KNOWLEDGE AND PRACTICE ON NONALCOHOLIC FATTY LIVER DISEASE MANAGEMENT OF INTERNAL MEDICINE PRACTITIONERS

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has an estimated prevalence of 20% in the general population.(1) It is is a common cause of chronic liver disease worldwide. In China, Japan, and Korea, the prevalence of NAFLD is 12% to 24% in subgroups depending on age, gender, ethnicity, and location.(2) In a study done at UP PGH, the prevalence of NAFLD was found to be at 12.2%. It was more common in females, obese, and diabetics.(3)

NAFLD is a multifactorial disease that embraces many histopathologic conditions and is highly linked to metabolic derangements. It is a spectrum of disease which encompasses simple fat depostion, hepatocyte injury and inflammation, to fibrosis and eventually cirrhosis.(4) Being a hepatic manifestation of metabolic syndrome, few studies have suggested that patients with NAFLD have an increased mortality compared to the general population, and cardiovascular disease being the most common cause.(5)

Nonalcoholic steatohepatitis (NASH) progresses to cirrhosis in 10–20% of cases within 10 years. NASH may lead to major complications such as portal hypertension, liver failure, and hepatocellular carcinoma (HCC).(6)

In developed countires, NAFLD is the third most common indication for liver trasplantation. With increasing prevalence of metabolic syndrome, NAFLD is becoming the leading cause of chronic liver disease in Asia. There have been several studies, majority from Western countries, that looked into the effects of several medications particularly metformin, thiazolidinediones, orlistat, hepatocyte protecting agents (ursodeoxycholic acid, silymarin) and antioxidants (vitamin E and C) in improving the biochemical and histologic profiles of patients with NAFLD. However, to-date there is

insufficient evidence of benefits, as well as outstanding concerns about adverse effects, and cost, to warrant recommendation for pharmacotherapy in NAFLD.(1, 2) At the present time, the cornerstone of therapy is lifestyle modification which addresses the metabolic derrangements associated with NAFLD, namely, obesity, insulin resistance or diabetes, hyperlipidemia, hypertension). It is the role of the physicians to identify and to manage risk factors for NAFLD in order to initiate treatment. Thus, to care for these patients, it is important to ensure that physicians have sufficient knowledge regarding this disease. The objective of this study is to evaluate the knowledge, the current practices and attitude of physicians caring for patients with NAFLD to guide further educational projects.

OBJECTIVE

This study aims to determine the current knowledge, behaviour, and practices of Internal Medicine physicians regarding the management of patients with nonalcoholic fatty liver disease (NAFLD).

REVIEW OF RELATED LITERATURE

Non-alcoholic fatty liver disease is viewed as a hepatic manifestation of metabolic syndrome. As such, it is closely linked to obesity, insulin resistance, diabetes mellitus and dyslipidemia. NAFLD may progress from simple fatty infiltration to cirrhosis and even cancer. Majority of patients with NAFLD die due to cardiovascular causes.

In the Philippines, based on the studyof De Lusong et al(3), patients with NAFLD had a mean age of 42 years old with majority being female with increased body mass index (BMI). NAFLD, in majority of the cases, were asymptomatic. However, of those with symptoms, they commonly presented with right upper quadrant pain and fatigue. Hepatomegaly was the most common physical finding. Female gender, diabetes mellitus, hepatomegaly, increased BMI (overweight and obesity) were the main risk factors noted to have a significant relationship with NAFLD.

