Diagnostic capabilities of kallistatin, IL-10 and IL-1β in patients with non-alcoholic fatty liver disease and hypertension

Alkole bağlı olmayan yağlı karaciğer hastalığı ve hipertansiyonu olan hastalarda kallistatin, IL-10 ve IL-1β’nin tanısal güçleri

Anastasiia O. Rozhdestvenska1, Natalia M. Zhelezniakova1

1Kharkiv National Medical University, Department of Internal Medicine 1, Kharkiv, Ukraine

ORCID ID: AOR 0000-0002-9716-6538
NMZ 0000-0002-5786-9378

Gönderim Tarihi: 19 Mayıs 2021, Kabul Tarihi: 23 Ağustos 2021

The research results were presented at Maltepe University International Student Congress E-MUSIC 2020-2021 “COVID-19 & HEALTH” in the form of a report “Kallistatin: diagnostic value of the new biomarker in patients with non-alcoholic fatty liver disease and hypertension”.

SUMMARY

Aim: Non-alcoholic fatty liver disease (NAFLD) is closely linked to hypertension (HT) and affects about 25% of the adult population. An important issue remains the search for non-invasive biomarkers for NAFLD diagnosis.

The objective of the study was to evaluate the diagnostic value of kallistatin, interleukin-10 (IL-10) and interleukin-1β (IL-1β) in NAFLD in combination with HT.

Materials and Methods: 115 patients with NAFLD at the stage of non-alcoholic steatohepatitis (NASH) were examined, including 63 patients with comorbidity of NASH and HT (main group) and 52 people with isolated NASH (comparison group). Clinical and laboratory parameters were evaluated; plasma kallistatin, IL-10 and IL-1β levels were measured in all patients.

Results: Kallistatin levels averaged 65.03 ng/ml, 83.42 ng/ml and 111.70 ng/ml in patients with NAFLD and HT, isolated NAFLD and control group, respectively. The IL-10 level was 2.69 ng/ml and 4.90 ng/ml in patients with comorbid and isolated NAFLD, respectively, while control results averaged 8.17 ng/ml. The IL-1β level in NAFLD and HT group was 4.76 pg/ml, and in isolated NAFLD group the indicator averaged 4.02 pg/ml, which exceeded the control values (0.59 pg/ml).

Conclusions: The course of both isolated NAFLD and comorbidity NAFLD with HT was accompanied by significant changes of kallistatin, IL-10 and IL-1β levels. Higher HT stage and BP grade, increased BMI and high CRP levels are associated with significantly more pronounced deviations of these indicators in patients with NAFLD and HT. The obtained data provide the possibility to consider the kallistatin, IL-10 and IL-1β as biomarkers of NAFLD severity.

Keywords: Hypertension, IL-10, IL-1β, kallistatin, NAFLD, NASH, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis

ÖZET

Giriş: Alkolüzdü yağlı karaciğer hastalığı, hipertansiyonla yakından bağlantılıdır ve yetişkin nüfusun yaklaşık%25’ini etkiler. Alkolüzdü yağlı karaciğer hastalığı teshisi için invazif olmayan biyobelirteçlerin araştırılması önemli bir konu olmayan devam etmektedir.

Çalışmanın amacı, hipertansiyon ile kombinasyon halinde alkolsüz yağlı karaciğer hastalığı tanıında kallistatin, interlökin-10 (IL-10) ve interlökin-1β (IL-1β)’nin tanısal değerlerini değerlendirilmektedir.

Materyal ve Metodlar: Alkolsüz steatohepatit ve hipertansiyonla kombinasyon halinde alkolsüz yağlı karaciğer hastalığı olan 115 hasta incelendi; bunlara eşlik eden alkolsüz steatohepatit ve hipertansiyonu olan 63 hasta (ana grup) ve izole alkolsüz steatohepatitli 52 kişi (karsılaştırma grubu) ve kontrolde değerler kullanılmıştır. Klinik ve laboratuvar parametreleri değerlendirildi.

