diabetes mellitus, who were symptomatic and had associated endoscopic lesions.

From the study, all ulcers and the cancer lesions including adenocarcinomas were associated with *H. pylori.* This indicates how prevalent *H. pylori* infection and *H. pylori* associated gastrointestinal disorders are in Kenya.

Presently, there is gap in knowledge regarding prevalence of *H. pylori* in diabetes mellitus, and whether there is an association between the two medical conditions in Kenyan population.

Majority of the published studies looking at an association between diabetes mellitus and *H. pylori*, looked at symptomatic (patients with dyspepsia) patients with diabetes mellitus. Many studies also focused on type 2 diabetes mellitus. Having alluded to the fact that about 90% remain asymptomatic after *H. pylori* infection, this study purposed to determine the prevalence of *H. pylori* in asymptomatic patients with either type 1 or 2 diabetes mellitus and non-diabetes mellitus using serology method at MTRH, Eldoret, Kenya. Serology test has been identified as the best method in initial screening of *H. pylori* with a sensitivity of more than 96% and a specificity of 60 to 90 % (Table 3).

Sang (2013), conducted a study at MTRH, Eldoret, looking at the prevalence of *H. pylori* among dyspeptic patients. This study employed endoscopy with biopsy and rapid urease test. The study found a prevalence of 52.3% using endoscopy findings.

CHAPTER THREE: METHODOLOGY

3.1 Study Setting

This study was conducted at Moi Teaching and Referral Hospital (MTRH), Eldoret, Uasin Gishu County, Kenya. MTRH is a Level 6 (National Referral) hospital that serves as a referral center for the western part of Kenya. With a catchment population estimated at 24 million, it has an emergency department, general and specialist outpatient clinics and an inpatient facility with a capacity of around 991 beds. The emergency and outpatient facilities handle about 1500 patients daily. Target clinics for the study were Diabetic Outpatient Clinic (DOPC), Ear Nose Throat (ENT) and Eye clinics. Participants with DM (Group A) were recruited from DOPC whereas participants without DM (Group B) were recruited from the Eye and ENT clinics. Participants included in the study were walk in patients coming for routine follow up or reviews.

3.2 Study Population

Participants above the age of 18 years attending DOPC, ENT and Eye clinics at MTRH.

3.3 Study Design

This was a cross sectional comparative study. Comparing *H. pylori* prevalence in DM and non-DM

3.4 Sample Size

The aim of this study was to compare proportions of participants who test positive for *H. pylori* among those with diabetes mellitus and in those without diabetes mellitus, to determine if there is any significant difference in the proportions. This was to ascertain if there is an association between DM and *H. pylori.*

Generation of sample size was by use of the formula for comparison of proportions:

$$\frac{r+1}{r}\ \frac{(p^*)(1-p*)(Z_\beta\ +Z_{\frac{\alpha}{2}}\ )^2}{(P_1\ -P_2\ )}$$

r: ratio of DM to non-DM = 1

p*: average of proportion in exposed (p1 + p2) ÷ 2 = 0.33 zβ: variate for power at 90% = 1.28

zα/2: level of significance at 5% = 1.96

p1- p2: difference in proportion based on previous studies; 0.35 - 0.28 = 0.07 (Ugwu, Ugwuja, Ejikeme, & Obeka, 2008)

Substitution gives n = 232 participants per arm

3.5 Eligibility Criteria

All patients above the age of 18 years were eligible to participate in this study.

3.5.1 Inclusion Criteria

1. For the DM group, who were designated as Group A, inclusion criteria was;
    1. Both type 1 and 2 diabetes mellitus (established diagnosis)
    2. Has had diabetes mellitus for >1 year

The reason for choosing a period of one year for the diabetes mellitus was to allow enough time for interplay between DM and *H. pylori*. In addition, from literature, majority of the studies looked at *H. pylori* and chronic DM.

2. For the non-DM group, who were designated as group B, inclusion criteria was;
    1. No known history of diabetes mellitus
    2. Random blood glucose < 7 mmol/L

Although the acceptable cut off for assessment of impaired glucose tolerance is 7.8 mmol/L (Nathan et al., 2007), we chose a tighter criterion of less than 7 mmol/l because this was using only one reading to rule out DM and to ensure that none of the participants recruited and enrolled in the study had DM or was prediabetic.

3.5.2 Exclusion Criteria

In both groups, the exclusion criteria included any participants or patients who;

1. Were on immunosuppressive agents/treatment
2. Had terminal illness
3. Had history of gastrectomy
4. Had previous history of anti *H. pylori* treatment – within the last one year
5. Were pregnant
6. Had dyspepsia

Unlike in other studies, this study excluded dyspeptic patients because from literature, once acquired, *H. pylori* remains asymptomatic in up to 90%. Only about 5-10% develop dyspepsia after development of complications such as duodenitis and peptic ulcer disease (Meurer and Bower, 2002; Sugano et al., 2015).

3.6 Recruitment procedure

Participants attending DOPC, ENT and Eye clinics were identified, approached to participate, and written informed consent obtained from them. After signing consent forms (Appendix 1 and 2 [consent form translated in Kiswahili]), all respondents had standard interviewer administered written questionnaires on sociodemographic characteristics and health history (Appendix 3) and socioeconomic factors (Appendix 4) administered to them. Parameters on the questionnaires included age, gender, height, weight, level of education, history and duration of diabetes, type of blood glucose control, alcohol and smoking history, number of members per household, presence of pets or livestock in homes, type of toilet facility, source of drinking water, type of toilet facility and method of waste disposal.

3.7 Sampling Technique and Procedure

This study employed two different types of sampling methods. For the DM group, with a finite population and documented records, systematic random sampling method was used. For the non-DM group, simple random sampling method was used. The DM group was designated as group A. The first step involved assigning a number to every member in the DM population. DOPC runs every Monday, Thursday, and Friday. In 2019, the total number of registered DM patients attending DOPC at MTRH was 4347. Those registered from beginning of the year 2018 were 2333, that is one-year period, for those who were to be excluded from the study. The difference came to 2014 as the population size (N). An interval size (k) was determined by dividing the population size (N) by the determined sample size of 232, which gave 8. By randomly selecting an integer between 1 and k, every 5^{th} person was picked during recruitment. Those who were on Insulin only, were classified as insulin dependent diabetics type 1. This is because treatment of type 1 DM requires insulin, because the body does not produce insulin. For those who were on either oral hypoglycemic agent alone or oral hypoglycemic agent plus insulin were classified as type 2. This is because for type 2, the body does not make use of insulin properly, therefore oral agents in addition to Insulin may be required for blood glucose control.

For the non-DM group, designated as group B, prior identification of the population from ENT and Eye clinic registers was done. ENT clinic runs every Monday and Tuesday with an average of 60 adult patients seen per day. Eye clinic runs every Monday, Wednesday, Thursday, and Friday. Wednesday has the largest turn out, with an average of 90 adult patients, and about 50 adult patients the rest of the clinic days. From the list of patients scheduled for clinic, each member was marked with a number, then using a random number generator software, random numbers were

chosen for recruitment.