NAFLD is often discovered by abdominal ultrasonography performed for persistent elevation of liver enzymes or other unrelated conditions.(7, 8) In a cohort of patients evaluated for elevated liver transaminases, NAFLD was diagnosed in 26.4% with 7.6% having advanced fibrosis.(9) Although histologic analysis is still the gold standard in the assessment of NASH patients, improvement in the liver enzymes has been shown to correlate very well with the resolution of inflammation on histology. Furthermore, CAP and fibroscan have been shown to have good correlation with the degree of hepatic steatosis and fibrosis, respectively, on histology. (10, 11)

Based on the current guidelines from the American Association for the Study of Liver Diseases (AASLD) on the management of NAFLD, it consists of treating the associated metabolic comorbid illnesses such as obesity, hyperlipidemia, insulin

resistance and diabetes mellitus, as well as gradual weight loss of at least 3-5% through diet and exercise.(1)

In the Philippines, most of the patients having medical complaints go seek the help of physicians practicing internal medicine regardless of subspecialty. Locally, there is scant information about physician's awareness regarding NAFLD diagnosis and management. Conflicting guidelines regarding actively screening for NAFLD exist. Chinese and European guidelines endorse screening for NAFLD using liver enzymes and imaging studies in patients who are obese and diabetic.(12, 13) However, in the published US guidelines from AASLD, screening for NAFLD in obese and diabetics is not recommended at this time due to uncertainties in the diagnostic testing, management and long term outcomes.(1) In one study examining attitudes of physicians toward NAFLD showed lack of adherence to guidelines for screening of liver diseases. It didn't include physician's longterm management issues.(14)

MATERIALS AND METHODS

Study Design and Participants

The research was a cross-sectional study which included Internal Medicine physicians, both trainees and consultants, handling patients with NAFLD. A formal letter of invitation, an overview of the research protocol and the 14-item questionnaire were given to the said doctors who attended a local conference on gastrointestinal diseases last May 2016.

Survey Instrument

The 14-item questionnaire was adapted from a foreign study entitled "Improving Nonalcoholic Fatty Liver Disease Management by General Practitioners: a Critical Evaluation and Impact of an Educational Training Program". The questionnaire, as shown in the Appendix, consisted of 14 multiple choice questions concerning epidemiology, clinical impact, diagnosis, evolution, and treatment of NAFLD.

Data Collection

The study was conducted last May 2016 during a local postgraduate course on gastrointestinal diseases attended by internal medicine trainees. The invitation, overview of the research with the 14-item questionnaire was given to the participants before the start of the course.

Responses were checked for completion and the data were assimilated. Incomplete and vague responses were considered invalid.

Ethical Considerations

This study was conducted in accordance with the applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice Guidelines (GCP).

Privacy and Confidentiality

Each respondent was given a Personal Identification Code. An identifier was assigned by the investigator to each respondent to protect his/her identity. This identifier was used in lieu of the respondent's name when the investigator reports or make a research related data.

Benefits

Data from this paper can be used to improve current knowledge, behaviour, and practices of physicians regarding patients with nonalcoholic fatty liver. This paper can also increase the awareness regarding the impact of NAFLD to the general health of the population.

Risk

Respondents were asked to answer the 14- item questionnaire and no major risk was caused during the conduct of the study.

Compensation and Expenses

No monetary incentives in cash or kind were provided to respondents. The investigators likewise did not receive any compensation for the study.

Informed Consent Process / Voluntary Participation / Withdrawal Process

Informed consent was obtained from each respondent prior to any data gathering. Consent for free withdrawal at any point of the study was explained to each of the subjects in the study.

Conflict of Interest

There was no conflict of interest arising from financial, familial considerations of the principal investigator and the study.

Statistical Analysis

Data was presented as a whole. In particular, the responses were tabulated as frequencies and percentages. IBM SPSS v20.0 was used for data analysis.

RESULTS

A total of 92 internal medicine physicians attended the local conference on gastrointestinal diseases held last May 2016. All were recruited to participate in the study. Of those recruited, 22 didn't complete the survey while 17 opted out of the study. At the end of the recruitment, forty respondents were legible for the research with a total response rate of 43.5%.

The mean age of the respondents was 34 years old with 22 (45%) being female. Of the 40 respondents, 25 (62.5%) were trainees in internal medicine while the rest are practicing internists with an average years in practice of 13 years. See Table 1 at the Appendix.