Bulgular: Alkolsüz yağlı karaciğer hastalığı ve hipertansiyonu olan hastalarda, izole alkolsüz yağlı karaciğer hastalığı ve kontrol grubunda ortalamalı kallistatin seviyeleri sırasıyla 65.03 ng/ml, 83.42 ng/ml ve 111.70 ng/ml olmuştur. IL-10 seviyesi, komorbid ve izole alkolsüz yağlı karaciğer hastalığı olan hastalarda sırasıyla 2.69 ng/ml ve 4.90 ng/ml idi. HT grubunda ise 8.17 ng/ml idi. Alkolsüz yağlı karaciğer hastalığı ve HT grubunda 4.76 pg/ml ve izole alkolsüz yağlı karaciğer hastalığı grubunda gösterge ortalamalı 4.02 pg/ml ve bu da kontroldegerlerini (0.59 pg/ml) aşmıştır.

Sonuç: Hem izole alkolsüz yağlı karaciğer hastalığı hem de alkolsüz yağlı karaciğer hastalığı ile birlikte hipertansiyonun seyrine kallistatin, IL-10 ve IL-1β seviyelerinde önemli değişiklikler eşlik etti. Alkolsüz yağlı karaciğer hastalığı ve hipertansiyonu olan hastalarda daha yüksek hipertansiyon evresi ve kan basıncı derecesi, artan vücut kitle indeksi ve yüksek C-reactif protein seviyeleri, bu göstergelerin önemli ölçüde daha belirgin sapmalarıyla ilişkilidir. Elde edilen veriler, kallistatin, IL-10 ve IL-1β’nin alkolsüz yağlı karaciğer hastalığı ciddiyetinin biyolojik belirteçleri olarak dikkate alınması sağlar.

Anahtar Kelimeler: Alkolden bağımsız karaciğer hastalığı, alkolden bağımsız karaciğer yağlanması, IL-1β, IL-10, kallistatin, yüksek tansiyon
INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases. The prevalence of pathology in the world averages 25.2% worldwide, and the prevalence of non-alcoholic steatohepatitis (NASH), a more severe type of NAFLD, averages 4% in the general population (1,2).

Non-alcoholic fatty liver disease is closely associated with metabolic disorders (3). Considerable attention is paid to the relationship between NAFLD and arterial hypertension (HT) that affects about one third of the world’s adult population. The prevalence of HT is significantly higher in individuals with NAFLD than in the general population, and near 50% of patients with hypertension have NAFLD (4).

NAFLD can contribute to the development of hypertension, as well as occur on the background of increased blood pressure (5). It is also known that cardiovascular diseases significantly complicate the course of NAFLD (6). Therefore, diagnosis of fatty changes in the liver is especially important in the case of a comorbid combination of NAFLD and HT.

The liver biopsy is the "gold standard" for the NAFLD diagnosis. But this expensive invasive procedure is associated with a high risk of complications and false negative results in patients with NASH (7). It is the reason why a lot of studies are connected with the determination of biomarkers to create models for steatosis and fibrosis diagnosing and predicting the course of NAFLD (8).

Cytokines play an important role in the pathogenesis of NAFLD, as NAFLD is associated with inflammatory processes in the liver (9). The variety of effects of cytokines determines their active role in the development and progression of NAFLD by stimulating hepatic inflammation, necrosis, apoptosis, and fibrosis (10).

The importance of IL-1β in the development of NAFLD has been actively studied, it is known that its activity increases in patients with NASH and correlates with the severity of fatty liver infiltration (10,11). At the same time, there is evidence that interleukin-10 (IL-10) acts as an anti-inflammatory cytokine, therefore, on the contrary, limits organ damage and prevents the progression of hepatic steatosis (12,13). Only a few studies have been performed to investigate the role of endogenous IL-10 in the progression of NAFLD (14).

Changes in cytokine balance are also observed in patients with persistently elevated blood pressure. Hypertension is thought to be associated with increased production of proinflammatory cytokines, including IL-1 (15). However, IL-10 shows protective activity under conditions of high pressure, as it counteracts the activity of the angiotensin-mediated system, as well as prevents the development of vascular dysfunction (16).

Kallistatin (kallikrein-binding protein) belongs to the family of serine protease inhibitors, which are synthesized in the liver and distributed between the tissues of the heart and blood vessels (17).

This protein maintains the level of blood pressure (BP) and exhibits anti-inflammatory, antioxidant, antiangiogenesis and antitumor effects (18,19). Various studies confirm that kallistatin may be an effective biomarker for detection of liver fibrosis in various liver diseases (20,21).

