Nonalcoholic Fatty Liver Disease and Topiramate as an Antiobesity Drug

Nonalkolik Yağlı Karaciğer Hastalığı ve Antiobezite İlaçlarından Topiramat

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) affects approximately one out of every 4 people and is the most common chronic liver disease worldwide. There are some risks factor such as obesity, type 2 diabetes mellitus, dyslipidemia and metabolic syndrome for the fatty liver. NAFLD can be presented as simple steatosis or steatohepatitis and can progress to liver cirrhosis. There is an important role of oxidative stress in etiopathogenesis of NAFLD so it is possible that antioxidant agents may have a positive effect on NAFLD. Although there is currently no approved pharmacological agent for the treatment of NAFLD, treatment guidelines for this desease include the use of vitamin E for its antioxidant activity. There are yet many advances to be made in the pharmacotherapy of NAFLD. Topiramate (TPM) is primarily used for epilepsy but it is also known for its weight loss, neuroprotective and antioxidant effects and many studies regarding these effects are available in the literature. In this sense, considering that TPM has both weight loss and antioxidant effects, it may be an option for the treatment of NAFLD. In this review, we aimed to focus on NAFLD and the properties and potential effects of TPM.

Keywords: Nonalcoholic fatty liver disease, hepatic steatosis, oxidative stress, obesity, vitamin E, topiramate

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ÖZET

Nonalkolik yağlı karaciğer hastalığı (NAYKH) yaklaşık olarak her 4 kişiden birini etkilemektedir ve dünya çapında en sık görülen kronik karaciğer hastalığıdır. Yağlı karaciğer için obezite, tip 2 diabetes mellitus, dislipidemi ve metabolik sendrom gibi bazı risk faktörleri vardır. NAYKH, basit steatoz veya steatohepatit olarak prezente olabilir ve karaciğer sirozuna ilerleyebilir. NAYKH etiyopatogenezinde oksidatif stresin önemli bir rolü vardır, bu nedenle antioksidan ajanların NAYKH üzerine olumlu etkisi olabilir. NAYKH için günümüzde onaylanmış bir farmakolojik ilaç tedavisi bulunmasa da tedavi kılavuzlarında antioksidan etkinliği nedeniyle E vitamini kullanımına yer verilmiştir. NAYKH tedavisi bu konuda gelişmelere açıktır. Topiramat (TPM) ön planda epilepsi için kullanılmakla birlikte kilo verdirici, nöroprotektif ve antioksidan etkileri ile de bilinmektedir ve bu etkileri ile ilgili literatürde birçok çalışma mevcuttur. Bu anlamda TPM, hem kilo verdirici hem de antioksidan etkileri olduğu göz önünde bulundurulduğunda, NAYKH tedavisi için bir seçenek olabilir. Bu derlemede, NAYKH'ye ve TPM'nin özelliklerine ve potansiyel etkilerine odaklanmayı amaçladık.

Anahtar Sözcükler: Nonalkolik yağlı karaciğer hastalığı, hepatik steatoz, oksidatif stres, obezite, vitamin E, topiramat

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world and it is prevelance about 25% (1). This rate is much higher in obese individuals (2). NAFLD includes a wide spectrum of clinical conditions, starting from simple steatosis to steatohepatitis and liver cirrhosis. At the end point NAFLD can even lead to hepatic cancer (1).

Obesity, type 2 diabetes mellitus, dyslipidemia and metabolic syndrome are the main risk factors for fatty liver (3). Although clinical, laboratory and radiological findings are useful, the gold standard for diagnosis is liver biopsy (4). Lifestyle modifications such as weight loss and exercise are recommended for the treatment of NAFLD. There is currently no approved pharmacological agent for the treatment of this desease. On the other hand, treatment guidelines for NAFLD include the use of vitamin E due to its antioxidant activity (5). Therefore, NAFLD pharmacotherapy is still requires advances.

Topiramate (TPM) is a new generation antiepileptic drug and it was approved by the FDA in 1996 (6). Subsequently, it has attracted attention with its weight-reducing effect, which is frequently seen. Studies focused on TPM's full effects in in-vivo conditions also reveal its neuroprotective and antioxidant effects (7).

Therefore, it is an agent that can be used for many different indications. Although TPM monotherapy is effective in the treatment of obesity, its FDA-approved its combination with phentermine for this desease. The purpose of combined therapy is to reduce the side effects of TPM by reducing the dose of topiramate (6,8). Obesity is currently one of the biggest global chronic health problems and it is considered as an epidemic. Obesity leads to many health problems including NAFLD, and cause significant morbidity and mortality.

