ОРИГИНАЛЬНЫЕ ИССЛЕДОВАНИЯ

УДК: 616.36-002.17:[616.36-002.2-022.6+616.36-003.826]-091.8 DOI: 10.34673/ismu.2019.96.18.007

СЫВОРОТОЧНЫЙ УРОВЕНЬ M2BPGI В ДИАГНОСТИКЕ ФИБРОЗА ПЕЧЕНИ У ПАЦИЕНТОВ С ИЗБЫТОЧНОЙ МАССОЙ ТЕЛА И ОЖИРЕНИЕМ В МОНГОЛИИ

Уранбайгаль Энхбаяр, Даваалхам Дамбадаржаа, Отгонбаяр Раднаа
(Монгольский национальный университет медицинских наук, Улан-Батор, Монголия)

Резюме.
Цель работы: оценить диагностические возможности сывороточного биомаркера M2BPGiв выявлении фиброза печени среди людей с избыточной массой тела и ожирением в возрасте от 40 до 65 лет в Монголии.
Материалы и методы. Обследовали 3315 человек в возрасте 40-65 лет, проживающих в городских и сельских районах. От участников исследования были получены заполненные анкеты, были проведены антропометрические измерения, УЗИ и лабораторные исследования. Уровень M2BPGi в сыворотке измеряли непосредственно с помощью хемилюминесцентного иммуноферментного метода с использованием автоматического иммуноанализатора. Статистический анализ был выполнен на SPSS вер. 20.0 (SPSSInc., Чикаго, Иллинойс, США). Мы использовали хи-квадрат Пирсона для оценки разницы между параметрами в процентах, а критерий Т – для оценки медианной разницы. Значение p<0,05 считается статистически значимым.
Результаты. Из 3315 участников исследования 1955 человек были набраны в Улан-Баторе (59,0%), 1360 человек были из сельской местности. Среди обследованных 1141 (34,4%) были мужчины и 2174 (65,6%) – женщины. 1326 (40%) опрошенных имели избыточную массу, а 1038 (31,3%) страдали ожирением. Фиброз печени был обнаружен у 51,2% пациентов с ожирением и избыточной массой. Повышение уровня биомаркера M2BPGI в сыворотке значительно отличалось от массы тела, возрастной группы и пола (p <0,0001).
Заключение. Из общего числа участников 40% имели избыточный вес и 31,3% страдали ожирением. Фиброз печени был обнаружен у 51,2% пациентов с ожирением и избыточной массой.
Ключевые слова: M2BPGI; HCC; неалкогольная жировая болезнь печени; Y93H; Монголия.

THE SERUM M2BPGI LEVEL CAN BE PRACTICAL TEST TO DIAGNOSE LIVER FIBROSIS AMONGOVERWEIGHT AND OBESE PATIENTS IN MONGOLIA

Uranbaigali Enkhbayar, Davaalkham Dambadarjaa, Otgonbayar Radnaa
(Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia)

Summary.
Aim: To diagnose liver fibrosis among overweight and obese population of 40-65 years in Mongolia by serum M2BPGi glyco-biomarker level.
Methods. We enrolled 3315 people aged 40-65 years old who live in urban and rural areas. Questionnaires were obtained from participants, and anthropometric measurements, ultrasound, and laboratory tests were done. Serum M2BPGi level was directly measured with the chemilumines centenzyme immune method using an automatic immunoanalyzer. Statistical analysis was performed on SPSS ver. 20.0; SPSS Inc., Chicago, IL software. We used Pearson chi squaretest to estimate difference between parameters with percentage, and T test was used to estimate median difference. Ap value less than 0.05considered statistically significant.
Results. 3315 people participated in this study. 1955 people were recruited from Ulaanbaatar (59.0%) 1360 people were from rural areas, and 1141 (34.4%) were male and 2174 were female (65.6%). 1326 (40%) of the surveyed were overweight and 1038 (31.3%) were obese. Elevation of serum M2BPGI glyco-biomarker was significantly different from body weight, age group and sex (p<0.0001).
Conclusion. From total participants, 40% were overweight and 31.3% were obese. The liver fibrosis was found in 51.2% of obese and overweight patient.
Key words: M2BPGI;HCC; NAFLD; Y93H; Mongolia.