Different studies suggest that patients with NAFLD have an imbalance of pro-inflammatory and anti-inflammatory cytokines (22). Therefore, the determination of the activity of biomarkers can play a significant role in diagnosing the impact of concomitant hypertension on the course of NAFLD and determining the optimal management of this category of patients.

The aim of the study to determine the role of kallistatin, IL-1β and IL-10 as diagnostic biomarkers of NAFLD severity in patients with concomitant HT.

MATERIALS AND METHODS

The study was approved by the Ethics and Bioethics Commission of institution in which the study was conducted. The experimental part of this study respects the ethical standards in the Helsinki Declaration of 1975, as well as the principles of Good Clinical Practice (GCP) and the national law. All patients voluntarily decided to participate in the study and signed the patient’s informed consent.

We examined 115 patients with NAFLD at the stage of non-alcoholic steatohepatitis (NASH). Participants included 57 men and 58 women aged 38 to 59 years (Mean=48,4). The patients were divided into two groups depending on the presence of concomitant HT. The main group (n=63) consisted of 32 men and 31 women aged 38 to 59 years (Mean=48,4) with NAFLD and HT, and the comparison group (n=52) included 25 men and 27 women aged 38 to 59 years (Mean=48,3) with an isolated course of NAFLD. NAFLD and HT I stage were observed in 42 patients (20 men and 22 women; aged 39 to 57 years (Mean=46,9), and NAFLD and HT II stage were in 42 patients (20 men and 22 women; aged 38 to 59 (Mean=46,9)).

The control group (n=20) consisted of practically healthy 12 women and 8 men aged 38 to 56 years (Mean=47,1), randomized by age and sex.

NAFLD was diagnosed in the previous stages of managing patients according to the EASL-EASD-EASO Clinical Practice Guidelines, 2016. Hypertension was diagnosed in the patients according to the EASL-EASD-EASO Clinical Practice Guidelines, 2016.
Among the indicators of the functional state of the liver, the levels of hepatic transaminases had exceeded normal values and were significantly higher in patients with NAFLD and HT compared with the group of isolated NAFLD. Alkaline phosphatase and gamma-glutamyl transpeptidase were predominantly within the normal range, but in the group with comorbid NAFLD its levels were statistically significantly higher than in the group with isolated NAFLD and in the control group (Table 1).

### RESULTS

There were no significant differences between anthropometric parameters of patients with NAFLD and HT comorbidity and isolated NAFLD. At the same time, significant differences were found in comparison with the control group in almost all indicators of both the main and the comparison group. It was expected that blood pressure values differed significantly between groups (Table 1).
The kallistatin level in patients with NAFLD and HT was 65.98 ng/ml (95% CI 62.85-69.12; CV=22.28%). It was respectively in 1.3 (p<0.001) and 1.7 times (p<0.001) less, than in isolated NAFLD (83.42 ng/ml (95% CI 81.89-84.94; CV=6.56%)) and control group (111.70 ng/ml (95% CI 106.14-113.22; CV=6.90%)) (Fig. 1).

Figure 1. Kallistatin levels in the examined patients

The IL-10 level in the group of patients with NAFLD and HT averaged 12.69 ng/ml (95% CI 11.93-12.95; CV=15.88%), and in the group with isolated NAFLD it was 14.34 ng/ml (95% CI 13.27-14.34; CV=16.34%). It was 1.27 (p<0.001) and 1.1 (p<0.001) times less than in the control group (16.19 ng/ml (95% CI 15.15-17.74; CV=16.82%)), respectively (Fig. 2).

Figure 2. Interleukin-10 levels in the examined patients

At the same time, the level of IL-1β significantly exceeded the control values in both groups of patients with NAFLD. In the group with comorbidity of NAFLD and HT, the cytokine level was 17.55 pg/ml (95% CI 17.06-19.73; CV=28.81%), and in the group with isolated NAFLD the indicator averaged 15.72 pg/ml (95% CI 15.25-17.44; CV=23.97%), which exceeded the control values (8.26 pg/ml (95% CI 7.79-8.46; CV=8.77%)) by 2.1 and 1.9 times, respectively (Fig. 3).

