Original paper

Correlation between H Pylori Infection and Nonalcoholic Fatty Liver Disease in Karbala City

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ABSTRACT

Background: NAFLD patients had higher anti IgG H pylori and might be a clue that H pylori infection had a strong link the pathogenesis of early stage NAFLD mostly had simple steatosis. H pylori infection had a role in pathogenesis of IR and NAFLD. H pylori is strong inducer of pro inflammatory cytokine (IL6, IL8, TNF- α).Serum triglyceride was higher in H pylori positive group and NASH. Recent study have investigated weather H pylori induce insulin resistance mediated through fetuin which decrease in patients with sero positive Hpylori IgG patients.

Patient and method: Fifty six patients were collecting randomly as a case of fatty liver by ultrasound In Imam AL- Hussain Medical City in Karbala .Obese, DM, alcoholic patients, renal and hepatic diseases were exclude from this study. Fasting blood sample was taken and sent for IgG antibody H pylori, lipid profile, liver function test including ALT and AST.

Result: The mean age of patients was 45+10 and majority (65%) was females.

(67)% of patients who were fatty liver had Hpylori sero positive IgG (p value<0.05).

(66)% of patients who were fatty liver had normal liver function ALT mean±SD(31±7) and only 34% had increased liver function, ALT mean SD±(110±13)with p value<0.01.

(71)% of patients who were fatty liver and H pylori sero positive IgG had normal liver function mostly ALT mean±SD (29±10) in comparism with 29% who had increase liver function mostly ALT mean ±SD(98±18) p value <0.01.

(83)% of fatty liver patients had hyperlipidaemia mean±SD (290±20), (395±22) respectively p value<0.01.

(75)% of fatty liver patients with H pylori sero positive IgG had hyperlipidaemia mean±SD (279±15),(320±20) respectively p value <0.01.

Conclusion This study shown significant correlation between chronic H pylori infection and NAFLD .The pathogenic mediator include fetuin-A, TNF-α and adiponectin and on long term IR.

Keywords: Hpylori, liver, lipid.

Introduction

H.pylori is aubiquitous Gram-negative organism that presented in 50% of general pobulation [1, 2]

H.pylori multiple in the stomach and may stay at all life in the stomach, if persist diseases occurs mostly in adults mainly chronic gastritis and atrophic with metaplastic change in the stomach [1, 3] and sometime lymphoma, and gastric cancer as chronic bad sequel [3, 4]. Orol-to oral or fecal to oral was common route of the infection pass on long term a chronic inflammation and mediated immuno response [5].

H pylori had two genes VACA and CAGA and serology had >90% specificity and sensitivity for diagnosis.

The new search speech about the relation between H.Pylori infection and

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nonalcoholic fatty liver disease (NAFLD) [6,7] NAFLD appear in various and multiple stages [8], the first step was simple steatosis and may go to nonalcoholic steatohepatitis with marked feature which included hepatic injury, inflammation with or without fibrosis [9,10], NASH may progress to liver cirrhosis and some time to hepatocellular carcinoma [11] NAFLD is now consider as the liver manifestation of the metabolic syndrome (MetS) [1,12,46] The patients had a lot of clinical and pathological problems likes obesity, DM, cardiovascular disease (CVD) and hyperlipidemia [13] and call insulin resistance [14] and a lot of fact about the relation between NAFLD and IR [15,16]