Introduction

Fatty liver is classified as alcoholic and non-alcoholic causes, and non-alcoholic fatty liver is caused by obesity. Recent study proved that fatty liver was found in 90% of the obese patients [8,17,18]. By collaboration study of the WHO, Millennium Challenge Account and Public Health Institute, in 2009, 42.7 percent of the population aged 15-64 years had overweight andobesity. Nonalcoholic fatty liver disease (NAFLD) is characterized by increased hepatic triglyceride accumulation in the absence of excessive alcohol consumption. This condition is a precursor of other liver pathological conditions, including steatohepatitis, liver fibrosis, liver cirrhosis, and liver failure or hepatocellular carcinoma [4]. Mongolia has the highest hepatocellular carcinoma incidence in the world (78.1/100,000, 3.5* higher than China) [3,5]. Most common etiology for HCC was HCV infection 45.6%, followed by HBV infection 34.4% in Mongolia [6]. Prevalence of HCV infection was 15.6% among apparently healthy populations in Mongolia [4] and ledipasvir/sofosbuvir therapy achieves a high SVR rate in Mongolia chronic hepatitis C genotype 1b patients without baseline Y93H RAS [13].

Furthermore, NAFLD has become more prevalent globally, affecting approximately 25% of the general population [29]. It has an estimated worldwide prevalence ranging from 20% to 46%, varying with study population and diagnostic criteria used [7]. In the United States, NAFLD is estimated to affect approximately 30% (100 million) of the population [14,20]. The prevalence is even higher amongst obese (70%) and diabetic (90%) individuals [11]. In addition, NAFLD is an independent cardiovascular disease risk factor with a 70% overall mortality increase, driven by a about 300% increase in cardiovascular disease mortality [2]. This has generated a need to investigate tools for improving the management of lifestyle or other factors.

To diagnosing liver fibrosis is important for predict the survival rate of chronic liver disease and for the appropriate treatment. Liver biopsy is a golden standard for diagnosing liver fibrosis, but there are several weaknesses. Liver biopsy has several complications such as pain and bleeding which accounts for 1-14%. Therefore, it is necessary to introduce non-invasive methods for assessing liver fibrosis in clinical use. Non-invasive radiologic method and laboratory analysis are used for the detection of liver fibrosis. Moreover, there are several disadvantages for using the diagnostic elastographic to diagnose liver fibrosis. It is challenging to evaluate the function and structure of liver due to deep location where anatomically located under the ribs, and he fluid of abdomen and pregnant women, overweight and obese people have more thick adipose tissue. Japanese scientists have identified the structure of the glycoprotein in the hepatocyte cell wall, which is characterized by a hepatic glyco-biomarker M2BPGI known as the liver fibrous marker. This biomarker may be able to identify fibrosis changes in fatty liver disease and viral hepatitis. Clinical trials compared the M2BPGi test with the liver biopsy tests and it demonstrated same results. In other words, M2BPGi showed negative results in patients with non-inflammatory chronic liver disease,M2BPGI COI = 1.0-3.0 + result in patients with fibrosis group and showed M2BPGI COI> 3.0 + + result in patients with liver cirrhosis [1, 10, 22, 28]. The diagnostic ability of M2BPGi on liver fibrosis is comparableto that of Virtual Touch Tissue Quantification (Siemens, Mountain View, CA, USA) [23], one of the latest shear wave elastography, and superior to other surrogate markers(liver-to-major psoas muscle intensity ratio, serum markers including hyaluronic acid, type 4 collagen and aspartate transaminase to platelet ratio index) [22]. The glyco-biomarker is the most suitable method for use in non-hospital-based research and it is effective, regardless of the cause of liver disease.

Aim: To diagnose the liver fibrotic changes among Mongolian population who aged 40-65 with excess weight using M2BPGi serum glyco-biomarker.

Objectives:

1. Identify changes in body weight among the population aged 40-65 years in Mongolia.

2. Assess the fibrotic change of a liver in the population with the body weight change using serum M2BPGi glyco-biomarker.