Majority of the physicians (24%) answered to request for a liver ultrasonography if faced with patients with undefined hypertransaminasemia and only 7% will check for metabolic alterations (Figure 1). With regard the prevalence of NAFLD in the general adult population, 18% of the physicians estimated it to be at 20-40%. For most of the physicians (57.5%), NAFLD is a hepatocyte fatty degeneration in patients with altered glucose or lipid metabolism followed by 37.5% of the pysicians stating that NAFLD is a condition at high risk of evolution towards end stage liver disease. Among type 2 diabetes, arterial hypertension, metabolic syndrome, dyslipidemia, and coronary heart disease, majority (47.5%) chose metabolic syndrome followed closely by type 2 diabetes mellitus (27.5%) as the condition often associated with NAFLD. However, they identified obese subjects (52.5%) among patients who are more likely to have NALFD over patients who are diabetic (30%), patients with coronary artery disease (2.5%), none among hypertensive. Some physicians (15%) noted that patients with cholelithiasis are likely to have NAFLD.

Among the criteria for NAFLD diagnosis (Figure 2), majority (45%) answered that elevation of at least one serum aminotransferase plus fatty liver at ultrasonography was most useful over high serum triglycerides levels plus elevation of serum transaminases (22.5%), fatty liver on ultrasonography plus high serum lipid levels (17.5%), liver biopsy with histology (7.5%), or after exclusion of all other causes of liver steatosis (7.5%). Most of the physicians feel that patients with concomitant other liver disease (32.5%) or those with coronary artery disease (30%) are the reasons to seek referral to other specialists. Only a few of the physicians will refer patients with associated metabolic syndrome (17.5%) or young patients (20%) to a specialist. Among the specialists, most of the physicians will choose to refer to a gastroenterologist (82.5%) to evaluate patients with NAFLD. Forty sever percent of the physicians will search for associated conditions when working up patients with NAFLD and only a few (5%) will refer a patient to a specialist (Figure 3). Physicians (35%) will choose diabetic patients over 50 years old with long standing hypertransaminemia as an indication to do liver biopsy however a good number (30%) feels that there is no indication to do liver biopsy on patients with NAFLD. Physicians choose low lipid content diet (52.5%) over low carbohydrate diet (22.5%), or hypocaloric diet (20%), or high protein diet (5%) as best diet in a patient with NAFLD (Figure 4). Most of the physicians (57.5%) indicated diet as the first and best approach to NAFLD over other medications like hepatoprotective agents (7.5%), metformin or glitazones (20%), antioxidants (2.5%). Among the medications listed, physicians identified statins (42.5%) and amiodarone (32.5%) as top drugs that can worsen NAFLD. Majority (32.5) have shown just enough interest in joining educational projects about NAFLD.

DISCUSSION

In the Philippines, the estimated prevalence of NAFLD was 12%. Female gender, diabetes mellitus, hepatomegaly, increased BMI (overweight and obesity) were the main risk factors noted to have a significant relationship with NAFLD.(3) Identification of NAFLD in patients with metabolic syndrome has been recommended by multidisciplinary position papers both for adults and for children.

Majority of the internists estimated the prevalence of NAFLD to be between 20 to 40% reflecting their awareness on the burden of the disease. Although NAFLD was viewed as a metabolic derangement, particularly those with diabetes and obesity, causing fatty degeneration of hepatocytes, only a few noted that NAFLD is a condition at high risk to progress into end stage liver disease. There was still a percentage of internists who still associated cholelithiasis with development of NAFLD. This necessitates reiteration of the primary risk factors for NAFLD since early recognition of the metabolic risk factors are important in order to initiate screening and treatment of patients.