Figure 3. Interleukin-1β levels in the examined patients

The level of kallistatin in patients with NAFLD and HT I was 71.82 ng/ml (95% CI 70.16-79.51; CV=13.73%), which was significantly higher than in patients with HT II (58.62 ng/ml (95% CI 55.81-64.45; CV=23.06%; p<0.001). There were also differences between the levels of IL-1β, the activity of which in patients with NAFLD and HT II (19.47 pg/ml (95% CI 17.93-21.37; CV=28.14%)) significantly exceeded similar indicators in patients with NAFLD and HT I pg/ml (14.65 (95% CI 14.16-17.63; CV=23.97%), p=0.010) (Fig. 4).

Figure 4. Biomarker levels in patients with NAFLD on the background of HT depending on HT stage and BP grade
At the same time, a significant difference was found only between plasma kallistatin levels in patients with HT II, BP grade I and HT II, BP grade II (p=0.011) (Table 2).

### Table 2. Levels of biomarkers in patients with NAFLD on the background of HT depending on the HT stage and BP grade

| Biomarker | HT I (n = 23) | Reliability between groups | HT II (n = 42) | Reliability between groups |
|-----------|---------------|----------------------------|---------------|----------------------------|
| Kallistatin, ng/ml | | | | |
| BP grade I (n = 14) | 72.23 (95%) | 71.82 (95%) | 72.12 (95%) | 82.40 (95%) |
| CV=13.65% | CV=11.77% | CV=11.77% | CV=11.26% | p=0.009 |
| IL-10, pg/ml | 13.57 (95%) | 14.80 (95%) | 14.80 (95%) | 15.83 (95%) |
| CV=14.85% | CV=14.85% | CV=14.85% | CV=14.85% | p=0.05 |
| IL-1β, pg/ml | 14.35 (95%) | 15.37 (95%) | 15.37 (95%) | 16.37 (95%) |
| CV=18.31% | CV=18.31% | CV=18.31% | CV=18.31% | p=0.002 |

Note: p<0.05 – the difference is statistically significant between groups.

Analysis of kallistatin and interleukin levels in the distribution of patients in both groups by BMI (Fig. 5) revealed significant changes in all biomarkers with weight gain in the group of patients with NAFLD on the background of HT. But in patients with normal weight and overweight patients in the group with isolated NAFLD a significant difference was found only between plasma kallistatin levels (p = 0.002) (Table 3).

### Table 3. Biomarker levels in the examined patients depending on BMI

| Biomarker | NAFLD-HT (n = 65) | Reliability between groups | NAFLD-HT (n = 65) | Reliability between groups |
|-----------|--------------------|----------------------------|--------------------|----------------------------|
| Kallistatin, ng/ml | 71.94 (95%) | 71.94 (95%) | 72.12 (95%) | 82.40 (95%) |
| CV=10.34% | CV=10.34% | CV=11.77% | CV=11.26% | p=0.001 |
| IL-10, pg/ml | 13.31 (95%) | 14.82 (95%) | 14.82 (95%) | 15.83 (95%) |
| CV=14.85% | CV=14.85% | CV=14.85% | CV=14.85% | p=0.002 |
| IL-1β, pg/ml | 14.15 (95%) | 15.37 (95%) | 15.37 (95%) | 16.37 (95%) |
| CV=18.31% | CV=18.31% | CV=18.31% | CV=18.31% | p=0.002 |

Note: p<0.05 – the difference is statistically significant between groups.

In the group with NAFLD and HT, the level of kallistatin negatively correlated with the HT stage and BP grade (r=-0.52), and both relationships were defined as moderate. At the same time, with an increase in BP grade in patients with NAFLD and HT, the level of IL-10 significantly decreased (r=-0.32). The relationship between the levels of the proinflammatory cytokine IL-1β and the HT stage in the group with NAFLD and HT was regarded as a direct weak (r=0.33), but the relationship with BP grade was moderate (r=0.42).

Kallistatin levels were decreased in patients with increasing body mass index (BMI) both in the group with NAFLD and HT (r=-0.58; p<0.001) and in the group with isolated NAFLD (r=-0.54; p=0.002). With an increase in body weight, the activity of IL-1β also increased (r=0.32) and the strength of the anti-inflammatory protection of IL-10 (r=-0.27) decreased in the group with comorbidity of NAFLD and HT.