Materials and Methods

Sampling

The study was conducted from October 2016 to February 2019, based on the clinical laboratory of the University Hospital at the Mongolian National University of Medical Sciences. In order to reflect the administrative and geographical features of Mongolia, we involved 3315 participants age of 40-65 from Ulaanbaatar city, Gobi-Altai, Uvs provinces from Western region, Arkhangai and Khuvsgul provinces from Khangai region, Dornogobi, Umnugobi and Tuv provinces from Central region, and Sukhbaatar province from Eastern region. This study was conducted using "Analytical cross sectional survey" type.

$$n = DE \cdot \frac{Z^2 \cdot p \cdot (1-p) \cdot 1.2}{e^2} = 1.5 \cdot \frac{1.96^2 \cdot 0.10 \cdot (1-0.10) \cdot 1.2}{0.014^2} = 3175$$

Parameters: n– sample size, p – expected prevalence, z – statistic for a level of confidence, e – the acceptable sampling error, DE – desired margin of error.

Inclusion criteria:

– 40-64 years old while participating in the study,

– Citizen of Mongolia,

– Participant and the caregiver must have given approval to participate in the study.

Exclusion criteria:

– Liver cancer is diagnosed.

Questionnaire, body measurement, abdominal ultrasound and lab tests were done on all participants.

Obesity is calculated using BMI and classified as below.

BMI=Body weight (kg)/ Height (m^2)

<18,5 kg/m^2 – underweight,

18,5-24,9 kg/m^2 – normal weight,

25,0 – 29,9 kg/m^2 – overweight,

>30,0 kg/m^2 – obesity.

Laboratory testing

Serum M2BPGi analysis was performed using Japanese fully automatic HISCL-5000 immunology analyzer by chemiluminescent enzyme immunoassay method.

1. If 1.0 < COI < 3.0s then (+)
2. IfCOI> 3.0 then (++)
3. If COI< 1.0 then (negative)

Statistical analysis was done on SPSS ver.20.0 SPSS ver. 20.0; SPSS Inc., Chicago, IL software and the result was detailed as descriptive, narrow statistical analysis. After determining whether the variable percentage is normal, the margin between parameters were calculated by using Pearson's Chi square test of variables expressed in percentage, the margin of averages was calculated by using T-test. If the p value is less than 0.05, the margin is assumed to be statistically true.

Ethical statement

The research study was approved by the Research Ethics Committee of the Mongolian National University of Medical Sciences (№8/3/2016-08). All participants gave written informed consent.

Results and Discussion

A total of 3451 people aged 40-65 years were elected by random sampling and statistical data were provided for 3315 people covered by all the research stages. Of the respondents, 1955 (59.0%) were from Ulaanbaatar and 1360 (41.0%) were from rural areas. Of these, 1141 (34.4%) were male and 2174 (65.6%) were female and 990 (29.9%) were 40-44 years old, 786 (23.7%) were 45-49 years old, 702 (21.2%) were 50-54 years old, 547 (16.5%) were 55-59 years old and 290 (8.7%) were 60-64 years old.

Table 1

Baseline characteristics of the participants (Region, age, sex)

Baseline characteristics			
Region		number	%
	Rural	1360	41.0
	Urban	1955	59.0
Sex			
	Male	1141	34.4
	Female	2174	65.6
Age			
	40-44	990	29.9
	45-49	786	23.7
	50-54	702	21.2
	55-59	547	16.5
	60-64	290	8.7

Body weight changes and obesity was measured by BMI. Of total participants, 33 (1%) of had underweight, 918 (27.7%) had a normal weight, 1326 (40%) were overweight and 1038 (31.3%) had obesity. The proportion of people with underweight was 1.4% in age 40-44, 0.5% -0.7% in age group 45-59, and 2.4% in age 60-64 years. Percentage of people with normal weight in age group was close, but the proportion of overweight among 40-44 and 50-54 years old was higher, and the proportion of people with obesity was significantly increased from 28.3% to 40.7% in older age groups ($p < 0.0001$).In urban and rural areas, the body weight was similar, but 30.6% of men and 26.2% of women have normal body weight. Overweight and obesity were significantly higher in women than men ($p = 0.049$).

