The activity and polymorphism of the PON1 in patients with chronic liver disease: A systematic review and meta-analysis

Abstract

Background: Liver diseases are among the ten deadliest diseases in the world. Measuring PON1 is a test to assess the degree of liver disorder. There are several preliminary studies on the rate of PON1 activity in people with liver disease, and there are differences between the results of these studies, therefore, the aim of this research work is to determine the level of PON1 activity in people with liver disease using meta-analysis.
Method: The study searched to select articles that were published electronically from 2002 to 2020, in national and international databases of SID, MagIran, Embase, ScienceDirect, Scopus, PubMed and Web of Science (WoS).
Results: Among the articles included in the meta-analysis, the samples in the case (patients) and control groups were 807 and 2276 respectively. The mean activity of PON1 in individuals with liver disease in the case and control groups were 142.06 ± 7.7 and 272.19 ± 39.6 respectively, and this was statistically significant ($P < 0.05$). The mean difference analysis highlights a difference of -2.75 ± 0.48 between the patient and control groups, indicating that liver disease significantly reduces PON1 activity.
Conclusion: The results of this study demonstrate that the polynomorphism of the PON1 is associated with an increased risk of liver disease, with lower levels of PON1 activity in people with liver disease than in healthy patients and this decrease was more in patients with liver cirrhosis than in other liver diseases. Given the importance of this gene's activity, studies such as this could provide a promising path for better drug design and treatment in future.

Keywords: PON1, Liver Diseases, Meta-Analysis.

Background

The liver weighs approximately 1500 grams, is the largest internal organ and the most important organ after the heart and brain in the human body, without which it is impossible to survive [1]. Liver disease is one of the top 10 deadliest diseases in the world and is the 5th leading cause of death in Europe after cancer, stroke and heart and respiratory diseases [2]. Early detection of liver disease is vital for treatment. Despite significant advancements in medical sciences, it is still difficult to diagnose liver disease early [3].

Liver is one of the most important organs in the body. Due its overal purifying role, naturally any liver disease and its complications will affect the entire body. Therefore, timely and accurate diagnosis and treatment of liver diseases are vital [3-6]. Currently, the non-invasive test that is available for assessing the severity of liver disease includes evaluation of clinical and laboratory symptoms, routine tests, imaging, and a combination of clinical and blood test results. Unfortunately, the use of these tests is limited, and liver sampling remains the only reliable tool for diagnosing most liver diseases and the degree of severity of liver damage [6,7]. This method has its own limitations such as high cost and invasiveness. It may also entail

sampling errors, and conducting the test may be associated with other complications and in rare cases it may lead to death [7, 8].

Chronic liver disease refers to a series of liver diseases with various causes and severity that is associated with the inflammation of the liver and progressive necrosis for at least six months, and it eventually leads to liver cirrhosis [8]. It is one of the most dangerous diseases, the actions towards it are mainly supportive and there is no specific treatment. In recent years, liver transplantation as an acceptable treatment has been effective in the early stages of progressive liver disease [8]. Liver disease is relatively common in different societies. According to a study, about 45% of chronic liver patients are suffering from periodontitis [7, 8]. Moreover, chronic hepatitis can cause several complications such as liver cirrhosis, hepatocellular carcinoma and can even lead to mortality [7, 8]. Hepatic cirrhosis is the most common non-neoplastic liver disease, leading to death in liver patients [9, 10].

Fatty liver disease is one of the risk factors for the progression of chronic hepatitis B infection and has been considered in recent studies as one of the causes of cirrhosis and liver failure [11, 12]. Researchers have reported that higher rates of steatosis are significantly associated with liver fibrosis [13]. Another study found that people with chronic hepatitis B had higher levels of ALT liver enzyme as a marker of liver cell damage in people with fatty liver compared to those without it, and this finding was more common in people with negative hepatitis B e-antigen (HBeAg). In other words, fatty liver disease is one of the predictors of elevated ALT levels in these patients [14].