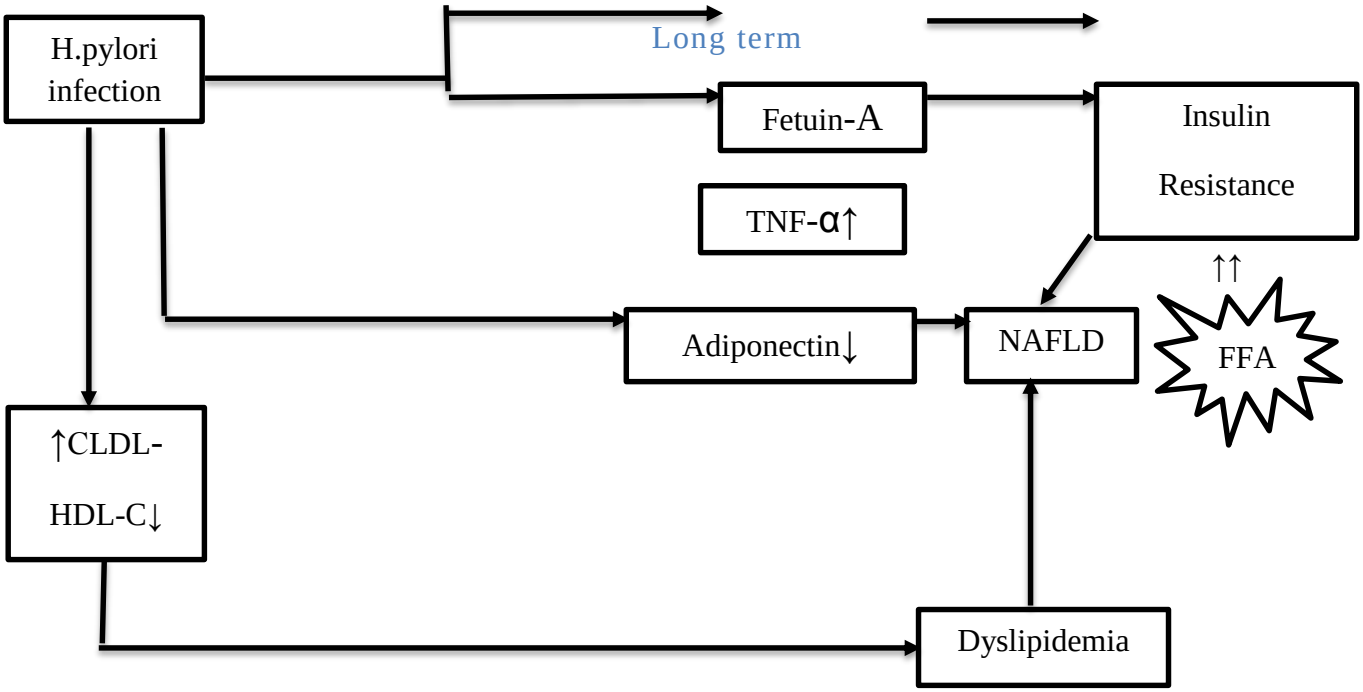

Figure 1. Fatty liver correlation with H pylori infection [15]

H pylori causes NAFLD through IR and IR increase deposition of (FFA) in the liver, another way IR may be mediated through fetuin-A.

(TNF)-α plays a golden role in the inflammation caused by chronic Hpylori infection

The reduction of adiponectin had correlated between Hpylori and NAFLD, Hpylori toxin come from the stomach and duodenum area may causes liver damage. H pylori may change lipid profile, this finally lead to NAFLD [15, 16]

H.pylori infection causes NAFLD by insulin resistance.

Insulin resistance is a state in which a given concentration of insulin produce less than expected biological effect, it had an important role in NASH [17,18]. It produces hyperinsulinemia and deposition of (FFA) in the liver as a result of lower mitochondrial β-oxidation, so that insulin inhibits hepatic mitochondrial B oxidation of fatty acid [19]. IR promote the hepatobiliary system to oxidative stress by stimulating microsomal lipid peroxidases [20].

H.pylori infection was change normal biological processes [21], initiated inflammation, metabolism change and oncogenic conversion [22, 23].Hpylori causes IR and IR calculated by HOMA-IR formula, [24] HOMA-IR in clinical practice consider most practical one ([25] by using this method, a high HOMA-IR score consider low insulin sensitivity and increase IR.HOMA-IR =fasting plasma

insulin (mμ)/l×fasting plasma glucose (mmol)÷22.5

IR is closely associated with NAFLD and it was also one of the independently risk factors of it excessive accumulation of fat in the liver parenchymal cells .this process is associated with IR [1,26],which can lead to dysfunction of intracellular triglyceride synthesis and transport.