Serum M2BPGI glyco-biomarker was negative in 60.6% of people with normal weigh, 35.1% (+), 4.3% (++), 51.6% of people with overweight, 45.4% (+) (++) in 3.0% (++), 45.3% in obese people, 50.6% in (+), 4.0% (++), indicating higher

Table 2

Body Mass Index: Age, sex, region difference

		Underweight		Normal weight		Overweight		Obese		P value
		n	%	n	%	n	%	n	%	
Age										0.0001
	40-44	14	1.4%	279	28.2%	417	42.1%	280	28.3%	
	45-49	4	0.5%	253	32.2%	304	38.7%	225	28.6%	
	50-54	4	0.6%	184	26.2%	290	41.3%	224	31.9%	
	55-59	4	0.7%	135	24.7%	217	39.7%	191	34.9%	
	60-64	7	2.4%	67	23.1%	98	33.8%	118	40.7%	
Sex										0.049
	Male	12	1.1%	349	30.6%	445	39.0%	335	29.4%	
	Female	21	1.0%	569	26.2%	881	40.5%	703	32.3%	
Region										0.472
	Rural	11	0.8%	390	28.7%	528	38.8%	431	31.7%	
	Urban	22	1.1%	528	27.0%	798	40.8%	607	31.0%	

the body mass index higher the M2BPGI glyco-biomarker (p <0.0001). There was a statistically significant difference between BMI, age group and sex (p <0.0001).

Table 3

M2BPGI change: Age, sex, region

M2BPGi		COI< 1.0 (negative)		1.0<COI< 3.0 (+)		COI >3.0 (++)		P value
		n	%	n	%	n	%	
BMI								0.0001
	Underweight	24	77.4%	7	22.6%	0	0.0%	
	Normal	524	60.6%	303	35.1%	37	4.3%	
	Overweight	643	51.6%	566	45.4%	38	3.0%	
	Obese	438	45.3%	489	50.6%	39	4.0%	
Age								0.0001
	40-44	567	60.0%	360	38.1%	18	1.9%	
	45-49	444	59.0%	287	38.2%	21	2.8%	
	50-54	321	47.6%	318	47.2%	35	5.2%	
	55-59	228	44.1%	267	51.6%	22	4.3%	
	60-64	105	37.6%	154	55.2%	20	7.2%	
Sex								0.002
	Male	613	56.9%	425	39.5%	39	3.6%	
	Female	1052	50.3%	961	46.0%	77	3.7%	
Region								0.001
	Rural	767	56.2%	559	41.0%	39	2.9%	
	Urban	898	49.8%	827	45.9%	77	4.3%	

Increased M2BPGI protein significantly increases abnormalities in the abdominal ultrasound (p <0.0001).

Table 4

Abdominal ultrasound changes

		COI< 1.0 (negative)		1.0<COI< 3.0 (+)		COI>3.0 (++)		P value
		n	%	n	%	n	%	
Echogenicity								0.0001
	Normal	794	48.7%	545	39.9%	48	41.7%	
	Slightly increased	362	22.2%	323	23.6%	30	26.1%	
	Increased	473	29.0%	497	36.4%	37	32.2%	
	Decreased	3	0.2%	1	0.1%	0	0.0%	
Structure								0.0001
	Regular	1545	96.1%	1252	92.7%	87	77.0%	
	Irregular	63	3.9%	99	7.3%	26	23.0%	
Capsular contour								0.0001
	Smooth	1521	98.7%	1270	97.5%	90	84.9%	
	Coarse	20	1.3%	32	2.5%	16	15.1%	
Hepatic vein								0.104
	Normal	1559	98.6%	1306	98.0%	107	99.1%	
	Dilated	6	0.4%	2	0.2%	1	0.9%	
	Narrowed	16	1.0%	24	1.8%	0	0.0%	
Hepatocystic duct								0.294
	Normal	1564	99.2%	1311	98.9%	105	99.1%	
	Dilated	2	0.1%	3	0.2%	1	0.9%	
	Narrowed	10	0.6%	12	0.9%	0	0.0%	
Masses								0.108
	Not occured	1403	87.3%	1156	86.2%	91	80.5%	
	Occured	204	12.7%	185	13.8%	22	19.5%	

The survey covered 3315 people aged 40-65 years in Mongolia. NAFLD comprises a spectrum of disease that can be simplified into two categories: (1) Simple Steatosis (SS), 70-75% of cases, defined by excess liver fat without inflammation or cellular injury; and (2) nonalcoholic steatohepatitis (NASH), 25%-30% of cases, defined by the presence of excess liver fat with inflammation and cellular injury [7,26].