Diagnosis of NAFLD was mostly based on findings of an elevated transaminase with fatty liver on ultrasound. This knowledge was consistent with the result of the showing that among the internists, a liver ultrasound was requested on first encounter with patients with undefined hypertransaminasemia, and with a good number also checking for metabolic risk factors.

Internists manage patients with NAFLD. It was identified that the most important reason for referral to other specialist is when there is concomitant other liver disease or if with complicating coronary heart disease. Among the specialists, gastroenterologists This finding in the study shows that an overwhelming majority of internists handle patients

with NAFLD themselves proving that a handful of knowledge regarding the evaluation and management of NAFLD is essential. Referral to specialists is important in the management of patients with NAFLD for prognostication and updated therapies.

The cornerstone of NAFLD management discusses the underlying metabolic syndrome and is often preventive. Lifestyle intervention through weight loss in combination with exercise and diet is the mainstay of treatment. Internists were able to correctly identify weight loss as beneficial for NAFLD patients. However, they failed to identify the benefits of certain medications in patients with NAFLD. Recognition that oxidation injury serves as a precursor of NASH thus several trials have looked into the role of anti-oxidants such as vitamin E and C in treating patients with NAFLD. Among the anti-oxidants, vitamin E appears to have the strongest evidence for improving histology in patients with NAFLD. In the PIVENS trial, which was a 3-arm study comparing pioglitazone versus vitamin E (tocopherol) versus placebo, both pioglitazone and vitamin E resulted in significant improvement in liver enzymes and resolution of NASH on histology, compared to placebo.(15)

The ideal diet for NAFLD should reduce fat mass and inflammation, restore insulin sensitivity, and provide low amounts of substrates for de-novo lipogenesis, but scientific evidence currently lacks for the recommendation of specific diets. Low-calorie diets with reduction in saturated fatty acids and increase in mono and polyunsaturated fatty acids appeared to be beneficial in some studies. However and in particular, excessive consumption of high glycemic index carbohydrates appears deleterious, as it favours hyperglycemia and hyperinsulinemia and stimulates denovo lipogenesis.(16) In this study, only a minority of internists have identified the importance of hypocaloric diet.

This study showed that majority of internists reported NAFLD as an important public health problem however basic knowledge is barely adequate although management practices are based on current recommendations.

CONCLUSION

Internal medicine physicians are increasingly seeing patients with nonalcoholic fatty liver disease. Although internists are aware of the prevalence of the disease however little is known about the disease's impact on health specifically it's progression to end stage liver disease and it's complications. Consensus guidelines have been made to guide physicians in the management of patients with NAFLD however there still conflicting issues. Physicians especially generalist are unaware of it's existence thus emphasizing the need for referral to specialists to better prognosticate the disease and to offer patients access to innovative and new therapies. Since the cornerstone of therapy is prevention, structured educational programs on the proper diet, exercise and weight management should be available to physicians. Educational and training initiatives among internists should be promoted.

APPENDIX A

QUESTIONNAIRE

1. How do you manage a patient with a persistent undefined hypertransaminasemia?
   a. Ask for liver ultrasonography
   b. Check for HBV and HCV infection
   c. Register data in the patient's card and check it again in one month
   d. Check for metabolic alterations
   e. Refer the patient to a specialist

2. What is the prevalence of NAFLD in the general adult population?
   a. 5%
   b. 5-10%
   c. 20-40%
   d. 50%

3. Which of the following sentences about NAFLD is true?
   a. It is a benign condition at no risk of evolution
   b. It is a condition at high risk of evolution towards end-stage liver disease
   c. It is the most frequent cause of dyspepsia
   d. It is a hepatocyte fatty degeneration in patients with altered glucose or lipid metabolism
   e. It never affects children

4. Which of the following conditions is often associated with NAFLD?
   a. Type II diabetes
   b. Arterial hypertension
   c. Metabolic syndrome
   d. Hyper/dyslipidemia
   e. Coronary heart disease