In 2005, Aydemir et al [26], the first one prove the relation between H .pylori infection and IR, and their results showed that the HOME-IR of subjects in the H .pylori positive patients was much more higher than that in the H .pylori negative (p value< 0.05);

The level H pylori infection in NAFLD patient was more higher than control one, the study also examined the level of glucose, insulin, HOMA-IR, AST, ALT and TNF-α and when collect the result found increase in H pylori-serology positive patients compared to negative group, therefor, the author put forward that the H pylori infection may lead to the NAFLD pathogenesis these may occurred indirectly or directly by increase IR.

THE H. pylori –premote IR in NAFLD may be through prolong period of inflammation indirectly or directly by stimulated a lot of signaling cascades. Many basic and clinical studies had proved that chronic inflammation plays an important role in IR (Hossian, 2016 [27], paper have proved that the increase of (CRP), (TNF)-α, and (IL-6). These inflammatory markers cytokines would stimulate of kinases like a IKK / NF-KB and JNK, at the end trigger IR by up regulating Ser-phosphorylation or inhibition of the auto phosphorylation of the tyrosyl of the insulin receptor substrate [27].

fetuin-A:

Is a glycoprotein that screated from liver and adipose tissue, H. pylori may produce IR.

By fetuin-A and it concentration high in H. pylori-infected patients than control persons

They consider that fetuin-A as a global anti-inflammatory cytokine [1, 28]. Elevated fetuin-A level causes impaired glycemic control and impairment of insulin receptor, Toll like receptor 4 activation, macrophage migration, hepatocyte triglyserid accumulation and liver inflammation and fibrosis.

FetuinA had been demonstrate to play an important role in FFA induce IR in the liver and increase level had important role in the pathogenesis of NAFLD with impaired glucose tolerance as a marked of IR [29]. Fetuin-A was an endogenous inhibiter of insulin receptor tyrosine kinase in the liver [30, 31].

How cytokines and adiponectines induce chronic inflammation

The bacteria H pylor consider as a highly pro-inflammatory Cytokines effect [1, 32]. Prolong H. pylori infection causes inflammation by increase screation of pro-inflammatory cytokines and vasoactive mediater which include (IL)-6, IL-8, IL-1$_\beta$ and TNF-α [33, 34]. Patients who infected with H pylori had increase of pro-inflammatory cytokines [35]

TNF-α was pro-inflammatory with time causes IR. Therefor TNF-α consider gold mediator of both direct and indirect ways for H.pylori infection on NAFLD .TNF-α affect insulin gestures and finally Steatosis, and may had a pro-inflammatory role in the pathogenesis of NASH [36,37]

TNF-α induceSer phosphorylation on IRS-1 [38], and decrease in IRS [39]. TNF-α lower facing of key genes in adipose cells such as GLUT4 [40], so glucose transport become low [41]. TNF-α causes lipolysis, leading to an increase in FFAs, which causes hepatocytes injury by oxidative stress [42]. TNF-α induce and is activated by IR via activation of IKK-$_\beta$ [43, 44], which was finally activation of nuclear (NF-κB) [45].

Adiponectin level found low in H.pylori –positive patients with NAFLD, Adiponectin was adipocyte-specific

hormone and had a play roles in IR and NASH [46]

TNF-α and IR were significant higher circulating in H pylori infection with NAFLD. Adiponectin lower in H. pylori sero-positivity compared to H. pylori sero-negativity .H pylori infection may trigger TNF-α [47], adiponection enhance insulin sensitivity through increase fatty acid oxidation and inhibit hepatic glucose production.