The importance of oxidative stress in the etiopathogenesis of NAFLD is significant, and hence antioxidant agents does have a positive effect on NAFLD (4). For this reason, the guidelines recommend the use of vitamin E for the treatment of NAFLD (5). In this sense, considering that TPM has both weight loss and antioxidant effects, it may be an option for the treatment of NAFLD.

In this review; an overview of non-alcoholic fatty liver disease is given and the characteristics and possible effects of topiramate are discussed.

Nonalcoholic Fatty Liver Disease

NAFLD can be defined as the excess accumulation of lipids in the hepatocytes in patients who consume little or no alcohol. Excessive alcohol consumption is considered as consuming more than two standard drinks per day (140 g ethanol/week) for men and more than one standard drink per day (70 g ethanol/week) for women. NAFLD can also be regarded as the hepatic manifestation of metabolic syndrome (1,9). In NAFLD lipid accumulation is observed in at least 5% of hepatocytes, which is the minimal histological diagnostic criterion (10).

The term NAFLD covers a wide spectrum from simple steatosis to steatohepatitis (nonalcoholic steatohepatitis; NASH) which involves hepatocyte damage and inflammation, fibrosis and cirrhosis with its clinical consequences (1). The term NASH was first used by Ludwig et al. in 1980 (11). NASH represents a subset of NAFLD, which is characterized by hepatocellular damage and the presence of necroinflammation, and can progress to liver cirrhosis and liver failure (10). In addition to steatosis, NASH is characterized by balloon degeneration in hepatocytes, Mallory bodies which are located in cytoplasm, and varying degrees of fibrosis (12). Estimating the prevalence of NASH in a general population is difficult as it requires a liver biopsy for confirmation. In general, the prevalence of NASH in Western populations is reported to be between 3% and 10% (13). In the United States, it is estimated that one-third of the population has NAFLD, and approximately 2% to 5% of the population has NASH (4).

A meta-analysis of 86 studies covering approximately 8.5 million cases from 22 countries reported the global prevalence of NAFLD to be 25.24%. It was reported that Middle East and South America have the highest prevalence, while Africa has the lowest. It was also reported that NAFLD is accompanied by type 2 diabetes mellitus (T2DM) (22.51%), hyperlipidemia (69.16%), hypertension (39.34%), metabolic syndrome (42.54%) and obesity (51.34%) (9). A study from Japan reported the prevalence of NAFLD in children to be 2.6% and that NAFLD can be seen from the age of 6 (14). In another study from Italy, it was reported that this rate can be as high as 53% in obese children (15).

Considering that the half of the patients with obesity is accompanied by NAFLD, obesity is an important factor in this matter. World Health Organization (WHO), considers the problem of obesity as an epidemic (16).

WHO has declared obesity as one of the biggest global chronic health problems and which has become a more serious problem than malnutrition in adults (17). According to the 2016 data of WHO, 39% of all adults aged 18 and over are overweight and 13% are obese (18). The prevalence of obesity is increasing not only in adults but also among children and adolescents(19). Estimates based on current obesity trends predict that by 2030 there will be more than 65 million obese adults in the United States and 11 million in the United Kingdom (20).

Turkish Diabetes Epidemiology Study-I (TURDEP-I) was the first study providing important information about obesity in our country, which was conducted between 1997 and 1998 (21). According to the Turkey Nutrition and Health Survey (2017), prevelance of pre-obesity 36.9% and obesity is 32.1% in individuals aged 19-64 in Turkey (22).

Risk Factors of NAFLD

As mentioned above the most common risk factors for NAFLD is obesity, which is followed by T2DM, dyslipidemia and metabolic syndrome. In a study of patients undergoing bariatric surgery for severe obesity, the prevalence of NAFLD was found to be over 90%, and up to 5% of patients had previously unsuspected cirrhosis (3). In an ultrasonography study conducted on T2DM patients, the prevalence of NAFLD was found to be 69.4% (23). While serum triglyceride levels are tend to be high in patients with NAFLD, high-density lipoprotein (HDL) levels are generally found to be low. The prevalence of NAFLD among individuals with dyslipidemia is estimated to be 50% (3). The prevalence of metabolic syndrome is 41% among NAFLD patients, and 71% among NASH patients (9).