From the eye clinic register, since January 2019 to end of April 2019, only 130 patients were registered as patients with diabetes mellitus, referred from DOPC with possible complications. This is approximately a half of the total number of patients seen in a week. Most documented cases were allergies, trauma, congenital and age-related eye diseases. Therefore, it is safe to say that majority of the patients attending eye clinic are not those with diabetes mellitus related complications. With a determined sample size of 232, a sample size of 116 was derived from each clinic (Eye and ENT).

3.8 Data Collection and Management

3.8.1 Data Collection

Standardized interviewer administered written questionnaires were used for collection of data on sociodemographic characteristics and health related history (Appendix 3) and socioeconomic factors (Appendix 4). Data collected on socioeconomic factors included: number members per household; source of drinking water; type of toilet facility; waste disposal; and presence of pets or domestic animals in homes. These were used to adjust for confounders during analysis of data. Height and weight for calculation of body mass index (BMI), capillary blood glucose levels and results for *H. pylori* antibody test were also recorded on the forms.

Testing for blood glucose:

On Call Plus® blood glucose monitoring system was used to check for the level of random blood glucose. The blood glucose monitoring system comes with a blood glucose meter, lancing device, clear cap for the lancing device, sterile lancets, test strips, code chip, control solution, carrying case, user's manual, quick reference guide

and warranty card. For this study, control solution, the sterile lancets, blood glucose meter and the test strips were used to measure blood glucose levels.

The code number on the On Call Plus® code chip was matched to the code number on the test strips vials. It is important to do this because, if the codes do not match, erroneous readings may be obtained. After confirmation of the codes, the glucose meter was preset to display the blood glucose level in millimoles per liter (mmol/L), as this is the standard unit used in Kenya and MTRH.

After swabbing the finger, a prick was made using a sterile lancet at the fingertip to get a drop of blood. The test strip was connected to the blood glucose meter, with its opening held to the pricked area until enough blood was absorbed to begin the test. The blood glucose level was indicated on the glucometer with every test. The level of blood glucose was recoded on each participants questionnaire as part of data collection.

Quality control test using the control solution was done weekly and when using a new set of test strips. This test checks that the meter and the test strips are working together appropriately.

Testing for *H. pylori*:

A rapid *H. pylori* antibody test kit was used to test for *H. pylori*. The kit is manufactured by Pefric® (E.A) Ltd and comes with a test strip, a dropper pipette, wash buffer and instruction leaflet. The test strip has a sample pad on one end. After swabbing, a prick was made on the finger, then using the pipette, blood drawn and released into the sample pad end of the test strip. Buffer was added to the sample then left to flow through the pad containing the *H. pylori* antibodies. The result was interpreted as positive if both the test (T) and control (C) lines appeared, indicating

antibodies to *H. pylori* are present. The test was interpreted as negative if only the C line appears, meaning no antibodies to *H. pylori* were detected. The C line, which is the control line, should always appear irrespective of the presence of *H. pylori* antibodies.

3.8.2 Data Management

All data obtained were entered into a Microsoft Access® database, an electronic database encrypted, and a password set for confidentiality. Access was available to the principal investigator, data manager and biostatistician only. Data backup was done using pen drives and external hard disks stored in a different location to protect against data loss. Frequent checking on consistency and completeness was done. After complete conversion of the data into an electronic database, all questionnaires were secured in a cabinet with lock and key. Access was only granted to the principal investigator. All collected data will be shredded six years after publication of the study findings as per records disposal policy (Anon).

3.9 Data Analysis and Interpretation

Results from the two groups were analyzed and compared. Categorical data such as age, gender and BMI were summarized using frequencies and percentages. Continuous variables such as age, blood sugar levels and duration of diabetes were summarized using means, and standard deviations. Data was analyzed using R core team (2013). Bivariate analysis was used to test for an association between diabetes mellitus and *H. pylori*. P values of less than 0.05 was considered significant. Results obtained were presented using tables and graphs.

Dependent Variables and Independent Variables

Dependent variable: *H. pylori* test results.

Independent variable: Diabetes +/-

Categorical data / variables: Age, Sex, BMI, Alcohol use, Cigarette use, Level of education.

Additional variables for the DM group: Duration of diabetes mellitus and method of blood sugar control or treatment.

3.10 Ethical Consideration

This thesis was submitted to the Moi University /Moi Teaching and Referral Hospital Institutional Research and Ethics Committee (IREC) for approval. Once approval was obtained, permission to conduct the study was sought from the Chief Executive Officer (CEO), Moi Teaching and Referral Hospital.

All eligible patients were informed about the study aims and objectives, what was expected of them, how long it would take, and that they had the freedom to quit at any point in time. Those willing to participate were taken through the informed consent process and signed the document. They were assured of confidentiality and anonymity while participating in the study. Patients who had a positive for *H. pylori* antibody test were referred to their primary physician for further investigation and management.

Data management practices to ensure privacy and confidentiality such as storing data under lock and key and use of passwords, were applied throughout the study.

CHAPTER FOUR: RESULTS

This study was carried out between the months of December 2020 and April 2021 at outpatient clinics (DOPC, ENT and Eye) at MTRH, Eldoret, Kenya. A total of 485 participants were screened from the three clinics. Out of those who were screened, 15 were excluded as follows: 10 had random blood glucose levels of more than 7mmol/l from Eye and ENT clinics (5 from Eye clinic and 2 from ENT clinic), in the same clinics, 2 were called for review by the doctor before we could conduct *H. pylori* antibody test on them, and 3 declined *H. pylori* antibody testing (2 from DM clinic and 1 from Eye clinic). We ended up enrolling a total of 470 unmatched participants in the study, 258 females and 212 males, and 232 with DM and 238 without DM. For these unmatched participants who were enrolled in the study, *H. pylori* antibody tests were done, and results were recorded. The results were documented on the data collection forms, where demographics, socioeconomic factors and health history were also documented.

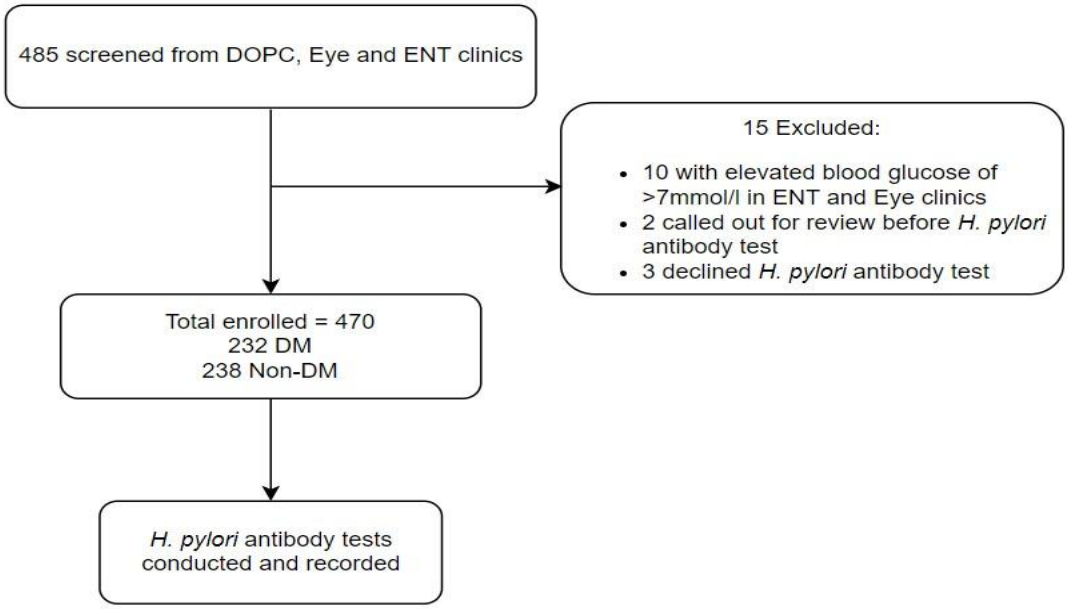

Figure 2: Recruitment Schema

Figure 2 is a summarized flow chart on the how recruitment and enrolment was done in this study.