The activity of kallistatin decreased with the progression of HT in patients with NAFLD (p<0.001). The correlations between kallistatin and CRP were very strong (r=-0.89) and strong (r=-0.61) in groups with comorbid and isolated NAFLD, respectively. At the same time, an inverse relationship between the level of CRP and IL-10 was observed in both groups of patients with NAFLD, but in cases with concomitant HT, the strength of the relationship was significantly higher (r=-0.69 and r=-0.30, respectively). In addition, in patients with NAFLD and HT with higher CRP levels, the activity of the proinflammatory cytokine IL-1β increased (r=0.61).

We also obtained data on the inverse relationship between kallistatin and hepatic transaminases in both groups of patients with NAFLD, while in cases with concomitant HT, the correlations were stronger. Also, an inverse relationship between the level of kallistatin and ALP was found in all patients with NAFLD, but inverse correlations between the kallistatin level and GGTP (r=-0.43) was found only in the group with NAFLD and HT (Table 4).

Figure 5. Biomarker levels in the examined patients depending on BMI.
**Table 4.** Correlation coefficients between biomarkers and clinical and laboratory parameters in the examined patients, r (p value)

| Groups of patients | NAFLD – HT (n = 63) | NAFLD (n = 62) |
|--------------------|---------------------|----------------|
|                    | Kallistatin (IL)    | Kallistatin (IL) |
| HT stage           | -0.22 (p < 0.05)    | -0.19 (p < 0.05) |
|                    | -0.05 (p < 0.05)    | -0.05 (p < 0.05) |
| BP grade           | -0.15 (p < 0.05)    | -0.12 (p < 0.05) |
|                    | -0.12 (p < 0.05)    | -0.12 (p < 0.05) |
| SBP                | -0.20 (p < 0.05)    | -0.17 (p < 0.05) |
|                    | -0.05 (p < 0.05)    | -0.05 (p < 0.05) |
| BMI                | -0.28 (p < 0.05)    | -0.27 (p < 0.05) |
|                    | -0.05 (p < 0.05)    | -0.05 (p < 0.05) |
| CRP                | -0.84 (p < 0.05)    | -0.80 (p < 0.05) |
|                    | -0.05 (p < 0.05)    | -0.05 (p < 0.05) |
| ALT                | -0.87 (p < 0.05)    | -0.01 (p < 0.05) |
|                    | -0.05 (p < 0.05)    | -0.05 (p < 0.05) |
| AST                | -0.55 (p < 0.05)    | -0.02 (p < 0.05) |
|                    | -0.05 (p < 0.05)    | -0.05 (p < 0.05) |
| ALP                | -0.47 (p < 0.05)    | -0.01 (p < 0.05) |
|                    | -0.05 (p < 0.05)    | -0.05 (p < 0.05) |
| GGTP               | -0.43 (p < 0.05)    | -0.37 (p < 0.05) |
|                    | -0.05 (p < 0.05)    | -0.05 (p < 0.05) |

**Note:** p<0.05 – the correlation is statistically significant

**DISCUSSION**

The effect of concomitant hypertension on the clinical manifestation of NAFLD has been determined in various studies. Ampuero J. et al. showed that HT was independently linked to significant fibrosis in patients with NAFLD (23). The possibility of the two-way relationship between these diseases remains under study. Prospective cohort study of Liu P. et al. also showed bidirectional association between NAFLD and hypertension was found (24).

The study of Ma J. showed that NAFLD is associated with increased odds of incident HT and patients with hypertension at baseline had higher odds of NAFLD development (25). According to Aneni E. C. et al. study results more prevalent NAFLD may occur early in the development of HT, even in conditions of the absence of other metabolic risk factors. Authors concluded that controlling blood pressure levels among even non-obese hypertensive patients may be important in preventing or limiting NAFLD (26).

In different studies high hs-CRP values was found in hypertensive patients and it was considered as an independent risk factor for HT. Authors concluded that this biomarker can aggravate hypertension by participating in local and systemic inflammatory responses (27). Significant differences in the CRP level obtained during the examination of patients with comorbid and isolated NAFLD course also confirm this statement. Summary from 19 prospective studies by Lonardo A. at al. suggest that HT can lead to differences in NAFLD course and condition the rapid deterioration of fatty liver patients and combination of this pathologies could be a precursor of the metabolic syndrome (28).

Various studies suggest that kallistatin concentrations vary in different chronic liver diseases, which may be associated with decreased hepatic protein secretion activity (4). Cheng Z. et al. found a significantly lower content of kallistatin in patients with liver fibrosis (29). Halla M. et al. proved that even a single determination of the biomarker level allows to detect patients in the initial liver fibrosis stages with a sensitivity of 96.7% and a specificity of 50% (7).