In addition, age, gender, ethnicity and diet are also risk factors for NAFLD. There are studies showing that the prevalence of NAFLD increases with age. Moreover, the disease is more likely to cause advanced fibrosis or death in elderly patients. There are also many studies indicating that male gender is a risk factor for NAFLD (3). For example, in a study that investigated 26,527 people who received medical health checkup, the prevalence of NAFLD was found to be 30.94% in men and 15.65% in women (3,24). It has been reported that NAFLD is more prevalent in hispanics compared to whites and less prevalent in blacks (25). Increased consumption of a high-fat and obesogenic foods are associated with obesity and NAFLD (26).

Other conditions associated with NAFLD are total parenteral nutrition, abdominal surgery, and the use of certain drugs (glucocorticoids, synthetic estrogens, diltiazem, methotrexate, etc). NAFLD is also associated with many deseases like; hepatitis C, HIV, hypobetalipoproteinemia, hypopituitarism, acute fatty liver of pregnancy (27).

Pathophysiology of NAFLD

Physiologically, the liver plays a crucial role in controlling fat metabolism by synthesizing, storing, secreting and oxidizing free fatty acids. The liver responds to and manages fatty acids that originate from ingested foods, adipose stores and its own de novo production. Even so, liver parenchyma is not a tissue with high fat content. Triglyceride accumulation in hepatocytes is a form of ectopic fat accumulation, and this is called hepatic steatosis (28).

NAFLD develops over the years with the combination of many factors. These factors include varying degrees of genetic predisposition, dietary habits, amount and composition of diet, physical inactivity, chronic stress, and lifestyle. The pathogenesis of NAFLD in humans is quite complex and there are still many unexplained points. For example, it is not fully understood why some patients with similar risk factors develop steatosis and steatohepatitis, while others do not (4).

Currently the most accepted model to explain the pathogenesis of NAFLD is the "double-hit hypothesis" (13). In this model, the first hit can be insulin resistance and steatosis, and the second hit can be most importantly oxidative stress, followed by lipid peroxidation, mitochondrial dysfunction, cytokine/adipokine imbalance, lipotoxicity of free fatty acids or hepatic cholesterol accumulation. According to this model, hepatic steatosis sensitizes hepatocytes to second hit, leading to hepatocyte damage, inflammation, and fibrosis (10).

The onset of fat accumulation in the liver, which is the "first hit", can occur by various mechanisms. Insulin resistance leads to increased level of lipolysis, which leads to increased release of free fatty acids from adipose tissue and excessive triglyceride accumulation in hepatocytes.

Conditions such as protein-energy malnutrition, jejunoileal bypass and parenteral nutrition cause triglyceride accumulation in the liver by affecting the lipoprotein synthesis of the liver and inhibiting lipid secretion (13).

Most patients with NAFLD have insulin resistance. However, NAFLD has also been observed in people who are not obese and have a normal oral glucose tolerance test. Insulin resistance is associated with increased peripheral lipolysis, triglyceride synthesis, and uptake of fatty acids by the liver, all of which contribute to hepatic fat accumulation. Adipokines play a role in the development of NASH mainly through their effects on insulin resistance (13).

"Second hit" causative factors include increased oxidative stress and lipid peroxidation, mitochondrial dysfunction, disturbance of cytokine/adipokine balance, lipotoxicity originating from free fatty acids, hepatic cholesterol accumulation, gut-derived lipopolysaccharides, and activation of the immune system (4).

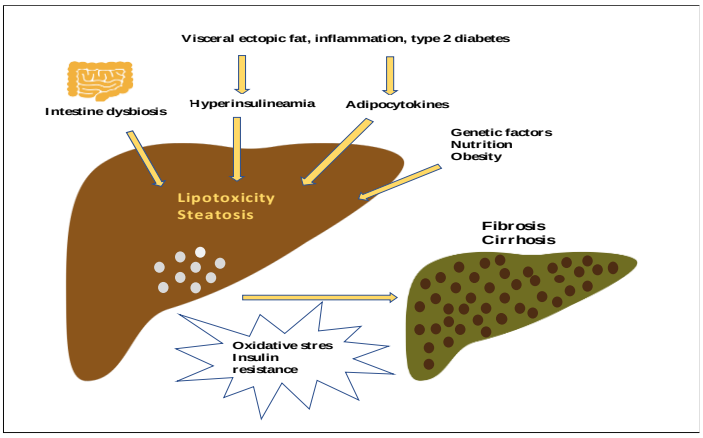

Figure 1: NAFLD pathophysiology

Histologic examination of liver biopsies is the gold standard method to accurately assess the degree of steatosis, necroinflammatory changes, and fibrosis (4).