It is important to appreciate that SS and NASH are not entirely distinct, with many patients falling along a spectrum of fatty accumulation, inflammation, and hepatocyte injury. Nonetheless, this simplification facilitates prognostication and assessment of clinical significance. In most cases, SS is non-progressive, and does not result in liver fibrosis or progressive liver disease. However, recent longitudinal paired biopsy studies have shown that some patients with SS can progress to develop inflammation and fibrosis [19], and up to 20-30% can progress to NASH [27]. Patients with NASH have a 20%–50% risk of developing progressive inflammation or liver fibrosis [21,26] and have a 2-20% 5-year cumulative incidence of hepatocellular carcinoma [25]. According to our study, 1326 (40%) of people surveyed were overweight and 1038 (31.3%) were obese. Clinical trials have shown that M2BPGi glyco-biomarker result was close to liver biopsy test, besides M2BPGi in a group of no chronic liver inflammation was negative, in a group of chronic liver inflammation with fibrotic change was (+), and in a group of cirrhotic patients was (++). Furthermore, the results in our study 51.6% participants from overweight group showed negative M2BPGi, 45.4% is (+), 3.0% (++); in obese group negative M2BPGi was in 45.3%, (+) in 50.6, and (++) in 4.0% of participants, which is close to the results of other research works, that claims liver inflammation and liver fibrosis changes occur in 20-50 percent of obese population. Abe M, Miyake T, Kuno A, et al study showed that M2BPGi glyco-biomarker is effective glyco-biomarker to assess fibrotic changes in alcoholic and non-alcoholic fatty liver disease patients [1]. M2BPGi is a significantly effective glyco-biomarker for the diagnosis of fibrosis levels in patients with hepatitis C [15] and is applicable in the evaluation of outcome of the combination therapy with pegylated interferon and ribavirin. The result of combined treatment of PEG-Interferon and Ribavirin for chronic HCV patients in Mongolia was 78% [24]. A high M2BPGi level predicts the onset of hepatic carcinoma[16]. The diagnostic ability of M2BPGi on liver fibrosis is comparable to that of Virtual Touch Tissue Quantification (Siemens, Mountain View, CA, USA) [23], one of the latest shear wave elastography, and superior to other surrogate markers (liver-to-major psoas muscle intensity ratio, serum markers including hyaluronic acid, type 4 collagen and aspartate transaminase to platelet ratio index) [22]. In the analysis of 707 patients infected with hepatitis C virus, the onset risk of hepatic carcinoma increased proportionally with the increase of M2BPGi levels [28]. M2BPGi is an effective glyco-biomarker for the evaluation of fibrosis in patients with nonalcoholic fatty liver disease [29]. The onset risk of hepatic carcinoma is significantly high in patients with M2BPGi levels of 4.2 and higher. Hepatocellular carcinoma is the most common cancer in Mongolia, occurring at a rate of 54.1 cases in 100,000 people [5]. M2BPGi and AFP are independent risk factors. M2BPGi is effective for the evaluation of fibrosis in patients infected with hepatitis B virus, but with a different cut-off value [10]. As stated above, we proved that M2BPGi is an effective glyco-biomarker for the objective evaluation of fibrosis, regardless of the causative liver disease. There fore, based on the data of the survey, there is an urgent need for monitoring of this disease in Mongolia, besides it is necessary to implement early detection, risk identification, epidemic and prevention strategies according to the WHO's Hepatic Disease Prevention Policy and Guidelines.

Conclusion

From total participants, 40% were overweight and 31.3% were obese. The proportion of people with obesity increases with age. The liver fibrosis was detected 49.7% in women and 43.1% in men and it was increasing 40% to 62.4% in age group. 48.4% of people with overweight and 54.6% of obesity patients have found liver fibrosis changes.

***Конфликт интересов**. Авторы заявляют об отсутствии конфликта интересов. / **Conflict of Interest.** The authors declare that they have no competing interests.*

***Прозрачность исследования.** Исследование не имело спонсорской поддержки. Исследователи несут полную ответственность за предоставление окончательной версии рукописи в печать. / **Transparency of research.** The study did not have sponsorship. Researchers are solely responsible for providing the final manuscript in print.*

***Декларация о финансовых и иных взаимодействиях.** Все авторы принимали участие в разработке концепции и дизайна исследования и в написании рукописи. Окончательная версия рукописи была одобрена всеми авторами. Авторы не получали гонорар за исследование. / **Declaration of financial and other interactions.** All authors participated in the development of the concept and design of the study and in the writing of the manuscript. The final version of the manuscript was approved by all authors. The authors did not receive a research fee.*