Frühbeck, G. et al. proved that kallistatin has a potential protective role in the obesity development in NAFLD (30). In our study, significant changes in kallistatin levels with weight gain in NAFLD patients with and without HT were detected. This may indicate the importance of the protein in protecting against metabolic changes in adipose tissue in NAFLD, but these findings require further investigation.

Another important issue is the kallistatin role in the cardiovascular diseases. The hypertension development is associated with activity of the kallikrein-kinin system decrease. Studies show that endogenous kallistatin is a protective agent against vascular oxidative stress, inflammation and fibrosis in animal hypertension models (31). The results of our study showed that kallistatin levels are significantly lower in patients with NAFLD and HT than in isolated NAFLD patients (p<0.001).

However, literature data indicate a relatively low sensitivity and specificity of kallistatin as an isolated indicator of liver parenchyma changes (21). Thus, it is necessary to consider the possibility of combining the kallistatin determination with other non-invasive NAFLD tests.

Our study showed that the level of anti-inflammatory cytokines (interleukin-10) in patients with isolated NAFLD was significantly higher than in patients with a combination of NAFLD and HT, and in the control group the anti-inflammatory activity was significantly higher than in patients with NAFLD. Meanwhile, the level of IL-1β in patients with concomitant pathology of NAFLD on the background of HT significantly exceeded the corresponding value in the group with isolated NAFLD, and in general the level of inflammatory marker in patients of the main group and the comparison group exceeded control values.

These results confirm the findings of Nelson J. and other authors that proinflammatory cytokines, such as IL-1β, are elevated in nonalcoholic steatohepatitis (32). Statistically significant differences were found between kallistatin and
IL-1β levels in patients with NAFLD on the background of HT depending on the stage of hypertension. We also obtained data indicating the effect of the progression of hypertension on the proinflammatory activity of IL-1β, as well as a significant inverse dependence of the anti-inflammatory activity of calistatin on blood pressure. These results indicate a deepening of pro-inflammatory and anti-inflammatory deviations in patients with comorbid NAFLD in the transition to more severe stages of HT and with an increase in BP grade. Also noteworthy was the fact that a significant decrease in the anti-inflammatory activity of kallistatin with increasing BMI was observed in all patients with NAFLD, and an increase in the effect of interleukins on the course of NAFLD with increased BMI was determined only under the additional influence of HT.

The lack of a clear significant relationships between IL-10 and clinical and laboratory parameters of the examined patients partially confirms the opinion of the authors that this cytokine has different effects. Thus, Saraiva M. and co-authors claim that its antifibrotic activity is detected only at the beginning of the disease, and with the progression of NAFLD the cytokine may even stimulate irreversible changes in the liver parenchyma (33). Therefore, it is important to measure the levels of these biomarkers in combination to diagnose the severity of NAFLD more accurately and to determine the effect of hypertension on the course of NAFLD.

CONCLUSIONS

The course of both isolated NAFLD and comorbidity NAFLD with HT was accompanied by significant changes of kallistatin, IL-10 and IL-1β levels, which confirmed the pathophysiological role of chronic low-grade systemic inflammation in NAFLD. The combination of NAFLD and HT led to a significant increase in the severity of deviations in these indicators, which makes it possible to consider HT as a trigger factor of NAFLD progression.

Higher HT stage and BP grade, increased BMI and high CRP levels are associated with significantly more pronounced deviations of these indicators and should be considered as additional factors of NAFLD progression in patients with HT.

The obtained data provide the possibility to consider the kallistatin, IL-10 and IL-1β as biomarkers of NAFLD severity severity.