There are two accepted scoring systems for the histological assessment of NAFLD; NAFLD Activity Score (NAS) which is developed by the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN), and Steatosis Activity Fibrosis (SAF) which is developed by the European Fatty Liver Inhibition of Progression (FLIP) Consortium. The basic histologic lesions evaluated by both are the same (steatosis, lobular inflammation, hepatocellular ballooning). However, while NAS does not include fibrosis stage, SAF evaluates it as well. (29).

Fat accumulation in the liver is mostly macrovesicular, but sometimes mediovesicles can also be seen. In macrovesicular steatosis, a large lipid vacuole fills almost the entire hepatocyte and pushes the nucleus aside, whereas in mediovesicular steatosis one or more smaller lipid vacuoles present in the cytoplasm. Microvesicular steatosis is quite rare, in which there are many small lipid vacuoles in the cytoplasm and the cell has a foamy appearance. While steatosis is often took place in the pericentral region (zone 3), it can be distributed evenly in the entire acini. As the disease progresses to cirrhosis, the distribution of steatosis may decrease and become irregular. Steatosis may even be partially or completely disappear in late stage cirrhosis (30).

Clinical and Laboratory Findings of NAFLD

Most patients with NAFLD are asymptomatic and symptoms are often nonspecific when present. Common symptoms include fatigue and vague discomfort in the right upper quadrant of the abdomen (28). Hepatomegaly is believed to be present in up to 75% of patients, although it may be difficult to identify on physical examination in patients with notable abdominal obesity (12).

Laboratory findings of NAFLD are also usually non-specific. However, Mandal et al. reported that ALT level is more distinctive than other liver enzymes for this group of patients (31). Although liver function tests are useful, their sensitivity and specificity are poor. An important way of using ALT and AST levels to contribute to the diagnosis of NAFLD is to calculate the ALT/AST ratio. While higher ALT level suggests the presence of NAFLD, higher AST level suggests alcoholic liver disease or cirrhosis (12).

An increase in gamma glutamyl transferase (GGT) levels in NAFLD patients is associated with advanced fibrosis and mortality (32). GGT is also a component of the fatty liver index and FibroTest panels which are used to evaluate hepatic steatosis and fibrosis in NAFLD (32).

Treatment of NAFLD

Non-Pharmacological Therapy

Currently, lifestyle modification is the accepted first-line therapy for patients with NAFLD/NASH. Lifestyle modification is often include, permanent weight loss and increase in the amount of exercise (5).

In recent years, several dietary models have been proposed for the control of NAFLD. Among these, the most highlighted one is the Mediterranean diet. Because it is generally accepted as healthy and effective in reducing the risk of cardiovascular diseases and cancer. The beneficial effects of the Mediterranean diet in patients with NAFLD have been demonstrated in many studies (5).

Increased physical activity is an independent factor that can greatly benefit NAFLD patients. Exercise alone may reduce hepatic steatosis in adults with NAFLD, but its ability to improve other histological changes in the liver is unclear (3). It has been suggested that exercise is an effective method to reduce intrahepatic lipid content by decreasing hepatic lipogenesis and increasing lipid mobilization from the liver (5).

In a randomized controlled study by Promrat et al., it was reported that with 48 weeks of lifestyle interventions (diet, exercise and behavioral modifications), NASH patients lost an average of 9.3% of their body weight, and their NASH histological activity score were improved. They also reported that percent weight reduction correlated significantly with improvement in histological activity score (33).

Pharmacological Therapy

When lifestyle modifications are not successful or sufficient, pharmacological agents that target underlying mechanisms such as insulin resistance, oxidative stress, inflammation and apoptosis can be used.

Vitamin E inactivates free radicals and reduces lipid peroxidation, thereby can be used in patients with NAFLD to suppress hepatic inflammation (5). In the PIVENS (Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients With Nonalcoholic Steatohepatitis) study, the effects of pioglitazone and vitamin E on liver histology were compared with placebo in non-diabetic biopsy-proven NASH patients. As a result of this multicenter, randomized controlled and double-blind study, it was revealed that vitamin E decreases serum ALT and AST levels, decreases hepatic steatosis, reduces lobular inflammation, and provides histological improvement (34). In the light of these findings, current guidelines recommend the use of 800 IU/day vitamin E in non-diabetic biopsy-proven NASH patients (3,5).