Leptin was hormone of energy made in adipose tissue, it inhibit hanger and opposed by gherlin, the serum level of leptin were increase in NAFLD patients .H pylori infection interfere with leptin screation, which suppress liver stearoyl – CoAdesaturase, this decrease VLDL-C and fatty deposits in the liver tissue .leptin may phosphorylate IRS [48], decrease sensitivity to leptin result to undetect satiety and so insulin resistance. leptin was pro-inflammatory.

Lipid and hepatic metabolism

A classical histological feature of NAFLD is the presence of at least 5% hepatocyte steatosis. A classical feature of NAFLD is the presence of the hepatic ectopic fat deposition. A study on the association between hepatic lipids and insulin clearance showed that liver lipid component was significantly linked to insulin clearance (mild elevation of liver enzyme in upper normal range were notes with metabolic syndrome and NAFLD) [49, 50]. and hepatic insulin sensitivity So that ,IR contributes to liver lipid deposition, while increase hepatic lipid deposition in turn further aggravates IR, leading to NAFLD, they found that serum triglyceride and total cholesterol increase in chronic Hpylori infection [51,52]

Liver destroy by toxin.

H. pylori toxins and antibody had harmful subsequent effect on the hepatobiliary system.

The pathogen H pylori colonized from the duodenum [53],the liver may be destroy by H pylori Toxins which passes to the blood coming throughout the stomach and duodenum area, and may increase intestinal permeability in the patient with NAFLD, and increase permeability to antigens stimulate imumo-complex result liver damage.

Statistical analysis

Level of significance was set at ≤0.05 to be significant difference, result and finding presented in figures using Microsoft word for window 2016. Descriptive statistic presented as frequencies, proportion (%) mean and stander deviation according to variable types.

Patient and methods

This study was done in Imam AL Hussein Medical city in Karbala in period from 2017 – 2018, 56 patients were collected from outpatient GIT clinic, all patient diagnosed by ultrasounds as a fatty liver.

Blood sample was taken for H pylori antibody, fasting serum cholesterol and triglyceride analyzing with liver function test.

H pylori antibody was performed by rapid chromatographic method , ABON kit (USA) .

Serum cholesterol and triglyceride were determined by kit from Biosystem Company (Spain)

Inclusions criteria.

Patients with GIT upset attended outpatient GIT clinic and out patients medical clinic.

Exclusion criteria.

1. DM were exclude because there was direct relation with NAFLD in most search.
2. BMI>30 consider one of causes of NAFLD.
3. Alcoholic patients which causes fatty liver.
4. Liver disease which increase liver function.
5. Renal disease increase lipid and the result fatty liver.

Results

Fifty-six patients with fatty liver, their age range (25 – 60y) with mean ± SD (45 ± 10), 20 were male (35 %) were found significant lower in number than female 36 (65 %) at level of significantly P value < 0.05, as show in following figure2.

Fatty liver and H pylori positive and negative patients.

The fatty liver patients with H pylori-sero positive was 67%, and this significantly higher in comparison with fatty liver patients who H pylori negative 33% , at level of significantly P value < 0.05, as show in the following figure 3.

Fatty liver and liver enzyme (ALT).

In this study found that the fatty liver patients with normal ALT mean ± SD (31±7) was 66% and this significantly higher in comparison with fatty liver patients who had increase ALT mean ± SD (110 ±13) 34 %, at level of significantly P value < 0.01, as show in following figure 4 .