5. Who among the following patients is more likely to have a NAFLD?
   a. Subject with cholelithiasis
   b. Diabetic subject
   c. Obese subject
   d. Patient with cardiovascular disease
   e. Hypertensive subject

6. Which of the following criteria can be useful for NAFLD diagnosis?
   a. Fatty liver at ultrasonography and high serum lipids levels
   b. High serum triglyceride levels and elevation of serum transaminases
   c. Elevation of at least one serum aminotransferase plus fatty liver at ultrasonography
   d. Liver biopsy and histology
   e. After exclusion of all other causes of liver steatosis

7. What is the best reason to ask for consultation?
   a. Concomitant other liver disease
   b. Association with metabolic syndrome
   c. Presence of coronary heart disease
   d. Young age at diagnosis

8. How do you approach a patient with NAFLD?
   a. Diet and check again after one month
   b. Search for associated conditions
   c. Diet and new check after six months
   d. Refer the patient to a specialist

9. Who is a good candidate for liver biopsy among the following NAFLD patients?
   a. 19 year old severely obese subject (BMI >40 Kg/m2)
   b. 40 year old female with high fasting glucose and hypertransaminasemia (2.5 UNV)
   c. 50 year old diabetic patient with a history of 20 years of hypertransaminasemia
   d. Young male subject (35 year old) with arterial hypertension

e. Never indicated

10. Who do you think is the most appropriate specialist to evaluate a NAFLD patient?

a. Gastroenterologist
b. Internist
c. Endocrinologist
d. Diabetologist
e. Lipidologist

11. Which is the best diet in a patient with NAFLD?

a. Hypocaloric diet
b. Low lipid content diet
c. Low carbohydrate content diet
d. High protein content diet

12. Which of the following medications has shown potential benefits in NAFLD patients?

a. Hepatoprotective agents
b. Diet regimen
c. Metformin and/or glitazones
d. Antioxidants
e. Lipid lowering agents

13. Which of the following drugs can precipitate or worsen a NAFLD condition?

a. ASA
b. Statins
c. Amiodarone
d. Paracetamol
e. Valproate

14. Are you interested in joining educational projects on NAFLD?

a. I am not interested
b. A little
c. Enough
d. I am very interested
e. I am very much interested

APPENDIX B

Table 1. Characteristics of Survey Respondents (n=40)

Age (years)	
Mean	34.13
Gender	
Male	18 (45%)
Female	22 (55%)
Practice	
Consultants	15 (37.5%)
Trainees	25 (62.5%)

Figure 1. Physicians evaluation of patients with undefined hypertransaminasemia (%)

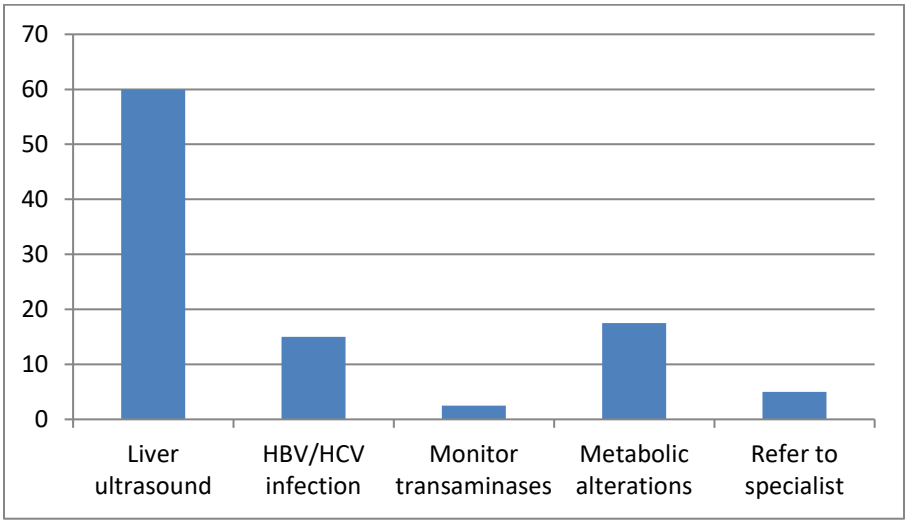


Figure 2. Criteria for NAFLD diagnosis by internists (%)