With the exception of Vit E, currently there is not any drug that is widely recommended for the treatment of NAFLD/NASH. On the other hand, there are numerous studies that suggest the use of certain drugs and few clinical trials are still ongoing. However, it should be noted that none of those recommendations are based on strong evidences and there is not any drug, which is approved for treatment of NAFLD/NASH (5).

Orlistat, an enteric lipase inhibitor that inhibits intestinal fat absorption and is used in the treatment of obesity, has also been considered for the treatment of NAFLD. In a randomized controlled study by Zelber-Sagi et al., patients with NAFLD who were given orlistat or placebo in addition to lifestyle modifications were compared, and it was reported that in addition to weight loss in patients receiving orlistat, a significant reduction in serum ALT levels and steatosis on USG was found compared to placebo. However, the effect of orlistat on liver histology could not be evaluated, since a significant number of the patients participating the study did not give consent for a second liver biopsy during their follow-up (35). On the other hand, in another randomized controlled study by Harrison et al., orlistat given in addition to calorie restriction and vitamin E was not able to improve body weight, liver enzyme levels, or liver histology significantly in patients with NASH. One of the major limitations of this study is the absence of a placebo control group (36).

Insulin resistance is one of the key factors in the pathogenesis of NAFLD, so metformin, an insulin-sensitizing drug, has been tried in patients with NASH. The general conclusion of these studies is that metformin has no significant effect on aminotransferases and liver histology, and the guidelines do not recommend metformin as a specific treatment for NASH patients (3).

Thiazolidinediones are another group of insulin-sensitizing drugs. In a randomized controlled study by Belfort et al., 45 mg/day pioglitazone given in addition to diet and placebo to patients with NASH and impaired glucose tolerance or T2DM was reported to improve aminotransferases, increase hepatic insulin sensitivity, decrease hepatic steatosis, and decrease ballooning necrosis and inflammation compared to placebo. In addition, pioglitazone reduces cytokine-mediated systemic inflammation by causing a decrease in plasma TNF-α and TGF-β levels, which contributes to its positive effect on NASH. Pioglitazone also decreases excessive lipolysis by increasing insulin resistance in the adipose tissue, thus reducing the amount of substrate reaching to the liver (37).

Cardiovascular diseases have been identified as the most common cause of death in NAFLD/NASH patients. Dyslipidemia, which is closely associated with NAFLD, is also a high risk factor for cardiovascular diseases. Statins are most commonly used antilipidemic drugs and studies have shown that they are safe in individuals with liver disease. However, there is no randomized controlled study with histological endpoints investigating whether statins can be used to treat NASH (3).

In the study of Yokohama et al., it was reported that losartan, an angiotensin II receptor antagonist, could reduce hepatic fibrosis by inactivating hepatic stellate cells in patients with NASH (38).

In limited and small-scale studies, pentoxifylline (a potent inhibitor of TNF-α) reduced serum transaminase levels and inflammation markers in NASH. However, these studies were limited due to the side effects of pentoxifylline (mainly nausea and vomiting) (13).

The search continues to find other agents that can show similar positive effects like vitamin E in NAYKH/NASH. In a study by Cunningham et al., NASH was developed in rats and the animals were given curcumin, a polyphenol with anti-inflammatory and antioxidant properties. They reported that curcumin treatment decreased hepatocellular inflammation, steatosis, NAFLD Activity Score, AST and alkaline phosphatase (ALP). In this respect, curcumin is likely to be a potential treatment option (2).

Although the above-mentioned and other experimental pharmacological agents are currently used in today's clinical practice, their effectiveness, including vitamin E, are not high. Therefore, the search for agents to treat NAFLD continues.

Topiramate

While the search for new drugs to treat NAFLD continues, it should be noted that oxidative stress is one of the key factors in the pathogenesis of the disease. Therefore, it is likely to be an important target point of research for a new drug development. Topiramate, one of the drugs that is used in the treatment of obesity, may be a new treatment option for NAFLD due to its antioxidant properties in many tissues. The close association of NAFLD with obesity further increases the potential of TPM to be a good treatment option.