The paraoxonase protein family (PON) consists of three enzymes, PON1, PON2, and PON3, and their coding genes are located on the long arm of chromosome 7 (7q21-22) [15]. PON1 can hydrolyze organophosphates such as paraxon. The ability to hydrolyze paraxon is called the paraoxonase activity [16, 17]. PON1 is an antioxidant enzyme and reduces oxidative stress by lipoprotein hydrolysis [15]. Numerous studies have shown abnormal changes in mitochondrial function and morphology of non-alcoholic fatty liver in patients. Increased beta-oxidation of fatty acids will produce lipid peroxidation and thus oxidative stress in non-alcoholic fatty liver [15]. Therefore, PON1 measurement is a test to assess the degree of liver disorders [15].

There are several preliminary studies on the rate of PON1 activity in people with liver disease, and there are inconsistencies between the results of these studies, thus, the aim of this study is to determine the level of PON1 activity in people with liver disease using meta-analysis.

Methods

Article search method

We have searched articles with no lower time limit and upto March 2020, in Persian databases of SID and MagIran, and the international databases of Embase, ScienceDirect, Scopus, PubMed and Web of Science (WoS) with the aim of finding relevant resources. The lists of references in the articles collected as part of the above were manually assessed with a view to find other possible sources. The keywords used for the search were selected from the MeSH topic-based medical database. The keywords were Paraoxonase 1, PON1, Chronic Liver, Chronic Hepatitis, Cirrhosis, Liver Disease, Hepatosteatosis, Hepatic, and Hepatitis Virus.

Article selection criteria

Articles with the following characteristics were selected for meta-analysis: 1) clinical trial studies, 2) articles that their full text is available.

Article exclusion criteria

The selected studies were examined in more detail. Studies that were review papers, or their samples were not selected from liver patients, as well as articles that conducted the research with previous secondary data, were excluded from the meta-analysis. Lastly, 26 studies entered the third stage for evaluating articles quality.

Article quality assessment

The quality of the articles was evaluated based on criteria outlined within the CONSORT checklist; the criteria include study plan, background and review of texts, place and time of study, outcome, entry criteria, sample size and statistical analysis. articles that satisfied 2 or less criteria were considered as low quality articles respectively [18].

Data extraction

All final papers entered into the meta-analysis process were prepared using a checklist. The checklist included the following fields: the title of the article, the name of the first author, the year of publication, the place of study, the sample size of the patient group, the sample mean of the control group, the mean and standard deviation of the patient group and the control group, the probability, disease type and mean age.

Statistical analysis

Since the aim of this study was to assess the level of PON1 activity in people with liver disease, frequency, rate, and the standardized means difference for each study were used to amalgamate the results of the collected studies. To investigate the homogeneity between the studies, the I^2 index was used. The funnel plots and the Egger's tests were also applied to assess the publication bias. Data analysis was performed within the Comprehensive Meta-Analysis software.

Results

In this study, all studies related to the level of PON1 activity in people with liver disease, without time constraints, and according to PRISMA guidelines were systematically reviewed.. Finally, 20 papers that were published between 2002 and March 2020, entered the final analysis (Figure 1).

(Figure 1 Here)

Among the studies included in the meta-analysis, the number of samples in the patients (case) and control groups were 807 and 2276 respectviely. The characteristics of these studies are presented in Table 1 (Table 1).

(Table 1 Here)

To amalgamate all of the collected results, the indices of standardized means difference and relative risk were used. In the articles that had presented standard deviation ± mean, the

standardized means difference index was used for meta-analysis. The results of meta-analysis demonstrate that there are homogeneities between the studies of the patients' group ($I^2 = 98.5$) and the control group ($I^2 = 99.9$), therefore, the random effects model was used to amalgamate refinal results of all the collected studies.

Based on the results of the meta-analysis, the standardized means differences in the patients and control groupes are the 142.06 ± 7.7 and 272.19 ± 39.6 respectively, which show that the level of PON1 activity decreases in patients with a liver disease. In the forest plots (Figures 2 and 3). The Egger's test was used to investigate the prevalence of publication bias in the studies. Based on the results of the Egger's test, there was no publication bias in the patients group (P = 0.180), nor the control group (P = 0.261) (Figures 4 and 5).