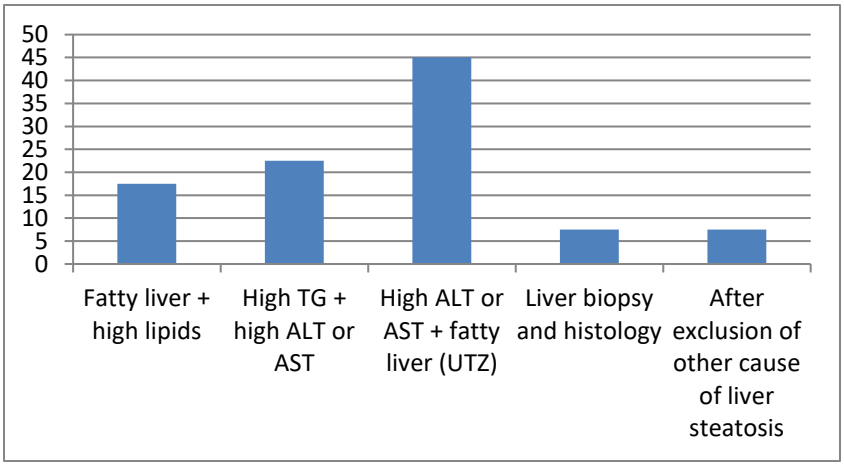


Figure 3. Physicians approach to patients with NAFLD (%)

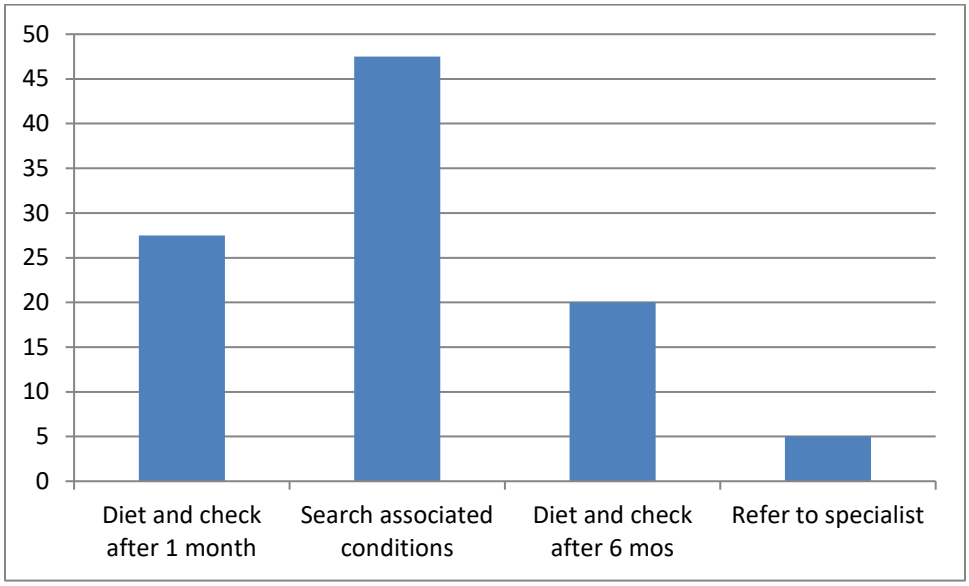


Figure 4. Best diet in patient with NAFLD by physician (%)