TPM is rapidly absorbed from the gastrointestinal tract (oral bioavailability ranges from 81% to 95%) and reaches its peak serum concentration (Cmax) in 2 to 4 hours. Taking it with food slightly delays the time to Cmax, but does not change the peak serum concentration can be reached for a given dose (39). TPM bounds to plasma proteins in low degree (9-17%). It is distributed to all tissues, including the brain (40). TPM is mainly excreted in unchanged form by the kidneys (39). Its half-life is approximately 20-30 hours in healthy individuals, but the rate of elimination is increased in patients receiving concomitant enzyme-inducing drugs such as phenytoin, carbamazepine, and barbiturates. Dose reduction may be necessary for patients with renal impairment, while additional doses could be required during hemodialysis. Dose adjustment is generally not required in hepatic failure (40).

Mechanism of Action and Indications of TPM

TPM was approved by the FDA for the treatment of epilepsy in 1996 (6). TPM is a broad spectrum antiepileptic agent that can be both used for partial and generalized seizures. It is widely used in the treatment of epilepsy due to its multiple mechanism of action which are (8): 1) It inhibits voltage-dependent sodium and calcium channels, similar to other anticonvulsants. 2) It reduces glutamate-mediated nerve stimulation by antagonizing ionotropic, Kainate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors of glutamate, an excitatory neurotransmitter. 3) It modulates GABA-A receptors of gamma-aminobutyric acid (GABA).

Besides for the treatment of epilepsy, TPM is currently used for other indications, including obesity, migraine prophylaxis, and alcohol abuse disorder.

One of the other main indications for TPM is migraine prophylaxis. It was approved by the FDA for migraine prophylaxis in 2004 (6). Migraine is the second most common neurological disorder (tension-type headache comes first) and is estimated to affect approximately one billion people worldwide. It is seen three times more frequently in women than in men, and its one-year estimated prevalence in the general population is approximately 15% (41). The pathophysiology of migraine is complex and not fully understood. At the molecular level, there is substantial evidence that overactivation of AMPA and/or kainate receptors and various voltage-dependent calcium channels are major contributors to migraine pathophysiology. The anti-migraine effect of TPM is due to its inhibitory effects on these receptors and channels (8).

TPM can also be used to treat alcohol abuse disorders (alcoholism). Although it is not currently officially approved for this indication, many studies have shown that TPM is an effective treatment option in these patients and has notable effect in reducing harmful drinking habits (42).

Two meta-analyses stated that TPM had positive effects on abstinence, craving and GGT levels, and that it reduces heavy drinking days and drinks per drinking day (43,44). It is believed that TPM reduces alcohol cravings by antagonizing glutamate receptors and inhibiting dopamine release (43). Due to similar mechanisms of action, TPM can also be used in the treatment of cocaine addiction, smoking and pathological gambling (42).

Binge eating disorder is a behavior pattern of consumption of a large amount of food within a discrete amount of time and there is a feeling of loss of control. It is potentially results from dysfunction of brain impulse control, reward and mood regulation systems involving dopaminergic mechanisms. TPM has emerged as a pharmacological treatment option in binge eating disorder with its effects on mood, appetite and reward systems (42).

The exact mechanism of TPM-induced weight loss is unknown, but reduction in caloric intake has been identified as an important factor. Animal studies suggest that increased energy expenditure and decreased energy efficiency contribute to weight loss in TPM monotherapy (6,45). Randomized controlled studies have shown that TPM monotherapy causes clinically significant weight loss in obese individuals, and also has positive effects on glucose tolerance and blood pressure (46,47). Furthermore, meta-analysis of 10 randomized controlled studies, the weight loss effect of TPM was clearly demonstrated (48). However, TPM has side effects that may limit its use as a single drug at optimal doses for weight loss. Cognitive slowing, which is relatively a common side effects, can sometimes reach a level that can limit its use. In addition, paresthesia, oligohidrosis, closed-angle glaucoma, dizziness, ataxia, agitation and mood disorders can be seen (8). Therefore, the combination of phentermine and TPM is more accepted in clinical practice for the treatment of obesity (6). Phentermine is a centrally acting sympathomimetic amine, which is structurally similar to amphetamine. It stimulates the release of norepinephrine and to a lesser extent dopamine. Randomized controlled trials, including the EQUIP study by Allison et al, the CONQUER study by Gadde et al, and the SEQUEL study by Garvey et al. reported the significant effect of phentermine/TPM on weight loss and its safety (6,49,50). Phentermine/TPM is approved by the FDA in 2012 in addition to a reduced-calorie diet and increased physical activity for chronic weight management in adult (≥18 years) obese (BMI ≥30 kg/m2) and overweight patients (BMI ≥27 kg/m2) with at least one weight-related comorbidity, including hypertension, T2DM, or dyslipidemia (45).