REFERENCES

1. Mitra S, De A, Chowdhury A. Epidemiology of non-alcoholic and alcoholic fatty liver diseases. Translational Gastroenterology and Hepatology. 2020;5:16. doi:10.21037/tgh.2019.09.08
2. Marieke V, Jan W, Karin K, et al. Prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) in Patients With Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis. The Journal of Clinical Endocrinology & Metabolism. 2020;105(12):3842–3853. doi:10.1210/clinem/dgaa575
3. Wu S, Wu F, Ding Y, et al. Association of non-alcoholic fatty liver disease with major adverse cardiovascular events: A systematic review and meta-analysis. Scientific Reports. 2016;6:33386. doi: 10.1038/srep33386.
4. Zhao YC, Zhao GJ, Chen Z, et al. Nonalcoholic Fatty Liver Disease: An Emerging Driver of Hypertension. Hypertension. 2020;75(2):275-284. doi: 10.1161/hypertensionaha.119.13419
5. Oikonomou D, Georgiopoulos G, Katsi V, et al. Non-alcoholic fatty liver disease and hypertension: coprevalent or correlated? European Journal of Gastroenterology & Hepatology. 2018;30(9):979-985. doi: 10.1097/MEG.0000000000001191.
6. Targher G, Byrne CD, Lonardo A, et al. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. Journal of Hepatology. 2016;65(3):589-600. doi: 10.1016/j.jhep.2016.05.013.
7. Halla MR, Fawzy AA, Nabila AEM, et al. Evaluation of kallistatin as a biomarker in chronic hepatitis C patients. World journal of pharmacy and pharmaceutical sciences. 2017;6(9):150-174. doi: 10.20959/WJPPS2017-90058
8. Ma C, Yin H, Zhong J, et al. Kallistatin exerts anti-lymphangiogenic effects by inhibiting lymphatic endothelial cell proliferation, migration and tube formation. International Journal of Oncology. 2017;50(6):2000–2010. doi:10.3892/ijo.2017.3972
9. Fathia A. Mannaa, Khaled G. Abdel-Wahhab. Physiological...
potential of cytokines and liver damages. Hepatoma Res 2016; 2: 131-143.
10. Tilg H, Effenberger M, Adolph TE. A role for IL-1 inhibitors in the treatment of non-alcoholic fatty liver disease (NAFLD)? Expert Opin Investig Drugs. 2020 Feb;29(2):103-106. doi: 10.1080/13543784.2020.1681397.
11. Nelson JE, Handa P, Aouizerat B, Wilson L, Vemulakonda LA, Yeh MM, Kowdlely KV; NASH Clinical Research Network. Increased parenchymal damage and steatohepatitis in Caucasian non-alcoholic fatty liver disease patients with common IL1B and IL6 polymorphisms. Aliment Pharmacol Ther. 2016 Dec;44(11-12):1253-1264. doi: 10.1111/apt.13824.
12. Fathia A. Mannaa, Khaled G. Abdel-Wahhab. Physiological potential of cytokines and liver damages. Hepatoma Res. 2016; 2: 131-143.
13. Steen, E. H., Wang, X., Balaji, S., Butte, M. J., Bollyky, P. L., & Keswani, S. G. The Role of the Anti-Inflammatory Cytokine Interleukin-10 in Tissue Fibrosis. Advances in Wound Care. 2019. doi:10.1089/wound.2019.1032.
14. Braunersreuther V, Viviani GL, Mach F, Montecucco F. Role of cytokines and chemokines in non-alcoholic fatty liver disease. World journal of gastroenterology. 2012; 18(8):727–735. https://doi.org/10.3748/wjg.v18.i8.727
15. Krishnan SM, Sobey CG, Latz E, Mansell A, Drummond GR. IL-1β and IL-18: inflammatory markers or mediators of hypertension?. Br J Pharmacol. 2014;171(24):5589-5602. doi:10.1111/bph.12876
16. Lima VV, Zemse SM, Chiao CW, Bomfim GF, Tostes RC, Clinton Webb R, Giachini FR. Interleukin-10 limits increased blood pressure and vascular RhoA/Rho-kinase signaling in angiotensin II-infused mice. Life Sci. 2016 Jan 15;145:137-143. doi:10.1016/j.lfs.2015.12.009.
17. Gateva A, Assyov Y, Velikova T, et al. Increased kallistatin levels in patients with obesity and prediabetes compared to normal glucose tolerance. Endocrine Research. 2017;42(2):163-168. doi:10.1080/07435880.2017.1286671