A total of 470 participants were included in the study; 232 (49.4%) had diabetes mellitus while 238 (50.6%) did not.

During recruitment, for those who had elevated blood glucose levels of > 7mmol/L in the ENT and Eye clinics were notified and referred to their primary doctors for further evaluation. In addition, those who were enrolled in the study and tested positive for *H. pylori* antibody test, were referred to their primary doctors for further evaluation and diagnosis of a possible active infection.

4.1 Participants Characteristics

Table 4 shows the socio-demographic characteristics in both DM and non-DM participants.

Table 4: Participant's characteristics

	DM (N=232)	Non-DM (N=238)	Total (N=470)	p value
Age in (years)				0.433[1]
Median	53.00	52.00	52.50	
Q1,Q3	40.75, 65.00	39.25, 63.00	40.00, 64.00	
Sex				0.011[2]
Female	141 (60.8%)	117 (49.2%)	258 (54.9%)	
Male	91 (39.2%)	121 (50.8%)	212 (45.1%)	
Education level				0.039[2]
None	17 (7.3%)	24 (10.1%)	41 (8.7%)	
Primary	82 (35.3%)	60 (25.2%)	142 (30.2%)	
Secondary	99 (42.7%)	102 (42.9%)	201 (42.8%)	
Graduate	34 (14.7%)	52 (21.8%)	86 (18.3%)	
BMI				0.603[1]
Count	232	238	470	
Median	26.15	26.57	26.43	
Q1,Q3	23.64, 30.44	23.89, 28.40	23.73, 29.30	
BMI in categories				0.002[2]
Obese	63 (27.2%)	38 (16.0%)	101 (21.5%)	
Overweight	75 (32.3%)	113 (47.5%)	188 (40.0%)	
Normal	89 (38.4%)	85 (35.7%)	174 (37.0%)	
Underweight	5 (2.2%)	2 (0.8%)	7 (1.5%)	
Alcohol use				<0.001[2]
No	177 (76.3%)	141 (59.2%)	318 (67.7%)	
Yes	55 (23.7%)	97 (40.8%)	152 (32.3%)	
Smoking				0.010[2]
No	220 (94.8%)	210 (88.2%)	430 (91.5%)	
Yes	12 (5.2%)	28 (11.8%)	40 (8.5%)	
Number in Household				0.101[2]
1-3	108 (46.6%)	93 (39.1%)	201 (42.8%)	
4+	124 (53.4%)	145 (60.9%)	269 (57.2%)	

Pets/Domestic animals				0.024[2]
No	49 (21.1%)	72 (30.3%)	121 (25.7%)	
Yes	183 (78.9%)	166 (69.7%)	349 (74.3%)	
Source of drinking water				0.270[2]
Borehole	120 (51.7%)	111 (46.6%)	231 (49.1%)	
Piped	112 (48.3%)	127 (53.4%)	239 (50.9%)	
Type of toilet facility				0.104[2]
Open air	0 (0.0%)	2 (0.8%)	2 (0.4%)	
Pit	158 (68.1%)	144 (60.5%)	302 (64.3%)	
Water closet	74 (31.9%)	92 (38.7%)	166 (35.3%)	
Method of Waste disposal				<0.001[2]
Burying	13 (5.6%)	32 (13.4%)	45 (9.6%)	
Open burning	130 (56.0%)	81 (34.1%)	211 (44.9%)	
Open space	16 (6.9%)	24 (10.1%)	40 (8.5%)	
Public waste bin	73 (31.5%)	101 (42.4%)	174 (37.0%)	
Random Blood Sugar category				< 0.001[2]
Normal	110(59.8%)	238 (100.0%)	348(82.5%)	
Elevated	74 (40.2%)	0 (0.0%)	74 (17.5%)	

1. Kruskal-Wallis rank sum test
2. Pearson's Chi-squared test

In this study, a p value of less than 0.05 was considered significant.

The median age for the DM participants was 53 (IQR40.8,65) years while that of the non-DM participants was 52 (IQR:39.3,63). In terms of gender distribution there were more females in the DM group, at 144(60.8%) compared to non-DM group at 117, (49.2%). There was a higher proportion with no education, 24 (10.1%) among the non-DM compared to the DM participants, 17 (7.3%). There was a higher proportion of participants who were obese/overweight among the non-DM group, 151(63.5%) compared to the DM group, 138(59.5%), but BMI was equally distributed in both groups. A higher proportion of participants in the non-DM group reported positive history of cigarette smoking and alcohol use, 28 (11.8%) vs 12 (5.2%) and (40.8%) vs

55 (23.7%) respectively. There was no significant difference in terms of household size, source of water for household use and drinking, and type of toilet facility in both groups. We found a statistically significant difference in both groups in terms of waste disposal, and a greater proportion in the DM group reported to have pets and domestic animals.

4.2 Clinical characteristics of the DM population.

In this study, majority of participants had been diabetic for more than 5 years 92(39.7%), and we observed that at the time of the study, 83 (35.8%) participants had been diabetic for a period of less than 3 years. We enrolled both type 1 and 2 DM patients. We had 43% Type 1 (on Insulin only) 57% Type 2 (on OHS/OHS plus Insulin). Of the patients with Type 2 DM, 74% were on OHS only and 26% were on OHS and Insulin.

We used blood glucose limits or levels as per ADA for diagnosis of diabetes mellitus, to determine whether blood glucose levels documented during the study were elevated on not. Among the 48 participants who had a fasting blood sugar measured, only 5 (10.4%) had levels that were not elevated, using a cut off of 7.2 mmol/l (Table 5). Among the 184 who had random blood glucose measured, only 110 (59.8%) had levels that were not elevated using a cut off of 11.1mmol/l (Table 5).

Table 5: Clinical characteristics of DM population.