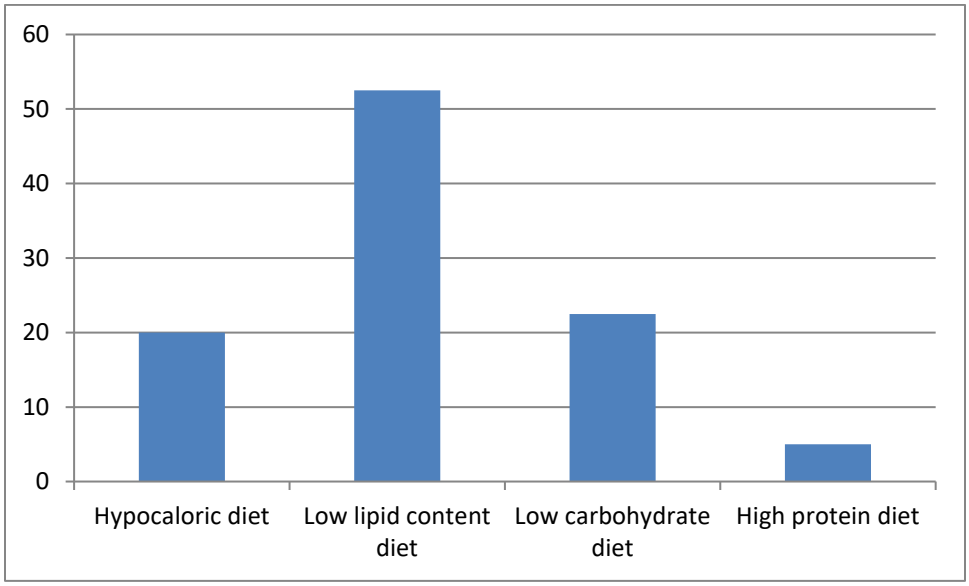
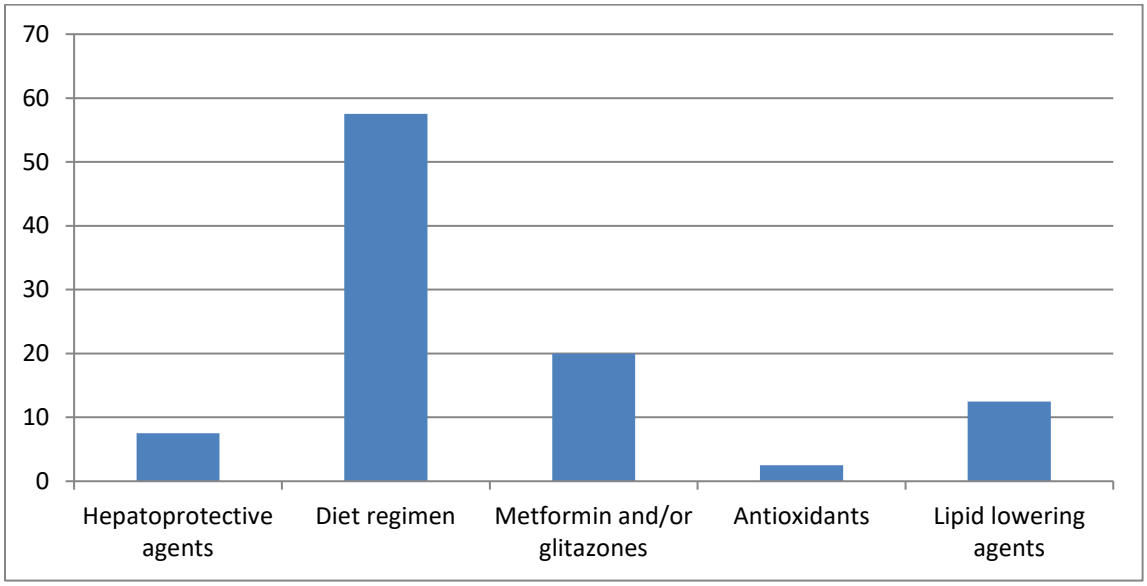


Figure 5. Medications with potential benefits for NAFLD (%)



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