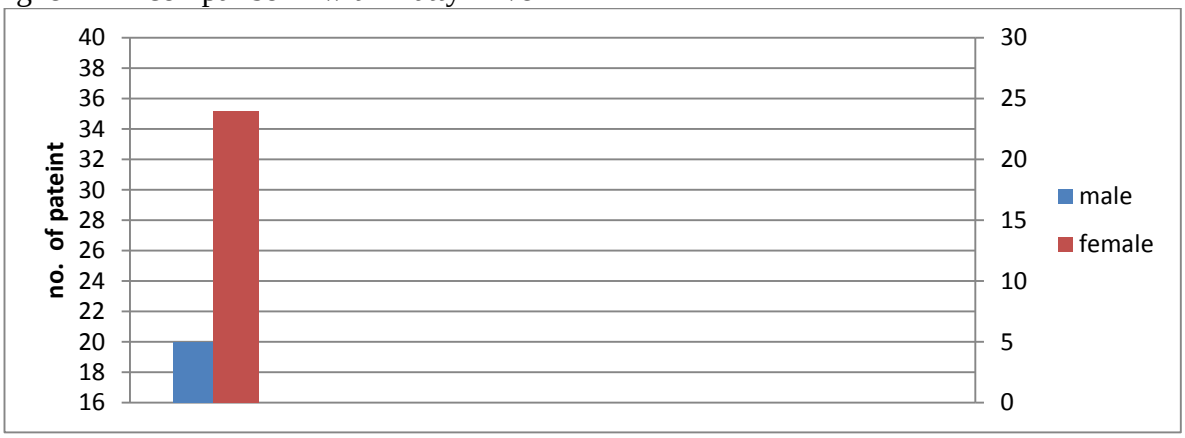

Figure 2. Gender distribution in a patients with NAFLD most patient females.

Figure 3. Distribution of H pylori infection in NAFLD group, most of patients had H pylori positive and few had negative.

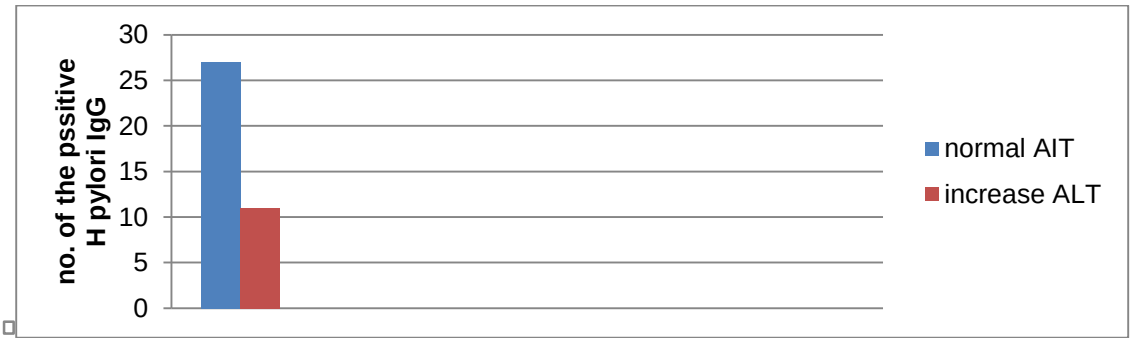

Figure 4. Distribution of liver function in a patients with NAFLD, most patients with fatty liver had normal liver function and few had increase liver function

H pylori sero- positive patients and liver enzyme (ALT).

In this study were showed that the patients who had H pylori sero- positive with increase ALT mean ± SD(98 ± 18) was 29% and this significantly lower in comparison with H pylori sero- positive patients who had normal ALT mean ± SD (29 ± 10) 71% , at level of significantly P value < 0.01, as show in following figure 5.

Fatty liver and combined hyperlipidemia.

The study showed that the fatty liver patients with combined hyperlipidemia (s cholesterol, s triglyceride) mean± SD (290±20), (395±22) respectively was 83% and this significantly higher in comparison with fatty liver patients who had normal lipidemia (s cholesterol, s triglyceride) mean±SD (188±8), (120±11) 17%, at level of significantly P value < 0.01, as show in following figure 6.