Variable	Freq (%)
Duration of DM	
N= 232	
1-3 years	83 (35.8%)
3-5 years	57 (24.6%)
>5 years	92 (39.7%)
Control of DM	
Diet	1 (0.4%)
Insulin	100 (43.1%)
OHS	97 (41.8%)
OHS and Insulin	34 (14.7%)
Fasting Blood Sugar category	
(Cut off of 7.2mmol/L)	
Not elevated	23 (47.9%)
Elevated	25 (52.1%)
Random Blood Sugar category	
(Cut off of 11.1mmol/L)	
Not elevated	110 (59.8%)
Elevated	74 (40.2%)

4.3 Objective 1 – Prevalence of *H. pylori*

4.3.1 Overall Prevalence of *H. Pylori* in both DM and non-DM

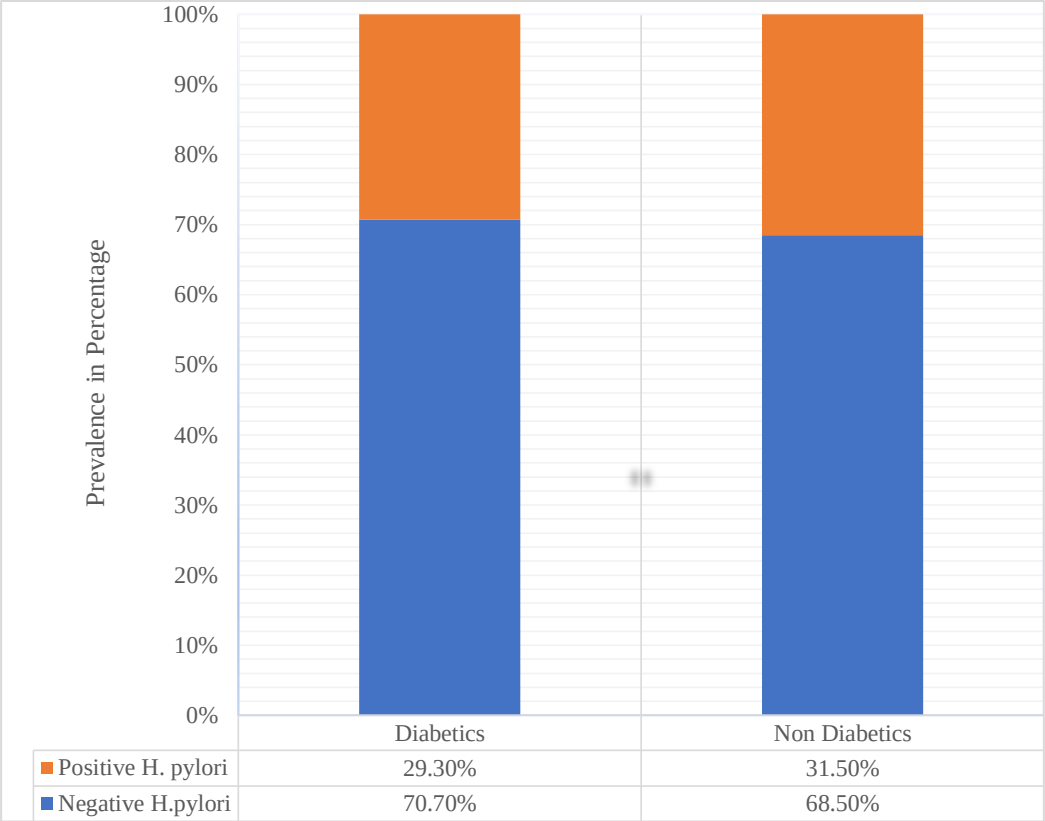

Figure 3: Graph showing overall prevalence of *H. pylori* in DM and non-DM.

The overall prevalence of *H pylori* was 30.4% (95%CI: 26.28, 34.81). In DM group it was 29.30% (95% CI: 23.54, 35.62) while in the non- DM group, the prevalence was 31.50% (95% CI:25.66, 37.82). The difference was not statistically significant (p-value=0.604). Based on the p value obtained, we concluded that there is no association between DM and *H. pylori* infection.

4.3.2 Prevalence of *H. pylori* in DM

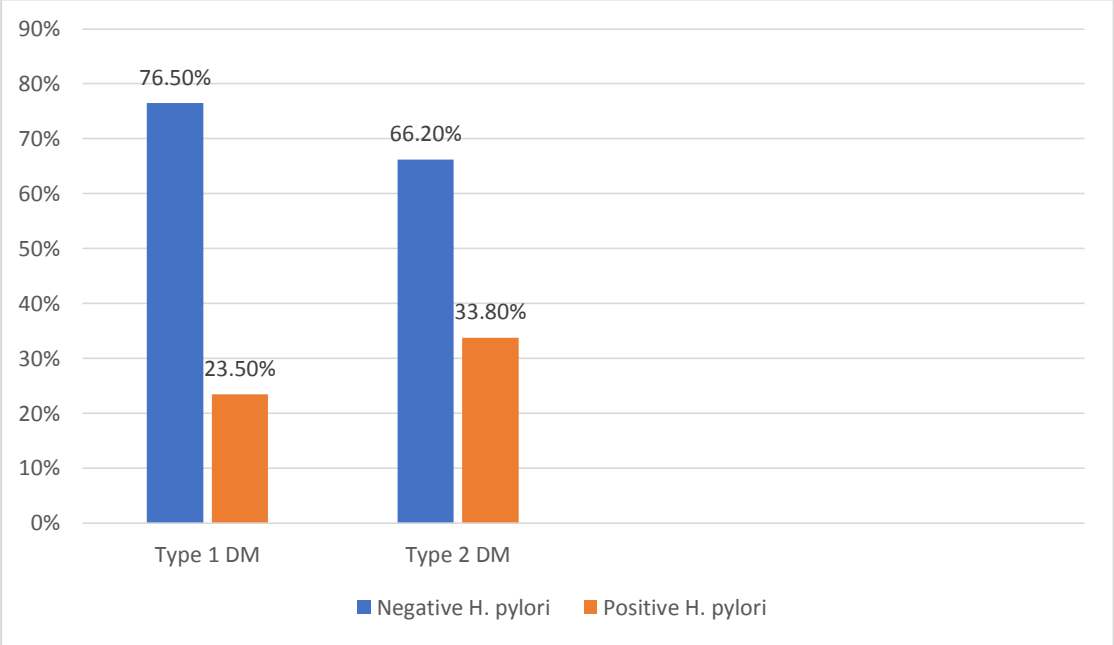

Figure 4: Graph showing prevalence of *H. pylori* in Type 1 and 2 diabetes mellitus.

A total of 68 out of 232 participants tested positive for *H. pylori* in the DM group. The prevalence of *H. pylori* among those with Type I DM was 23 (23.5%) while among those with Type II DM, it was 45 (33.8%). This difference was not statistically significant (p-value =0.088).

4.4 Objective 2 – Factors associated with *H. pylori*

4.4.1 Positive *H. pylori* and associated factors studied.

Bivariate analysis of the factors associated with *H. pylori* showed no statistical significance. Using bivariate analysis, none of the examined factors was found to have an association with a positive *H. pylori* antibody test.