***Благодарности.** Мы хотели бы поблагодарить сотрудников монгольского представительства корпорации Sysmex (Япония) и корпорации Sysmex Японии, Медицинский факультет, Монгольский национальный университет медицинских наук, Улан-Батор, Монголия), Университетской больницы общего профиля MNUMS, Научно-технологического фонда MNUMS и Proliance LLC, за помощь в завершении этого исследовательского проекта. / **Acknowledgements.** We would like to thank the staff at the Mongolian Representative Office of the Sysmex Corporation (Japan) and Sysmex Corporation of Japan, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia), University General Hospital of MNUMS, Science Technology Foundation of MNUMS and Proliance LLC, for their help in completing this research project.*

***Материал поступил в редакцию:** 31.08.2019 г.*

ЛИТЕРАТУРА – REFERENCES

1. *Abe M., Miyake T., Kuno A., et al.* Association between Wisteria floribunda agglutinin-positive Mac-2 binding protein and the fibrosis stage of non-alcoholic fatty liver disease // J. Gastroenterol. 2015. Vol. 50. №7. P.776-

2. *Athyros V.G., Tziomalos K., Katsiki N., et al.* Cardiovascular risk across the histological spectrum and the clinical manifestations of non-alcoholic fatty liver disease: An update // World J Gastroenterol. 2015. Vol. 21. P.6820-6834.

3. *Baatarkhuu O., Gerelchimeg T., Munkh-Orshikh D., et al.* Epidemiology, Genotype Distribution, Prognosis, Control, and Management of Viral Hepatitis B, C, D, and Hepatocellular Carcinoma in Mongolia // Euroasian Journal of Hepato-Gastroenterology. 2018. Vol. 8. №1. P.57-62. DOI: 10.5005/jp-journals-10018-1260.

4. *Baatarkhuu O., Kim D.Y., Ahn S.H., et al.* Prevalence and genotype distribution of hepatitis C virus among apparently healthy individuals in Mongolia: a population-based nationwide study // Liver Int. 2008. Vol. 28. №10. P.1389-1395.

5. *Baatarkhuu O., Kim D.Y., Bat-Ireedui P., Han K.H.* Current situation of hepatocellular carcinoma in Mongolia // Oncology. 2011. Vol. 81. Suppl. 1. P.148-151.

6. *Baatarkhuu O., Kim D.Y., Nymadawa P., et al.* Clinical features and prognosis of hepatocellular carcinoma in Mongolia: a multicentre study // Hepatol Int. 2012. Vol. 6. №4. P.763-769.

7. *Chalasani N., Younossi Z., Lavine J.E., et al; American Gastroenterological Association; American Association for the Study of Liver Diseases; American College of Gastroenterologyh.* The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology // Gastroenterology. 2012. Vol. 142. P.1592-1609.

8. *Dunn W., Xu R., Wingard D.L., et al.* Suspected Nonalcoholic Fatty Liver Disease and Mortality Risk in a Population Based Cohort Study // American Journal of Gastroenterology. 2008. Vol. 103. №9. P.2263-2271. DOI: 10.1111/j.1572-0241.2008.02034.x.

9. European association for the Study of the Liver, European Association for the Study of Diabetes. European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease // J Hepatol. 2016. Vol. 64. P.1388-1402. DOI: 10.1016/j.jhep.2015.11.004.

10. *Hanai T., Shiraki M., Ohnishi S., et al.* Impact of serum glycosylated Wisteria floribunda agglutinin-positive Mac-2 binding protein levels on liver functional reserves and mortality in patients with liver cirrhosis // Hepatol. Res. 2015. Vol. 45. №11. P.1083-1090. DOI: 10.1111/hepr.12473.

11. *Hannah W.N. Jr., Harrison S.A.* Nonalcoholic fatty liver disease and elastography: Incremental advances but work still to be done // Hepatology. 2016. Vol. 63. P.1762-1764.

12. *Harrison S.A., Torgerson S., Hayashi P.H.* The natural history of nonalcoholic fatty liver disease: a clinical histopathological study // Am J Gastroenterol. 2003. Vol. 98. P.2042-2047.

13. *Hsu S.J., Enkhzaya S., Lin Y.Y., et al.* Resistance-associated substitution and ledipasvir/sofosbuvir therapy in Mongolian chronic hepatitis C patients. // J Formos Med Assoc. 2019. pii: S0929-6646(19)30819-8. DOI: 10.1016/j.jfma.2019.10.003.