The study showen the H pylori sero-postive patients with combine hyperlipidemia (s cholesterol, s triglyceride) mean ± SD (279±15), (320±20) respectively was 75% and this significantly higher in comparism with H pylori-sero postive patients who had normal lipidemia (s cholesterol, s triglyceride) mean ± SD (140±11), (110±7) 25%, at level of significantly P value < 0.01, as show in following figure7.

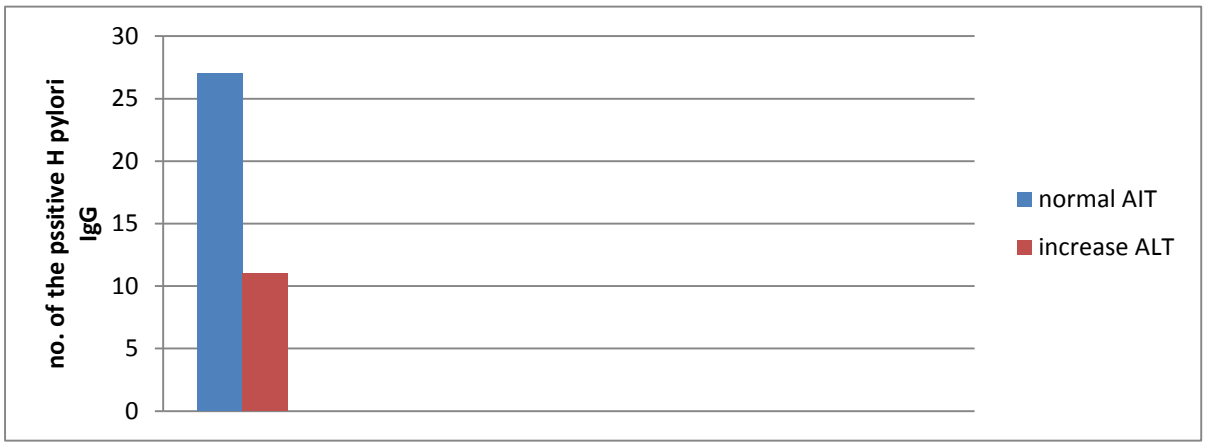

Figure 5. Distribution of IgG sero- positive H pylori patients with liver function.

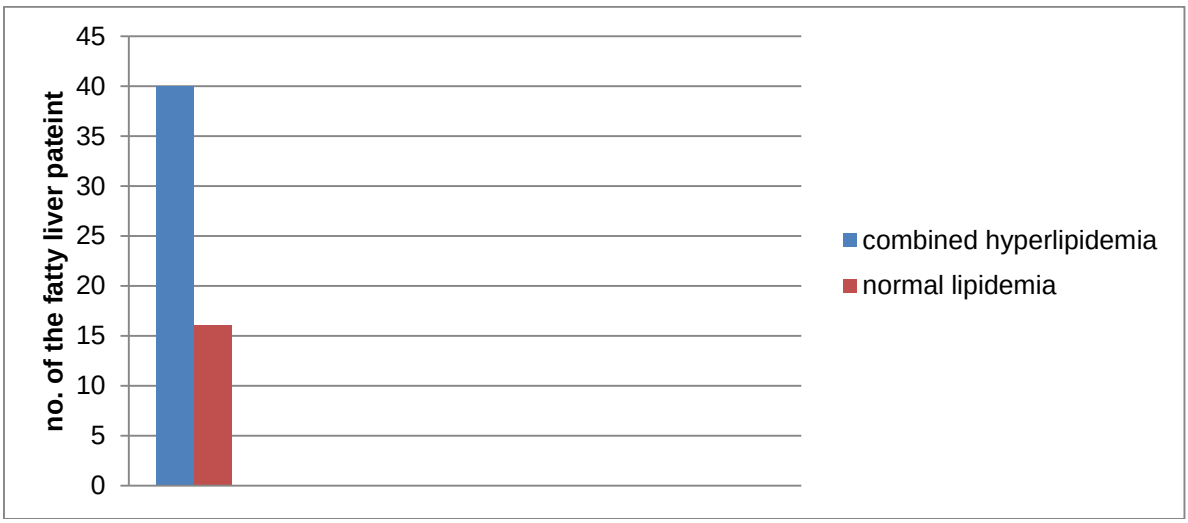

Figure 6. Distribution of a patients with combine hyperlipidemia in NAFLD as showen most patients with fatty liver had hyperlipidemia and few had normal lipidemia.
H pylori sero-positiveIgG patients and combined hyperlipidemia.