Table 6: Bivariate analysis of factors associated with *H. pylori.*

	H pylori Result		**p value**
Variable	**Negative (N=327) Freq (Row %)**	**Positive (N=142) Freq (Row %)**	
DM/Non-DM			0.604[1]
DM	164 (70.7%)	68 (29.3%)	
Non-DM	163 (68.5%)	75 (31.5%)	
Age in (years)			0.363[2]
Median	52.00	55.00	
Q1,Q3	40.00, 64.50	41.25, 62.00	
Sex			0.920[1]
Female	180 (69.8%)	78 (30.2%)	
Male	147 (69.3%)	65 (30.7%)	
Education level			0.385[1]
None	24 (58.5%)	17 (41.5%)	
Primary	98 (69.0%)	44 (31.0%)	
Secondary	142 (70.6%)	59 (29.4%)	
Graduate	63 (73.3%)	23 (26.7%)	
BMI in categories			0.356[1]
Obese	69 (68.3%)	32 (31.7%)	
Overweight	129 (68.6%)	59 (31.4%)	
Normal	122 (70.1%)	52 (29.9%)	
Underweight	7 (100.0%)	0 (0.0%)	
Alcohol status			0.555[1]
No	224 (70.4%)	94 (29.6%)	
Yes	103 (67.8%)	49 (32.2%)	

1.Pearson’s Chi-squared test

2.Kruskal-Wallis rank sum test

	H pylori Result		
Variable	**Negative (N=327) Freq (Row %)**	**Positive (N=142) Freq (Row %)**	**p value**
Smoking			0.511[1]
No	301 (70.0%)	129 (30.0%)	
Yes	26 (65.0%)	14 (35.0%)	
Number in Household			0.709[1]
1-3	138 (68.7%)	63 (31.3%)	
4+	189 (70.3%)	80 (29.7%)	
Pets			0.118[1]
No	91 (75.2%)	30 (24.8%)	
Yes	236 (67.6%)	113 (32.4%)	
Source of water			0.456[1]
Borehole	157 (68.0%)	74 (32.0%)	
Piped	170 (71.1%)	69 (28.9%)	
Type of toilet			0.716[1]
Open air	1 (50.0%)	1 (50.0%)	
Pit	213 (70.5%)	89 (29.5%)	
Water closet	113 (68.1%)	53 (31.9%)	
Waste disposal			0.764[1]
Burying	29 (64.4%)	16 (35.6%)	
Open burning	146 (69.2%)	65 (30.8%)	
Open space	30 (75.0%)	10 (25.0%)	
Public waste bin	122 (70.1%)	52 (29.9%)	

1.Pearson’s Chi-squared test

2.Kruskal-Wallis rank sum test

4.4.2 Positive *H. pylori* and diabetes mellitus – Subgroup analysis

In bivariate analysis separates for DM and non-DM, we observed that among the DM as well as the non-DM groups, there was no statistical significance in association of the factors studied and a positive *H. pylori* antibody test result.

Table 7: Bivariate analysis separates for DM and non-DM

	DM			Non-DM		
	H pylori result			H pylori result		
Variable	**Negative (N=164) Freq (Row %)**	**Positive (N=68) Freq (Row %)**	**p value**	**Negative (N=163) Freq (Row %)**	**Positive (N=75) Freq (Row %)**	**p value**
Age in (years)			0.157[1]			0.952[1]
Median	51.5	56		52	51	
Q1,Q3	39.0, 66.0	47.0, 62.0		40.0, 62.5	36.5, 65.0	
Sex			0.621[2]			0.602[2]
Female	98 (69.5%)	43 (30.5%)		82 (70.1%)	35 (29.9%)	
Male	66 (72.5%)	25 (27.5%)		81 (66.9%)	40 (33.1%)	
Education level			0.322[2]			0.693[2]
None	10 (58.8%)	7 (41.2%)		14 (58.3%)	10 (41.7%)	
Primary	56 (68.3%)	26 (31.7%)		42 (70.0%)	18 (30.0%)	
Secondary	70 (70.7%)	29 (29.3%)		72 (70.6%)	30 (29.4%)	
Graduate	28 (82.4%)	6 (17.6%)		35 (67.3%)	17 (32.7%)	
BMI in categories			0.490[2]			0.785[2]
Obese	44 (69.8%)	19 (30.2%)		25 (65.8%)	13 (34.2%)	
Overweight	51 (68.0%)	24 (32.0%)		78 (69.0%)	35 (31.0%)	
Normal	64 (71.9%)	25 (28.1%)		58 (68.2%)	27 (31.8%)	
Underweight	5 (100.0%)	0 (0.0%)		2 (100.0%)	0 (0.0%)	
Alcohol status			0.704[2]			0.330[2]
No	124 (70.1%)	53 (29.9%)		100 (70.9%)	41 (29.1%)	
Yes	40 (72.7%)	15 (27.3%)		63 (64.9%)	34 (35.1%)	
Smoking			0.334[2]			0.939[2]
No	157 (71.4%)	63 (28.6%)		144 (68.6%)	66 (31.4%)	
Yes	7 (58.3%)	5 (41.7%)		19 (67.9%)	9 (32.1%)	
Number in Household			0.632[2]			0.291[2]
1-3	78 (72.2%)	30 (27.8%)		60 (64.5%)	33 (35.5%)	
4+	86 (69.9%)	38 (30.6%)		103 (71.0%)	42 (29.0%)	
Pets			0.630[2]			0.084[2]
No	36 (73.5%)	13 (26.5%)		55 (76.4%)	17 (23.6%)	
Yes	128 (70.3%)	55 (30.1%)		108 (65.1%)	58 (34.9%)	

Source of water			0.598[2]			0.572[2]
Borehole	83 (69.2%)	37 (30.8%)		74 (66.7%)	37 (33.3%)	
Piped	81 (72.3%)	31 (27.7%)		89 (70.1%)	38 (29.9%)	
Type of toilet						0.566[2]
Open air	0	0	0.831[2]	1 (50.0%)	1 (50.0%)	
Pit	111 (70.3%)	46 (29.7%)		102 (70.8%)	42 (29.2%)	
Water closet	53 (71.6%)	21 (28.4%)		60 (65.2%)	32 (34.8%)	
Waste disposal			0.576[2]			0.574[2]
Burying						
Open burning	7 (53.8%)	6 (46.2%)		22 (68.8%)	10 (31.2%)	
Open space	94 (72.3%)	36 (27.7%)		52 (64.2%)	29 (35.8%)	
Public waste	11 (68.8%)	5 (31.2%)		19 (79.2%)	5 (20.8%)	
bin	52 (71.2%)	21 (28.8%)		70 (69.3%)	31 (30.7%)	
Duration DM			0.764[2]			
1-3 years	61 (73.5%)	22 (26.5%)				
3-5 years	40 (70.2%)	17 (29.8%)				
>5 years	63 (68.5%)	29 (31.5%)				
RBS			0.916[2]			
Elevated	51 (68.9%)	23 (31.1%)				
Normal	75 (68.2%)	35 (31.8%)				

1. Pearson's Chi-squared test
2. Kruskal-Wallis rank sum test

CHAPTER FIVE: DISCUSSION

5.1 Prevalence of *H. pylori* infection.

5.1.1 Prevalence of *H. pylori* in DM and Non-DM

The difference in the prevalence of *H. pylori* in diabetes mellitus (29.31%) and non-diabetes mellitus (31.51%) participants was not statistically significant (p = 0.604). Therefore, the results in this study population indicate that *H. pylori* infection is not significantly correlated with diabetes mellitus. The absence of a difference that is statistically significant between *H. pylori* infection in diabetes mellitus and in those without diabetes mellitus implies that the infection is not increased in diabetes mellitus.