TPM has some other metabolic effects beyond providing weight loss. One of the most striking of these is its effects on oxidant-antioxidant systems and there are many studies in the literature investigating this issue. TPM shows neuroprotective effects due to its antioxidant activity (7). Considering that oxidative stress also plays an important role in the pathogenesis of epilepsy (51), antioxidant property of TPM may also play a role for its antiepileptic effects. Although not approved for this indication, TPM is also be used to treat hypoxic ischemic encephalopathy and seizures caused by it, which also can be associated with its antioxidant activity.

The antioxidant effect of TPM is not limited to nervous system, studies with other tissues such as testis and kidney generally yielded similar results (52,53). On the other hand, there are also few studies reporting that TPM increase oxidative stress and decrease antioxidant parameters (54,55). However, the dose and duration of TPM administration should be considered when evaluating these results, that TPM could exhibit antioxidant effect at low doses, while it could be oxidant at higher doses. In many of the studies claiming that TPM is an oxidant, it has administered at higher doses.

However, this prediction cannot explain all the findings in the literature. For example, Agarwal et al. reported oxidant activity in the brain despite using low-dose TPM (54).

Another metabolic effect of TPM is carbonic anhydrase enzyme inhibition. TPM may cause metabolic acidosis due to carbonic anhydrase inhibition. As a matter of fact, metabolic acidosis cases related to the use of TPM have been reported (56). Considering the potential of metabolic acidosis to cause oxidative stress, metabolic acidosis could be the reason why TPM causes oxidative stress in some studies. The use of TPM may cause a decrease in blood pH, even if it does not exceed the limit to be defined as acidosis, which could be seen as a natural consequence of carbonic anhydrase inhibition.

Changes in blood pH does have varying effects on fat metabolism as well as on many metabolic pathways. In Chan et al.s' study, increased acid load due to diet content was significantly correlated with the frequency of NAFLD (57). Low-level acidosis caused by increased acid load due to dietary content is similar to pH change with TPM. Therefore, it could also be possible that TPM pose a risk for NAFLD.

There are still many points that need to be clarified in order for TPM to become an option for the treatment of NAFLD. First of all, although TPM has an antioxidant effect in various tissues, its effect on healthy liver tissue should be clearly demonstrated. In addition, the direct effects of TPM on fatty liver should be investigated in detail, as well.

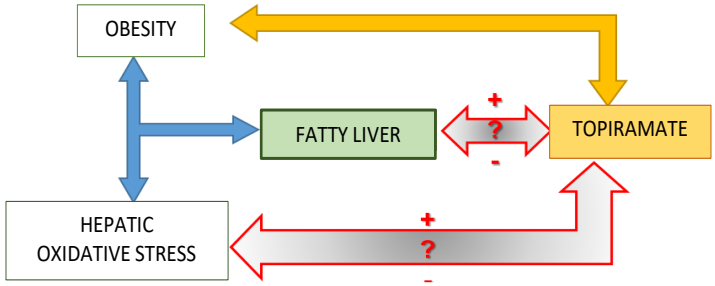

Figure 2: The relationship between obesity, fatty liver, oxidative stress and topiramate

CONCLUSION

NAFLD is the most common chronic liver disease worldwide, and it both limits life expectancy and reduces the quality of life with its progressive character. Many factors, especially insulin resistance and oxidative stress, play a role in the etiopathogenesis of NAFLD. Vitamin E, which has antioxidant properties, is recommended as a treatment option for certain patient groups in current clinical guidelines. Drugs for insulin resistance and dyslipidemia are also being used in clinical practice. However, there is no approved and licensed drug for the pharmacological treatment of NAFLD. Therefore, the search for other agents to treat NAFLD continues.

TPM is an antiepileptic drug with antioxidant properties which is also used in the treatment of obesity. Many studies have shown that TPM has neuroprotective effects due to its antioxidant properties. Considering the close relationship of NAFLD with obesity and the important role of oxidant stress in its pathogenesis, TPM is likely to be an ideal treatment option. However, there are many questions that need to be answered and many studies that need to be done before TPM can be used for this purpose.

Conflict of interest

No conflict of interest was declared by the authors.

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