Figure 7. Distribution of IgG sero- positive H pylori patients with combine hyperlipidemia as shown most patients who H pylori positive had hyperlipidemia and few had normal lipedemia.

Discussion

In asses fatty liver ultrasound was used in which there was increase in echogenicity more than kidney which operator dependent .In the second figure numbers of females patients more than males we exclude obese patient in order to get a good result as a percentage 65% versus 35% with P value <0.05 .In the third figure 67% of patients had IgG positive H pylori infection in comparism 33% who had negative result at the of significantly P value <0.05 all these had fatty liver this give idea that there was a relationship between seropositive H pylori and fatty liver disease, polyzos 2013 (17) found at single center higher rates of anti- H pylori infection were observed in NAFLD also Eshraghian et at (42) found the prevalence of NAFLD was significantly higher in the patients with H pylori IgG seropositive than other. in the fourth figure there was only 34% of patients with NAFLD had increase in liver function mostly ALT mean +SD(110±13) in compare with 66% who had normal liver function all these patients had fatty liver with P value <0.01.Musso et at 2009 (49) found serum ALT were significantly association with NAFLD. When go to figure no. five and do comparism between patients who had fatty liver with IgG positive H pylori who had increase liver function find only 29% had increase in liver function mostly ALT mean+SD (98±18) and 71% had normal liver function mostly ALT mean +SD(29±10)with P value <0.01, from this correlation find that chronic H pylori infection causes only mild effect (steatosis) and most patients had normal liver function and those who had elevated liver function as a small percentage with mild elevation of liver function may consider as stage 2 of fatty liver (steatoheoatitis), Dembalya sanyla found mild elevation in liver enzyme in metabolic syndrome with NAFLD (50). figure number six found most patient with fatty liver had hyperlipidemia 83% mean +SD(290±20) for total cholesterol and mean +SD(395±22) for serum triglyceride in comparison with only 17% who had normal lipid mean +SD(188±8) for total cholesterol and mean+SD (120±11) for serum triglyceride .In figure no. seven, patients who had fatty liver and IgG positive H pylori found 75% of patients who H pylori positive had hyperlipidemia (serum total cholesterol, serum triglyceride) mean+SD (279±15),(320±20) respectively and only 25% had normal hyperlipidemia (serum cholesterol, serum triglyceride) mean+SD (140±11), (11±07) with significant P value<0.01.

In 1999, laurila (51) found that the serum triglyceride and total cholesterol were

significantly higher with positive IgG antibody for H pylori. Satoh H (52) demonstrated that H pylori infection is significantly associated with increase lipid profile. A common feature of NALD is fat deposition in the liver and association with insulin clearance with hepatic insulin sensitivity there for insulin resistance contributed to lipid deposition and steatosis .

Conclusion

From this study found there was relation between chronic H pylori infection and NAFLD and the mechanism that the chronic inflammation increase inflammatory cytokines such as IL-6, TNF-α then activating IKK/NF-KB and lead to insulin resistance also H pylori infection decrease the release of leptin which promote liver stearoyl-co A desaturases then fat deposit in the liver. Recent studies prove that fetuin significantly decrease in H pylori infection which induce IR.

Recommendation

Eradication of seropositive H pylori role in NAFLD and on liver function.
Limitation of study.
1. Single center.
2. Ultrasound was operator dependent.
3. Sample mostly females

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