Similar findings were reported in Nigeria (Oluyemi et al., 2012). However, this study looked at *H. pylori* infection in type 2 diabetes mellitus. The results showed no significant difference between infection prevalence in the type 2 DM group and non-DM control group (p = 0.52). Another case control study conducted in South-East region of Nigeria also reported similar results. This study looked at *H. pylori* infection in type 2 diabetes mellitus. The results showed a prevalence of 35% in DM and 28% in non-DM ($p = 0.432$) (Ugwu et al., 2008). A multicenter cross-sectional study conducted in Saudi Arabia, including four centers recorded a prevalence of 26.9% in type 2 diabetes mellitus vs 26.3% in age matched non-DM control group. This study however, recruited participants aged 40 years and above and performed stool antigen test for detection of *H. pylori* infection (Alzahrani et al., 2020). Some studies conducted in both developed – Italy (Dore et al., 2000), Australia (Xia et al., 2001) and developing countries – Romania (Stanciu et al., 2003), China (Woodward, 2000), Turkey (Demir et al., 2008), also showed no statistical difference between diabetes mellitus and *H. pylori* infection.

A case control study conducted in Cameroon found a significant association between DM and *H. pylori*. Using different serum biomarkers, the study found a prevalence of 88.2% in DM group versus 667.7 in non-DM (p=0.015). This study recruited type 2 DM patients who were on follow up, with recordings of history of dyspepsia (Ebule et al., 2017). A multicenter (2) study conducted in Douala Cameroon recorded an overall prevalence of *H. pylori* infection at 64.87%, with the highest prevalence in the DM arm at 73.11% versus 58.03% in the non-DM group (p 0.0279). This study recruited dyspeptic participants aged 35 to 75 years and used serology antibody testing for detection of *H. pylori*. This study also determined that there is an increased risk of up to 1.967 times in developing *H. pylori* infection when one has type 2 diabetes mellitus (Kouitcheu et al., 2020). Another prospective cohort study conducted in Italy, using rapid urease test and histology from endoscopy biopsy, showed a higher prevalence in dyspeptic DM (65%) compared to dyspeptic controls (48%) (Marollo, M. et al., 2001). In Carlifornia, USA, a prospective cohort study using serology testing documented 2.7 times likelihood of developing diabetes mellitus in patients who tested positive for *H. pylori* at baseline (HR 2.69) (Jeon et al., 2012).

In Kenya, the prevalence of *H. pylori* in patients with diabetes mellitus was found to be at 77.5% via histology results and urea breath test post endoscopy. This study was conducted at Kenyatta National Hospital in dyspeptic patients from 18 years of age attending DM outpatient clinic. This study did not have a non-DM group for comparison (Wafula et al., 2002). The high prevalence in this study could be attributed to the fact that only symptomatic patients were recruited, with biopsy of active lesions on endoscopy being taken for histological examination.

The overall prevalence of *H. pylori* in diabetes mellitus has been estimated to range from 30% to 80%. This is as stated by Anastasios et al. (2002) while quoting several studies conducted globally. Our study supports this statement, as we found the prevalence of *H. pylori* to be 29.3% (33.8% in type 2 DM and 23.5% in type 1 DM).

5.1.2 Local *H. pylori* infection Prevalence data compared with study results.

The prevalence of *H. pylori* infection differs broadly depending on the method of *H. pylori* detection and the study population. Predominantly, seroprevalence studies are the most conducted, but their values also vary depending on the method of *H. pylori* infection diagnosis and the population being studied (Oluyemi et al., 2012).

Africa records the highest prevalence of *H. pylori* infection, with Nigeria as the leading country in infection rates and prevalence at around 87% (Smith et al., 2019). In Kenya, the prevalence of *H. pylori* also varies depending on the study area, method of detection or diagnosis and study population.

An article written by Kimang'a and published in 2019, placed the overall prevalence of *H. pylori* in Kenya at 67.5% in all age groups. This article also alluded to the fact that *H. pylori* acquisition is increased in areas with poor sanitation and sewerage systems in Nairobi (Kimang'a, 2019). In 2010, a study examining dyspeptic patients via rapid urease test, culture and histological examination of biopsied lesions placed the prevalence of *H. pylori* at 73.3% in children and 54.8% in adults (Kimang'a 2010). The great difference in the prevalence between children and adults in the study could be because *H. pylori* acquisition period as proven by majority of studies, is during childhood especially in developing countries thought to have poor sanitation.

This study, which was conducted at MTRH, found the overall prevalence of *H. pylori* to be 30.4 % in asymptomatic patients. This prevalence is lower than that found by Sang in 2013 which was 52.3%. Sang (2013) however, examined the prevalence of *H. pylori* infection and endoscopic features in dyspeptic patients at MTRH with a sample size of 126 participants. Recruitment of dyspeptic patients in the Sang (2013) study perhaps increased the probability of having a positive *H. pylori* test. In addition, the test used which was endoscopy with biopsy has a specificity of more than 95 percent. This could explain why the study got a higher prevalence compared to our study findings. In addition, our study did not recruit dyspeptic patients and we used serology testing which has an overall sensitivity of more than 95 percent but a specificity of about 60 to 90 percent.

From literature, studies conducted in Kenya have looked at the prevalence of *H. pylori* in symptomatic dyspeptic patients. This study however, focused on asymptomatic patients, a cohort that has not been studied even from international literature. The reason for choosing asymptomatic patients was based on the fact that 90% remain asymptomatic upon acquisition of *H. pylori,* especially in developing countries (Meurer and Bower, 2002).

The prevalence of *H. pylori* varies depending on epidemiological distribution of *H. pylori* (Alzahrani et al., 2020). The difference in the prevalence of *H. pylori* in Nairobi and Eldoret is a clear indication that this fact could be true. The prevalence is higher in studies conducted in Nairobi compared to those conducted in Eldoret.

Nairobi is reported to have more than 40 areas identified as slums. Also, the largest slum in Kenya, Kibera is found in Nairobi. In Nairobi, it is approximated that 60% live-in low-income settlements which are unplanned, and have poor sanitation and

sewerage systems (Fèvre, 2020). This could explain the higher prevalence of *H. pylori* infection in Nairobi area. Eldoret on the other hand has only one major slum, Langas, reported as the second largest in Kenya. This is not comparable to the large numbers reported in Nairobi.

The low prevalence of *H. pylori* in Eldoret town can possibly be explained by the fact that Eldoret Water and Sanitation Company (ELDOWAS) has over the years ensured and worked towards improving sanitation systems in Eldoret. This has been achieved by continuous expansion of pipeline networks and this has made it possible for majority to access portable water. Preceding formation of ELDOWAS, in 1994/1995, only about 68,000 people had access to treated piped water in Eldoret. This number rose to more than 150,000 in 2002/2003 after formation of ELDOWAS. There is a steady increase in number of residents in Eldoret with access to piped water. ELDOWAS in partnership with Eldoret Municipal Council have also set up water kiosks with safe water for the residents who are unable to afford water connections (Implementation of a Commercialization Policy with Social Inclusion and Service Improvement Goals, 2010). ELDOWAS also manages the largest organic sewage treatment based out of Nairobi. The treatment works by recycling waste products from sewer lines up to 190 kilometer around Eldoret before discharging as clean water. The whole process involves analysis and extraction of water from waste material such as human fecal matter, the extracted water is then purified and stored in tanks for treatment before being released into Sosiani river (Rutto, 2021).

Alluding to this, it is fair to say that a good number of people in Eldoret have access to treated piped water, and this is comparable to other towns. In addition, those who are unable to afford piped water have various options to access reliable and safe water

from water kiosks and pathogen free water released into Sosiani river. MTRH however, is a referral facility serving a much bigger catchment than Eldoret, therefore, completely restricting the low prevalence to ELDOWAS improvement in sanitation may not be appropriate or accurate and a true representative of Uasin Gishu area.