(Figure 2 Here)

(Figure 3 Here)

(Figure 4 Here)

(Figure 5 Here)

Standard difference in means

The results of the means difference between the patients and the control groups, based on the meta-analysis, are illustrated in Figure 6. The difference between the patient group and PON1 activity was -2.75 ± 0.48, which indicates a significant difference between the two groups in terms of PON1 activity, and this mean is low por negative in patients with a liver disease. According to the results of the Egger's test in figure 7, there was no publications bias in the mean difference between the patients and control groups (P = 0.052) (Figure 7).

(Figure 6 Here)

(Figure 7 Here)

Subgroup analysis

Subgroup analysis was performed based on the type of liver disease, and according to this analysis, the standard difference in means for the patients and control groups in Cirrhosis disease was reported as -7.9 ± 2.08, and in chronic hepatitis -2.06 ± 0.47. The mean difference in the case of the cirrhosis disease was greater than in chronic hepatitis.

(Table 2 Here)

Discussion

Medical ultrasound is a non-invasive, inexpensive and widely available method for diagnosing liver disorders with a sensitivity of 60-94% and a specificity of 65-96%; it also leads to an estimate of the penetration of fat into the liver using a three-point scoring system (i.e. mild, moderate, and severe). This method has limitations such as low sensitivity to mild steatosis, inability to differentiate mild fibrosis from steatosis and lack of precise determination of the amount of fat penetration and its dependence on the operator and the observer's opinion by up to 72%, and it has limited application for over-weight patients or the ones who have gas in the intestine [29-33]. Paraoxonase activity can be affected by lipoproteins and their metabolism, biological macromolecules, drug therapies, nutrients, and lifestyle [34]. Numerous laboratory and clinical studies have shown that paraoxonases protect against atherosclerosis and heart disease by preventing LDL oxidation [35]. Therefore, the aim of this study was to determine the level of PON1 activity in people with liver disease as one of the diagnostic methods of liver disorders, and highlight some of the challenges and opportunities using meta-analysis.

According to the results of this systemic review and meta-analysis, the average activity of PON1 in patients with liver disease was lower than the control group, and this was statistically significant. The rate of this reduction was higher in patients with liver cirrhosis than in other liver diseases.

Fat oxidation disorder in mitochondria is one of the unwanted activities responsible for the accumulation of fat in liver. Liver damage can be associated with oxidative stress and lipid peroxidation, and PON1 can play an important role in the development and progression of liver damage. Oxidative stress in the pathogenesis of various diseases, such as hyperlipidemia, diabetes, and high blood pressure, all of which are associated with obesity and metabolic syndrome, [36]. Disruption in release of the oxygen free radicals has been suggested as an activity in the development of the hepatostatic. Paraxonase is an antioxidant enzyme and reduces lipid peroxidation substances [36].

Preliminary studies in 1970 showed a significant reduction in serum PON1 activity in a small group of patients with liver cirrhosis [5]. These results were confirmed in a larger group of patients with varying degrees of chronic liver damage [37]. The results of a study by Jagannttha et al. (2013) demonstrate that in patients with viral cirrhosis and chronic viral hepatitis, the release of oxygen free radicals is higher whilst the PON1 activity is lower; moreover, in these patients, there is an increase in the oxidative stress whilst there is a decrease in the PON1 activity due to reduced detoxification in cirrhosis [38]. PON1 synthesis is positively regulated by Peroxisome Proliferator- Activated Receptors (PPAR). Several drug combinations (e.g. antioxidants) stimulate both the PPAR activity and the PON1 expression. Recent evidence suggests that PON1 and Monocyte Chemoattractant Protein 1 (MCP-1) is involved in coordinating the inflammatory response in damaged tissue [39].