18. Ma L, Wu J, Zheng Y, et al. Heparin Blocks the Inhibition of Tissue Kallikrein 1 by Kallistatin through Electrostatic Repulsion. Biomolecules. 2020;10(6):828. doi:10.3390/biom10060828
19. Wu H, Li R, Zhang Z, et al. Kallistatin inhibits tumour progression and golden resistance in high-grade serous ovarian cancer. Journal of Ovarian Research. 2019;12(1):125. doi:10.1186/s13048-019-0601-6
20. Al-Shimaa MA, Moustafa SA, Noha MS, et al. Evaluation of clinical significance of kallistatin and macrophage inflammatory protein-1b for the diagnosis of liver cirrhosis and hepatocellular carcinoma in Egyptian patients. Research Journal of Pharmacy and Technology. 2019;12(1):43-49. doi: 10.5958/0974-360X.2019.00009.X
21. Prystupa A, Kiciński P, Luchowska-Kocot D, et al. Factors influencing serum chemerin and kallistatin concentrations in patients with alcohol-induced liver cirrhosis. Annals of Agricultural and Environmental Medicine. 2019;26(1):143-147. doi:10.26444/aaem/100536
22. Bocsan IC, Milaciu MV, Pop RM, Vesa SC, Ciumarnean L, Matei DM, Buzoianu AD. Cytokines Genotype-Phenotype Correlation in Nonalcoholic Steatohepatitis. Oxidative Medicine and Cellular Longevity. 2017;1:1–7. doi:10.1155/2017/4297206
23. Ampuero J, Aller R, Gallego-Durán R, Crespo J, Calleja, JL, Garcia-Monzón C, Romero GM. Significant fibrosis predicts new-onset diabetes mellitus and arterial hypertension in patients with NASH. Journal of Hepatology.2020; 73(1):17-25. doi: 10.1016/j.jhep.2020.02.028.
24. Liu P, Tang Y, Guo X, Zhu X, He M, Yuan J, Yao P. Bidirectional association between nonalcoholic fatty liver disease and hypertension from the Dongfeng-Tongji cohort study. Journal of the American Society of Hypertension. 2018. doi:10.1016/j.jash.2018.06.013
25. Ma J, Hwang SJ, Pedley A, Massaro JM, Hoffmann U, Chung RT, Long MT. Bi-directional analysis between fatty liver and cardiovascular disease risk factors. Journal of Hepatology. 2017;66(2):390–397. doi:10.1016/j.jhep.2016.09.022
26. Aneni EC, Oni ET, Martin SS, Blaha MJ, Agatston AS, Feldman T, Nasir K. Blood pressure is associated with the presence and severity of nonalcoholic fatty liver disease across the spectrum of cardiometabolic risk. Journal of Hypertension. 2015;33(6):1207-1214. doi:10.1097/HJH.0000000000000532.
27. Ilan Y. Analogy between non-alcoholic steatohepatitis (NASH) and hypertension: a stepwise patient-tailored approach for NASH treatment. Annals of gastroenterology. 2018;31(3):296–304.
28. Lonardo A, Ballestri S, Marchesini G, Angulo P, Loria P. Nonalcoholic fatty liver disease: a precursor of the metabolic syndrome. Digestive and liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2015;47: 181-190.
29. Cheng Z, Lv Y, Pang S, et al. Kallistatin, a new and reliable biomarker for the diagnosis of liver cirrhosis. Acta Pharmaceutica Sinica B. 2015;5(3):194-200. doi:10.1016/j.apsb.2015.02.003.
30. Frühbeck G, Gómez-Ambrosi J, Rodríguez A, et al. Novel protective role of kallistatin in obesity by limiting adipose tissue low grade inflammation and oxidative stress. Metabolism. 2018;87:123-135. doi:10.1111/met.2018.04.004
31. Chao J, Guo Y, Chao L. Protective Role of Endogenous Kallistatin in Vascular Injury and Senescence by Inhibiting Oxidative Stress and Inflammation. Oxidative Medicine and Cellular Longevity. 2018;2018:4138560. doi:10.1155/2018/4138560
32. Nelson JE, Handa P, Aouizerat B, Wilson L, Vemulakonda LA, Yeh MM, Kowdlely KV; NASH Clinical Research Network. Increased parenchymal damage and steatohepatitis in Caucasian non-alcoholic fatty liver disease patients with common IL1B and IL6 polymorphisms. Aliment Pharmacol Ther. 2016 Dec;44(11-12):1253-1264. doi: 10.1111/apt.13824.
33. Saraiva M, Vieira P, O’Garra A. Biology and therapeutic potential of interleukin-10. The Journal of Experimental Medicine. 2019;jem.20190418. doi:10.1084/jem.20190418