Using an antibody test is expected to give a higher figure for positivity rate since it does not distinguish past and present infection. Results of this study are surprising in this regard. The low prevalence could be due to adopting a strict criterion such as excluding symptomatic dyspeptic patients.

5.1.3 Association between Diabetes mellitus and *H. pylori* infection

In this study, we did not find an association between DM and *H. pylori* infection, ($p = 0.604$).

In addition, this study did not find a relationship between *H. pylori* infection and duration of diabetes mellitus. Therefore, this study does not support the implication that the prevalence of *H. pylori* is affected by the duration of diabetes mellitus or that patients with diabetes mellitus often acquire *H. pylori* infection over time.

This result was in accord with results from international literature; Nigeria (Oluyemi et al., 2012; Ugwu et al., 2008), Australia (Xia et al., 2001), Italy (Dore et al., 2000), and Turkey (Demir et al., 2008) but contradicted results from local literature (Wafula et al., 2002). There is still a debate in this subject as some studies have reported a relationship between *H. pylori* infection and duration of DM; The Netherlands (Oldenburg et al., 1996), Italy (Gasbarrini et al., 1998) whereas others reported a negative association; Spain (de Luis et al., 1998).

The Kenyan study conducted at Kenyatta National Hospital (KNH) found the prevalence of *H. pylori* in dyspeptic type 1 and 2 DM patients to be 77.5 %. The study also reported that the prevalence of *H. pylori* infection in DM rose with duration of DM, with peaks at 6 to 10 years from the time of diagnosis of DM. This is contrary to results from our study; we did not find an association between a positive *H. pylori* test and duration of DM. In the KNH study, what happens after 10 years from the time of diagnosis was not demonstrated. The mean age in the study was 53.13, slightly higher than ours which was 52.2 (Wafula et al., 2002). The difference in the prevalence as alluded earlier, could be due to the fact that only symptomatic dyspeptic patients were recruited in the study making the probability of having positive *H. pylori* test high.

In the Spain study, that reported a negative association. The initial seroprevalence of *H. pylori* infection in participants with type 1 DM for less than 3 years was 43%, and this number reduced to about 16 % in those who had DM for longer than 3 years (de Luis et al., 1998). It was alluded that the cause of this decline was because of repeated antibiotic exposure and use in those who have had diabetes mellitus for longer than 3 years.

5.2 *H. pylori* infection and risk factors.

Poor living conditions, poor socioeconomic status and poor hygiene have constantly been demonstrated as the main risk factors for acquiring *H. pylori* infection (Woodward et al., 2000). Based on literature, *H. pylori* has been associated with several factors including having DM, less education, increased BMI, increased number in household, keeping of domestic animals, in addition to other markers of poor living conditions such as use of other sources of water apart from piped water, use of pit latrines and inappropriate ways of waste disposal.

Using bivariate analysis, this study did not find a correlation between positive *H. pylori* antibody test result and socioeconomic and risk factors associated with *H. pylori* infection.

A major observation made on the studies that discovered a correlation between *H. pylori* infection and diabetes mellitus was that there was no correction for socioeconomic factors as a confounding variable (Dore et al., 2000).

CHAPTER SIX: CONCLUSION, STUDY STRENGTHS, LIMITATIONS AND RECOMMENDATIONS

6.1 Conclusion

The prevalence of *H. pylori* infection was slightly higher in non-DM population compared to those with DM at MTRH, Eldoret. However, the difference in the two groups was not statistically significant. This study revealed that the prevalence of *H. pylori* in asymptomatic patients (without dyspepsia) attending MTRH clinics at Eldoret, is similar in those with DM and in those without DM. As part of exploratory analysis, this study did not find a relationship between *H. pylori* infection and duration of DM.

This study did not also find an association between DM (asymptomatic without dyspepsia) and *H. pylori*. Based on this result, this study supported the evidence that having DM is not a risk factor for acquiring of *H. pylori* infection.

Traditional risk factors for *H. pylori* identified from literature do not seem to be at play in this population that was studied.

Based on the results obtained in this study, there was failure to reject the null hypothesis.

6.2 Study Strengths

This was a large study that recruited 464 participants.

This was a comparative study involving two groups. DM and Non-DM groups.

This study used serology testing which is deemed one of the best in epidemiological and prevalence studies, because of high sensitivity.

This study also used 90% as variate for power.

To the best of my knowledge, this is the first study conducted in Kenya, directly looking at an association between DM and *H. pylori.*

6.3 Limitations

This study was a single center-based study conducted at MTRH only. The results obtained may not be a true representation on the burden or prevalence of *H. pylori* in Uasin Gishu County or other regions in Kenya. Especially since *H. pylori* prevalence varies depending on region and the population studied.

This study used one reading of less than 7mmol/L for diagnosis of DM to rule out DM in the non-DM group. This is not the standardized level for diagnosis of DM, therefore may not be appropriate or accurate.

6.4 Recommendations

Based on the results obtained in this study, there is no need for routine screening of DM patients for *H. pylori*. The same *H. pylori* screening guidelines for general population should be used in DM patients.

Larger studies using different study designs in multiple centers in different settings and regions need to be conducted to corroborate this study findings and further clarify whether there is indeed an association between DM and increased risk of acquiring *H. pylori* infection.

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APPENDICES

Appendix 1: Consent Form (English)

Read this greeting to the respondent and proceed with the interview only after he/she gives consent

Good morning/ afternoon, my name is Dr. Jane Akinyi from Moi University. I am here today to collect information and data on a study on association of diabetes mellitus with Helicobacter infection. This research has been approved by the Institutional Research and Ethics Committee (IREC) of Moi University.

I will be asking you questions on sociodemographic, health history and, also collect blood samples from a visible vein in your arm. I will prick your finger using a small needle in order to obtain blood. The blood drawn will be used to measure your blood glucose levels, and to detect *H. pylori* antigen. You may experience some pain, but it will not last long.

For blood glucose levels, a test strip will be attached to a device known as a glucose meter. Blood obtained will be placed on the open end of the test strip. The glucose meter will give a reading once your blood is fully absorbed by the test strip.

For *H.pylori* test, blood drop will be placed on sample pad end of the test strip. Two drops of a buffer solution will be added to the blood sample, then let to flow through the strip. The test will be confirmed as positive when both the control and test line appears. A negative test will only show the control line.

All the test results will be shared with you.

Benefits

The findings of this research project will be used by the MTRH management, Government policy makers and health providers in creation of awareness and putting in place measures of screening and eradication of *H. pylori*.

Your participation will also enable us to gain a better understanding on the association of diabetes mellitus and *H. pylori*, and the prevalence rates. This will help us in providing better healthcare services.

Risks

I am aware that some questions regarding confidentiality during research participation may arise. I assure you that everything mentioned, and every information gotten from the study will remain confidential. Under no circumstance will we link your name to the data during analysis or dissemination of findings. **If at all you choose not to participate, it will not affect your management in any way. Also, if you feel uncomfortable at any point during the study, you can withdraw anytime.** If you agree to participate, it will take approximately 15 minutes to complete the interview.

If you have any further question, please do not hesitate to contact the research team using the contact information provided below.

May we proceed?