Two key polymorphisms have been reported in the coding region of the human PON1, one at position 192 and leads to the replacement of glutamine to arginine, and the other to mutation in leucine to methionine at position 55 [40]. Since PON1 polymorphisms affect serum blood activity. and also PON1 activity is associated with changes in plasma lipoprotein concentrations, PON1 polymorphisms can affect plasma lipoprotein levels. An important difference in the total cholesterol and LDL cholesterol levels has been demonstrated in people with Leu/Leu 55 and Met/Met 55 genotypes; people with Met/Met 55 PON1 have better plasma lipoprotein characteristics. Moreover, it has also been shown Leu/Leu 55 PON1 homozygotes

increase base of HDL, and 192 Q/R polymorphism is a stronger predictor of HDL cholesterol changes than Met/Leu 55 polymorphism [41].

Demographic environmental variables affect PON1 activity by 1-6%. For instance, the use of pregnancy prevention hormones has a positive effect on the PON 1 activity, whereas higher age and smoking negatively affect the enzyme activity. Moerover, the effects of different foods on the PON1 activity have been significantly investigated. It is possible that the effect on PON1 activity is mediated through lipoprotein metabolism. However, some of the unexplained variations of PON1 may be due to the consumption of different foods among the participants [42]. The combination of fatty acids in HDL can affect the activity of its associated enzyme (PON1). For instance, Stearic acid and Dihommo-gamma linolenic acid are directly related to PON1 activity [43]. The findings suggest that our knowledge about the level of the enzyme on a single substrate may not necessarily provide a jolistic physiological picture of the enzyme activity within human body. Phenotypic diversity accounts for 65-92% of PON1 activity. Genetic factors can affect the concentration of the enzyme (expression) or the specific activity of the enzyme, or both. Furthermore, PON3 compared to PON1, has a much lower activity in paraxon and phenyl acetate substrates. Therefore, although PON1 is the predominant paraoxonase enzyme in serum, PON3 may have an undeniable contribution to the PON lactonase activity of serum. PON1 is primarily controlled by changes in structural genes, however, changes in several other unknown genes also control its activity [42]. Nevertheless, some researchers believe that PON3 is not active against artificial substrates such as paraxon and phenylacetate [44]. In a given population with polymorphism at the positions 192 and 108, serum PON1 activity can be 40 times different [45].

Epigenetic regulation is considered as a key contributor to the pathogenesis of diseases [46]. This contribution could be particularly more in multifactorial diseases, that could even lead to death. Due to the importance of PON1 in the functionality of high-density lipoprotein (HDL) and its relationship with cardiovascular diseases, further studies on the epigenetic regulation of PON1, using advanced methods such as Methyl-Seq, may lead to the identification of new epigenetic contributors that may consequently bring about suitable (molecularly) targeted therapies (please see Figure 8).

(Figure 8 Here)

Limitation

One of the limitations of this research work is that some samples from the collected articles were not randomely selected. Moreover, lack of uniform reporting within the collected articles, non-uniformity of the used implementation methods, unavailability of the full text of the articles, were some of other limitations of this research work.

Conclusion

The results of this study demonstrate that PON1 polynomorphism is associated with an increased risk of liver disease.Moreover, PON1 activity is lower in people with a liver disease than in healthy people. This secreased level of PON1 activity was higher in patients with liver cirrhosis than in other liver diseases. Given the importance of this gene's activity, thorough assessment of it could offer a promising pathway for better drug design and treatment in future.

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Figures legend:

Figure 1: PRISMA flow diagram for article selection.

Figure 2: Forest plot from the studies entered in the meta-analysis using the standardized means difference index for the patients group.

Figure 3: Forest plot from the studies entered in the meta-analysis using the standardized means difference index for the control group.

Figure 4: Funnel plot for the meta-analysis depicting standard error by mean for the patients group.

Figure 5: Funnel plot for the meta-analysis depicting standard error by mean for the control group.

Figure 6: Forest plot for the studies entered in meta-analysis demonstrating the standard difference in means index for the patients and control groups.

Figure 7: Funnel plot for the studies in the meta-analysis demonstrating the standard error by standard difference in means for the patients and control groups.

Figure 8: Relationship between the activity and the polymorphism of PON1 gene.

Tables legend:

Table 1: Specifications of studies entered into the meta-analysis

Table 2: Subgroup analysis based on the type of the liver disease.