14. *Idowu M.O., Chhatrala R., Siddiqui M.B., et al.* De novo hepatic steatosis drives atherogenic risk in liver transplantation recipients // Liver Transpl. 2015. Vol. 21. P.1395-1402.

15. *Kuno A., Ikehara Y., Tanaka Y., et al.* A serum 'sweet-doughnut' protein facilitates fibrosis evaluation and therapy assessment in patients with viral hepatitis // Sci Rep. 2013. Vol. 3. P.1065.

16. *Kuno A., Kato Y., Matsuda A., et al.* Focused differential glycan analysis with the platform antibody-assisted lectin profiling for glycan-related biomarker verification // Mol Cell Proteomics. 2009. Vol. 8. №1. P.99-108.

17. *LeoniS., TovoliF., NapoliL., et al.* Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis // World J Gastroenterol. 2018. Vol. 24. №30. P.3361-3373.

18. *Lonardo A., Byrne C.D., Caldwell S.H., et al.* GlobalEpidemiology: Non alcoholic Fatty Liver Disease: Incidence and Prevalence // Hepatology. 2016. Vol. 64. №1. P.73-84.

19. *McPherson S., Hardy T., Henderson E., et al.* Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management // J Hepatol. 2015. Vol. 62. P.1148-1155.

20. *Rinella M.E.* Nonalcoholic fatty liver disease: a systematic review // JAMA. 2015. Vol. 313. P.2263-2273.

21. *Sorrentino P., Tarantino G., Conca P., et al.* Silent non-alcoholic fatty liver disease-a clinical-histological study // J Hepatol. 2004. Vol. 41. P.751-757.

22. *Toshima T., Shirabe K., Ikegami T., et al.* A novel serum marker, glycosylated Wisteria floribunda agglutinin-positive Mac-2 binding protein (WFA(+)-M2BP), for assessing liver fibrosis // J Gastroenterol. 2015. Vol. 50. №1. P.76-84. DOI:10.1007/s00535-014-0946-y.

23. *Toshima T., Shirabe K., Takeishi K., et al.* New method for assessing liver fibrosisbased on acoustic radiation force impulse:a special reference to the difference between right and left liver // J Gastroenterol. 2011. Vol. 46. №5. P.705-711.

24. *Uugantsetseg G., Kim Do.Y., Tserendagva D., et al.* Treatment result of peginterferon and ribavirin for chronic viral hepatitis C // Sibirskij Medicinskij Zurnal (Irkutsk). 2016. №8. P.19-22. (in Russian)

25. *White D.L., Kanwal F., El-Serag H.B.* Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review // Clin. Gastroenterol. Hepatol. 2012. Vol. 10. P.1342-1359.e2. DOI: 10.1016/j.cgh.2012.10.001.

26. *Williams C.D., Stengel J., Asike M.I., et al.* Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and

liver biopsy: a prospective study // Gastroenterology. 2011. Vol. 140. P.124-131.

27. *Wong V.W., Wong G.L., Choi P.C., et al.* Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years // Gut. 2010. Vol. 59. P.969-974.

28. *Yamasaki K., Tateyama M., Abiru S., et al.* Elevated serum levels of Wisteria floribundaagglutinin-positive human Mac-2 bindingprotein predict the development of hepatocellular carcinoma in hepatitis Cpatients // Hepatology. 2014. Vol. 60. №5. P.1563-1570.

29. *Younossi Z.M., Koenig A.B., Abdelatif D., et al.* Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes // Hepatology. 2016. Vol. 64. P.73-84.

Информация об авторах:
Отгонбаяр Раднаа – профессор, доктор медицины, доктор философии, профессор кафедры педиатрии, декан Школы медицины Монгольского Национального университета медицинских наук, e-mail: otgonbayar_r@mnums.edu.mn

Information About the Authors:
Otgonbayar Radnaa – MD, PhD, MPH, Professor of Department of Pediatrics,Dean School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia, e-mail:otgonbayar_r@mnums.edu.mn, Mongolian National University of Medical Sciences, Zorig street, POB-48/111, Ulaanbaatar-14210, Mongolia

УДК: 616.61+617.586]-02:616.379-008.64)-085 DOI: 10.34673/ismu.2019.39.61.008

РОЛЬ НЕКОТОРЫХ ЦИТОКИНОВ ПРИ ДИАБЕТИЧЕСКОЙ НЕФРОПАТИИ

Латифова Н.Ф.
(Азербайджанский Медицинский Университет, Баку, Азербайджан)

Резюме.

Цель работы: сравнительное изучение некоторых цитокинов (IL-6, IL-8, IL-10 и TNF-α) в сыворотке крови у больных сахарным диабетом 2-го типа на фоне изменения биохимических показателей начальной и терминальной стадии диабетической нефропатии.

Материалы и методы. Больные сахарным диабетом 2-го типа подразделены на 2 группы: 1-я – 21 больной, получившие медикаментозное лечение (начальная стадия диабетической нефропатии – консервативная группа), 2-я – 24 больных, которые регулярно подвергались гемодиализу («терминальная» стадия хронической болезни почек). В контрольную группу входили 17 практически здоровых доноров. Концентрации креатинина и мочевины в сыворотке крови были определены биохимическим методом с помощью набора реактивов «Lachema» (Чехия), концентрацию цитокинов IL-6, IL-8, IL-10 и TNF-α в сыворотке крови устанавливали иммуноферментным методом при помощи набора реактивов фирмы «Vector Best» (Россия). Статистическую значимость различий определяли методом ранговой вариационной статистики U-Mann-Whitney, с вычислением медианы (Me) и квартильных значений (Q1, Q3), с помощью статистического пакета IBM Statistics SPSS-21.

Результаты. При исследовании показателей, отображающих функцию почек, обнаружили значительное повышение креатинина мочевины в терминальной стадии в 2,8 и 7,9 раза, соответственно, относительно группы больных с начальной стадией и контрольной группы. При определении уровней провоспалительных цитокинов в группе с начальной стадией наблюдается статистически значительное увеличение содержания IL-8 и TNF-α в 1,7 ($p<0,001$) и 2,3 раза ($p=0,006$) по сравнению с контролем. В терминальной стадии также было выявлено более существенное повышение уровней IL-8 и TNF-α в 2,0 раза ($p<0,001$) и 4,6 раза ($p<0,001$) по сравнению с контролем, соответственно.

Заключение. Активация провоспалительных цитокинов у больных с диабетической нефропатией тесно связана с эндотелиальными поражениями почечных каналов, определяемыми повышенной концентрацией в крови креатинина и мочевины. Изучение цитокинового статуса позволяет говорить о значимости провоспалительных цитокинов в течении диабетической нефропатии, они могут быть применены для выбора наиболее оптимальной тактики лечения больных сахарным диабетом 2-го типа с нефропатией, профилактики развития почечной недостаточности.

Ключевые слова: диабетическая нефропатия; IL-6; IL-8; IL-10; TNF-α.

THE ROLE OF SOME CYTOKINES IN DIABETIC NEPHROPATHY

Latifova N.F.
(Azerbaijan Medical University, Baku, Azerbaijan)

Summary.

Aim: The aim of the work was a comparative study of certain cytokines (IL-6, IL-8, IL-10 and TNF-α) in blood serum of patients with type 2 diabetes amid a change in the biochemical parameters of the initial and terminal stages of diabetic nephropathy.

Material and methods. Type 2 diabetes patients are divided into 2 groups: 1) 21 patients who received medication (the initial stage of diabetic nephropathy – a conservative group), 2) 24 patients who underwent regular hemodialysis ("terminal" stage of chronic renal failure). The control group consisted of 17 healthy donors. Concentrations of creatinine and urea in blood serum were determined by the biochemical method using the "Lachema" reagents kit (Czech Republic), and the concentrations of IL-6, IL-8, IL-10, and TNF-α cytokines in blood serum were measured by enzyme immunoassay method using a set of reagents of "Vector Best" company (Russia). Statistical significance of differences was determined by the method of ranked variational statistics U-Mann-Whitney with the calculation of median (Me) and quarter values (Q1, Q3) with the help of statistical package IBM Statistics SPSS-21.

Results. The study of indicators representing renal function, revealed a significant increase in urea creatinine in the terminal stage by 2,8 and 7,9 times, respectively, relative to the group of patients with the initial stage and the control group. In determining the levels of pro-inflammatory cytokines there was a statistically significant increase in the concentration of IL-8 and TNF-α by 1,7 ($p<0,001$) and 2,3 times ($p=0,006$) in the group with the initial stage compared with the control values.