Yes
Signature…… Date…….
No
Signature…… Date…….

Thank you for participating.

Research team contacts
Dr. Jane E. Akinyi, Moi University
Telephone no: 0707825668
Email address: janeeve254.je@gmail.com

In case you need to report anything about the research, you can use the contacts below;

Institutional Research & Ethics Committee (IREC)

Moi Teaching & Referral Hospital building, 2nd floor. Door No. 219,

Office line: 0787723677

Email address: irecmtrh@gmail.com or contact@irec.or.ke

Appendix 2: Consent Form (Swahili)

Lazima kusoma salamu hii kwa mshiriki wa utafiti, na kuendelea na mahojiano tu baada 35u una35 kupeana ridhaa.

Habari ya leo, madam/bwana, jina langu ni Jane Akinyi. Mimi natoka 35u u kikuu cha Moi, Eldoret; maomi wa shahada ya juu. Leo hii ningependa kukusanya na kupata habari zaidi kuhusu utafiti unaoangalia uhusiano kati ya ugonjwa wa sukari na maambukizi ya *H. pylori.*

Nitakuuliza maswali kuhusu umri wako, makao yako, kiwango cha elimu ya shule na historia ya afya yako. Zaidi ya hayo, nitadunga kidole chako, ili kupata damu. Damu itatolewa kwa ajili ya kupima kiwango cha sukari na pia kupima maambukizi ya *H. pylori.* Ninatarajia ya kuwa huenda ukahisi maumivu kiwango ndogo, ambayo sidhani itakaa kwa muda mrefu, pindi damu itakapotolewa kwenye mshipa wa damu.

Ili kupima kiwango cha sukari, kuna kifaa ambacho kitatumika. Kifaa hicho kinakuja na ukanda wa mtihani utakaotumika kuwekea tone la damu ili kupima kiwango cha sukari.

Ili kupima *H.pylori* , tone la damu kitawekwa kwa ukanda wa mtihani, kisha tone mbili ya maji maalum, kwa kizungu inaitwa buffer solution, itaongezwa kwenye damu ili kusaidia na mwendo wa damu kwenye ukanda wa mtihani itatumika. Maambukizi ya *H. pylori* itakuwa + kama laini mbili itaonekana na itakuwa – kama laini moja tu itaonekana.

Utaonyeshwa na kuelezwa matokeao hayo yote.

Faida

Huu ni mradi wa utafiti; na matokeo yanaweza kutumika na wasimamizi wa MTRH na watunga sera serikalini kwa mipango ya kutoa huduma bora, na kubuni sera mwafaka wa ajili ya uchunguzi na kuangamiza maambukizi ya *H. pylori*.

Hatari

Mimi nina fahamu yakuwa baadhi ya maswali kuhusu ushiriki katika utafiti huu si rahisi kwako. Kila utakachonieleza kitakuwa siri. Hakuna wakati yeyote ambayo jina lako litaambatanishwa pamoja na takwimu wa utafiti, iwe ni wakati wa uchambuzi au usambazaji wa matokeo ya utafiti huu. **Kama utachagua kutoshiriki katika utafiti huu, haitakuathiri wewe kwa njia yeyote. Kama utakuwa na wasiwasi katika mwendo wowote wa utafiti huu, unaweza kuondoka wakati wowote**. Lau utakubali kushiriki, itachukua dakika 15 kukamilisha mahojiano haya. Kama una maswali yoyote zaidi katika kipindi cha utafiti 35u una katika siku zijazo, tafadhali usisite kuwasiliana na timu ya utafiti kwa kutumia namba za simu hapo chini.

Tuendelee?

Ndio Sahihi …….
Tarehe……..

Apana Sahihi ……. Tarehe …….

Asante kwa kushiriki

Mawasiliano ya timu ya utafiti

Dr. Jane E. Akinyi, Chuo kikuu cha Moi

Nambari ya simu: 0707825668

Barua pepe: janeeve254.je@gmail.com

Iwapo unahitaji kuripoti chochote kuhusu utafiti huu, unaweza kutumia anwani hapa chini;

Institutional Research & Ethics Committee (IREC)

Jengo la Moi Teaching & Referral Hospital, Sakafu ya pili. Mlango nambari 219,

Nambari ya simu ya ofisi: 0787723677

Barua pepe: irecmtrh@gmail.com or contact@irec.or.ke

Appendix 3: Data Collection Forms

SOCIODEMOGRAPHICS AND HEALTH HISTORY GROUP A

Participant Number	

Date of Birth	
Age	
Gender	□ Male □ Female
Height (cm)	
Weight (kg)	
Level of education	□ None □ Primary □ Secondary □ Graduate
Duration of diabetes (Years)	□ 1-3 □ 3-5 □ >5
Sugar control	□ Diet □ OHS □ Insulin
Alcohol use	□ Yes □ No
Smoking	□ Yes □ No

SOCIODEMOGRAPHICS AND HEALTH HISTORY

GROUP B

Participant Number	

Date of Birth	
Age	
Gender	□ Male □ Female
Height (cm)	
Weight (kg)	
Level of education	□ None □ Primary □ Secondary □ Graduate
Alcohol use	□ Yes □ No
Smoking	□ Yes □ No

Appendix 4: Socioeconomic Factors Assessment Form
Indicate 'Y' for 'Yes' where applicable.

Factor	Response
No of Siblings	□ 1-3 □ 4+
Pets or Livestock	□ Yes □ No
Source of drinking water	□ Borehole □ Pipe borne
Type of toilet facility	□ Open air □ Pit □ Water closet
Waste disposal	□ Open Space □ Burying □ Open burning □ Public Waste Bins

Appendix 5: IREC Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2019/164
Approval Number: 0003421

29th August, 2020

Dr. Jane Everlyne Akinyi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
4 AUG 2020
APPROVED
P. O. Box 4606-30100 ELDORET

Dear Dr. Akinyi,

RE: CONTINUING APPROVAL

The Institutional Research and Ethics Committee has reviewed your request for continuing approval to your study titled:-

"Association of Diabetes Mellitus with Helicobacter Pylori Infection".

Your proposal has been granted a Continuing Approval with effect from 29th August, 2020. You are therefore permitted to continue with your study.

Note that this approval is for 1 year; it will thus expire on 28th August, 2021. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc:	CEO	-	MTRH	Dean	-	SOD
	Principal	-	CHS	Dean	-	SPH
	Dean	-	SOM	Dean	-	SON

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2019/164
Approval Number: 0003421

29th August, 2019

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
29 AUG 2019
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dr. Jane Everlyne Akinyi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Akinyi,

ASSOCIATION OF DIABETES MELLITUS WITH HELICOBACTER PYLORI INFECTION

This is to inform you that ***MU/MTRH-IREC*** has reviewed and approved your above research proposal. Your application approval number is ***FAN:0003421.*** The approval period is ***29th August, 2019 – 28th August, 2020.***

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by ***MU/MTRH-IREC***.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to ***MU/MTRH-IREC*** within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to ***MU/MTRH-IREC*** within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to ***MU/MTRH-IREC.***

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and also obtain other clearances needed.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix 6: MTRH Approval

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

3rd September, 2019

Dr. Jane Everlyne Akinyi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Association of Diabetes Mellitus with Helicobacter Pylori Infection".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - Senior Director, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM