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Features of Metabolic Associated Fatty Liver Disease in the Central Asian Population in Low and High Altitudes

Características de la Enfermedad del Hígado Graso Asociada a Disfunción Metabólica en la Población de Asia Central en Altitudes Bajas y Altas

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SUMMARY

Currently, there is insufficient knowledge about the course of metabolically associated fatty liver disease (MAFLD) in Asian populations living at different altitudes. Our article presents the results of the study of MAFLD in individuals with different body weights in conditions of high-mountain hypoxia. The study assessed the course of MAFLD in lean and obese patients living in the conditions of low and high mountains of Kyrgyzstan. An open comparative study of Asian patients with MAFLD with and without type 2 diabetes mellitus (DM2) living in low and high mountains was performed. In each category of patients, the lean (BMI≤23) and obese (BMI> 23) groups were considered. The anthropometric parameters and biochemical parameters of blood were determined. The liver fibrosis index was calculated using the FIB Score. It was found that residents of the high mountains with MAFLD had a lower BMI compared to the lowlanders. Low blood glucose and HbA1c levels are observed in patients with high BMI living in high-altitude areas compared with lowlanders, especially in combination with DM2. In the group of obese patients with MAFLD living in highlands, low total cholesterol, low-density lipoproteins, and glomerular filtration rate are observed. A high risk of fibrosis was noted in the group of lean patients in both regions. Our results indicate that the study of the effect of chronic high-altitude hypoxia on the course of MAFLD requires prospective population-based studies.

Keywords: *High-altitude, low-altitude, metabolic associated fatty liver disease.*

RESUMEN

En la actualidad, no existe un conocimiento suficiente sobre el curso de la enfermedad del hígado graso asociada a disfunción metabólica (MAFLD) en poblaciones asiáticas que viven a diferentes altitudes. Nuestro artículo presenta los resultados del estudio de

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MAFLD en individuos con diferentes pesos corporales en condiciones de hipoxia de alta montaña. El estudio evaluó el curso de MAFLD en pacientes delgados y obesos que viven en las condiciones de las montañas bajas y altas de Kirguistán. Se realizó un estudio comparativo abierto de pacientes asiáticos con MAFLD con y sin diabetes mellitus tipo 2 (DM2) que viven montañas bajas y altas. En cada categoría de pacientes, se consideraron los grupos magro (IMC≤23) y obeso (IMC> 23). Se determinaron los parámetros antropométricos y bioquímicos de la sangre. El índice de fibrosis hepática se calculó usando la puntuación FIB. Se encontró que los residentes en las montañas altas con MAFLD tenían un IMC más bajo en comparación con los habitantes de las tierras bajas. Se observan niveles bajos de glucosa en sangre y HbA1c en pacientes con IMC alto que viven en áreas de gran altitud en comparación con los habitantes de tierras bajas, especialmente en combinación con DM2. En el grupo de pacientes obesos con MAFLD que viven en tierras altas, se observan colesterol total bajo, lipoproteínas de baja densidad y tasa de filtración glomerular. Se observó un alto riesgo de fibrosis en el grupo de pacientes delgados en ambas regiones. Nuestros resultados indican que el estudio del efecto de la hipoxia crónica a gran altitud en el curso de MAFLD requiere estudios prospectivos basados en la población.

Palabras clave: *Baja altitud, alta altitud, enfermedad del hígado graso asociada a disfunción metabólica.*

INTRODUCTION

In July 2020, a group of international experts proposed a new diagnosis of metabolic dysfunction-associated fatty liver disease, or metabolically associated fatty liver disease (MAFLD) for short, independent of other liver diseases, but able to include new conceptual criteria to avoid excluding certain subpopulations as a factor in alcohol consumption and infection with hepatitis viruses (1). The MAFLD definition identifies better the fatty liver group and is more practical for identifying patients with fatty liver disease at high risk of disease progression (2,3). The lack of knowledge about the features of the course of MAFLD in the Kyrgyz population, and the relevance of studying diseases in the mountains (4), prompted us to study MAFLD in people with different body weights living in the lowlands and highlands of Kyrgyzstan.

The study assessed the features of the course of or metabolically associated fatty liver disease in lean and obese patients living in the conditions of low mountains and high mountains of Kyrgyzstan.

MATERIALS AND METHODS

Place and time of the study

An open comparative study of patients with MAFLD (n = 338) living in low mountains (Bishkek, height above sea level - 750-800 m, n=137, with Diabetes mellitus 2 (DM2), n = 68, without DM2 n= 69) and high mountains (At-Bashy district, Naryn region, height above sea level - 2046-2300 m, n=201, with DM2 n=64, without DM2 – n =137) of Kyrgyzstan was carried out (Figure 1). The average age of the patients was 58 ± 0.7 years. The ratio of women and men in the low mountains group was 53.3 % and 46.7 %, respectively, and in the high mountains group – 71 % and 29 %.

Patients were recruited during outpatient examinations at the bases of the following institutions: the family medicine center (FMC) of At-Bashy district, Naryn regional FMC, the Endocrinological Center under the Ministry of Health of the Kyrgyz Republic, FMC in Bishkek. The analyzed group included outpatients who applied to the FMC from June 2019 to June 2021.

Studied populations

Two populations living in low mountains (Bishkek) and high mountains (At-Bashy district) were studied. Patients in each region were divided into the following categories: MAFLD with BMI ≤23 and BMI >23 with the Asian norm of 18.5-22.9 (5). Due to the lack of extensive research, the question of which classification should be applied to diagnose obesity in Kyrgyz remains open. Accumulated literature data indicate a higher amount of fat with low BMI and waist circumference in the Asian population, in connection with which the World Health Organization (WHO) classification was used. Because genetic factors may play a role in the development of NAFLD, only ethnic Kyrgyz were analyzed.

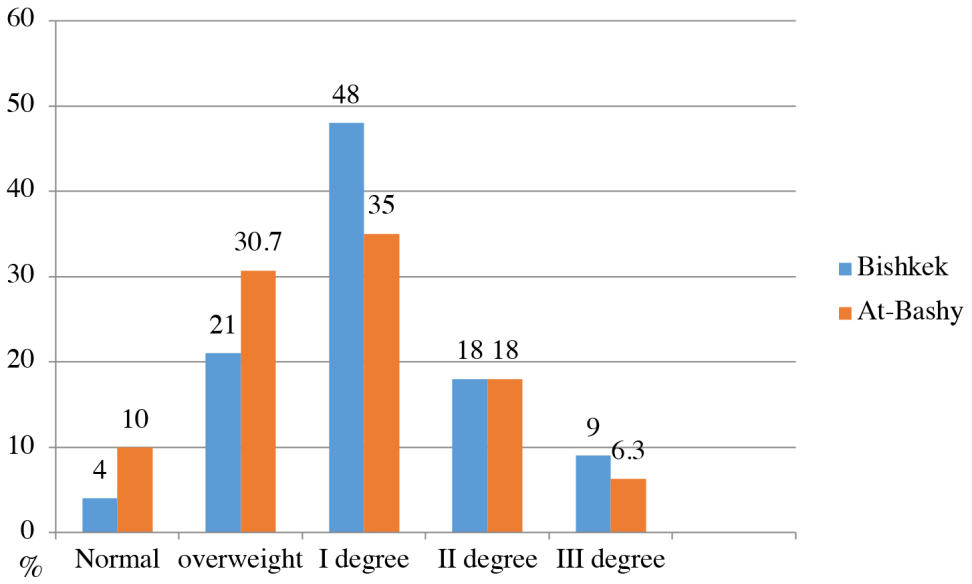

Figure 1. A schematic representation of the study design.

Inclusion criteria: overweight patients over 18 years of age with fatty liver according to liver ultrasound, low and normal weight patients with fatty liver on ultrasound with 2 or more components of the metabolic syndrome, the presence of an informed consent signed by the patient to participate in the study.

Exclusion criteria: pregnancy, breastfeeding, viral hepatitis, alcohol abuse, autoimmune hepatitis, use of drugs with hepatotoxic potential, liver storage diseases, severe physical and mental illness.

The method of forming a sample from the studied population

The analyzed group was formed by a continuous sampling method: all patients who applied during the study period with confirmed MAFLD.

Study design

An observational one-stage open comparative study was carried out according to the "case-control" principle. Patients with MAFLD in both regions (low and high mountains) were divided into 2 groups: with normal body weight (BMI <23) and with BMI>23. A comparative assessment of anthropometric parameters, percentage of fat, the structure of obesity, indicators of carbohydrate metabolism, lipid spectrum, and liver tests were carried out.

Methods

The Alcohol Use Disorders Identification Test (AUDIT) was used to detect early signs of hazardous and harmful alcohol use and detect mild dependence. The Finnish Diabetes Risk Scale FINDRISC was used to assess the risk of developing type 2 diabetes. The physical examination included the measurement of anthropometric parameters (height, body weight, waist circumference (WC)), the calculation of body mass index (BMI), the percentage of fat in the body of skeletal muscle mass (SMM), and blood pressure (6). According to WHO gradations (2000), the degree of obesity was assessed by BMI. Given the high value of measuring the fat percentage, and the lack of access to its determination by bioimpedance analysis (7), we

used the calculation formulas: for women, % body fat = 100 – (0.11077 x (WC, см) – 0.17666 x (Hight, м) +0.14354 x (weight, kg) + 51.033); for men, = 0.31457 x (WC, см) – 0.10969 x (weight, kg) + 10.834, with the subsequent calculation of SMM using the formula: SMM = Current Weight - (Current Weight x Current Body Fat %) (8). The US is thus suitable as a screening method with respect to fatty liver disease. All patients underwent ultrasound of the liver. Ultrasound is suitable as a screening method for fatty liver disease as it has good sensitivity (about 85 %) with a specificity of approximately 94 %.

Blood samples for research were taken in the morning on an empty stomach after at least 12 hours of fasting. Glycated hemoglobin (HbA1C) was determined using the D10 analyzer, which is based on the reference method - high-pressure liquid ion exchange chromatography (HPLC). The following blood serum parameters were determined on the BS-200 biochemical analyzer: glucose, total cholesterol (TC), high-density lipoproteins (HDL), low density lipoproteins (LDL), triglycerides (TG), levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein, creatinine, complete blood count with platelets (PLT). Liver fibrosis index was calculated using the formula FIB-4 = Age (years)×AST (U/L)/(PLT(109/L)×ALT1/2 (U/L).

Statistical analysis

The analysis of the obtained results was carried out using the statistical package of application programs SPSS 16.0 for Windows. To assess the probability that the analyzed samples belong to general populations with a normal distribution, the Kolmogorov-Smirnov test was used. Given the normal distribution of sample data ($p>0.05$), Student's t-test was used to compare them. The significance of differences between groups was determined by nonparametric statistical methods, and the results of descriptive processing were presented as the mean value and error of the mean value (M±m). The Pearson correlation test was used to determine the relationship between variables. A "p" value <0.05 was considered statistically significant at a 95 % confidence level.

Ethical review

The study was carried out in compliance with the principles of humanity outlined in the directives of the European Community (86/609/eec) and the Declaration of Helsinki. The study was approved by the local ethics committee of the scientific and production association "preventive medicine" of the Ministry of Health of the Kyrgyz Republic (Conclusion no. 6 dated October 08, 2019).

RESULTS AND DISCUSSION

Data on the structure of obesity in the studied groups with MAFLD are presented in Figure 2. It should be noted that residents of the high mountains with MAFLD had a lower BMI compared to the lowlanders. Normal body weight (BMI<23) was observed in 10 % of highlanders and only in 4 % of Bishkek residents. Among residents of high mountains with MAFLD, the prevalence of obesity was 59.3 % versus 75 % of residents of low mountains.

A study of body fat percentage in men with MAFLD revealed a trend towards higher rates, regardless of body weight and region of residence (Figure 3). Interestingly, the percentage of fat significantly exceeded the acceptable level (18-25 %) not only in obese men of low and high mountains (33.8 % and 33.5 %) but higher figures were also observed in men with normal weight, 32.6 % and 30.4 %, respectively. In obese women, this indicator was within acceptable limits (21-31 %), and thin women showed borderline values of body fat percentage in both regions (30.1 % and 31.8 %).

Table 1 shows a statistically significant low blood glucose level in patients with high BMI living in the highlands, both in the group of patients with DM2 or without DM2, compared with the lowlanders ($p<0.05$). It is known that the level of glycated hemoglobin (HbA1c) is an indicator of the severity and degree of compensation of carbohydrate metabolism disorders. In the analyzed groups, not more than 25 % of DM2 individuals reached the target values of glycohemoglobin at different

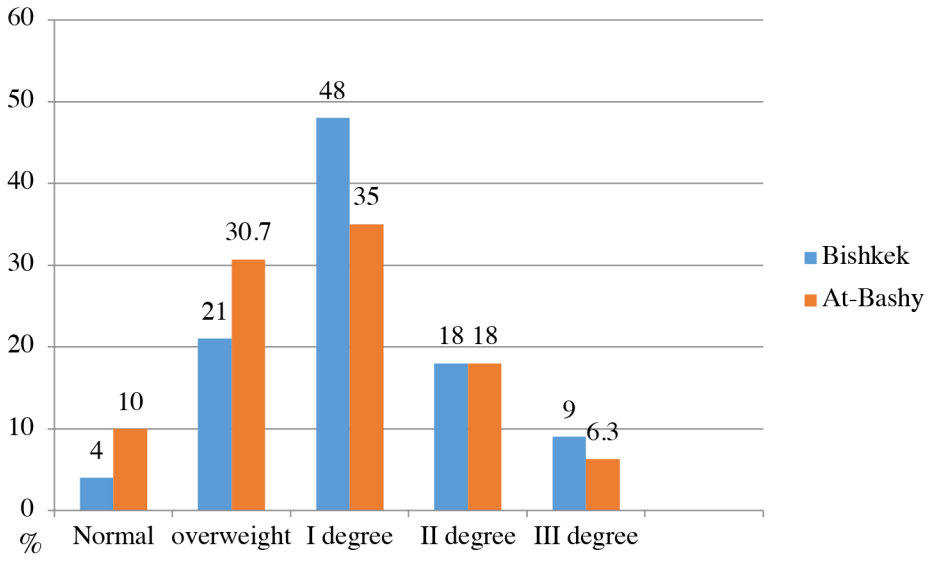

Figure 2. The structure of obesity in residents of low mountains (Bishkek, n=137) and high mountains (At-Bashy village, n=201) with MAFLD according to body mass index (BMI). Data are expressed in %.

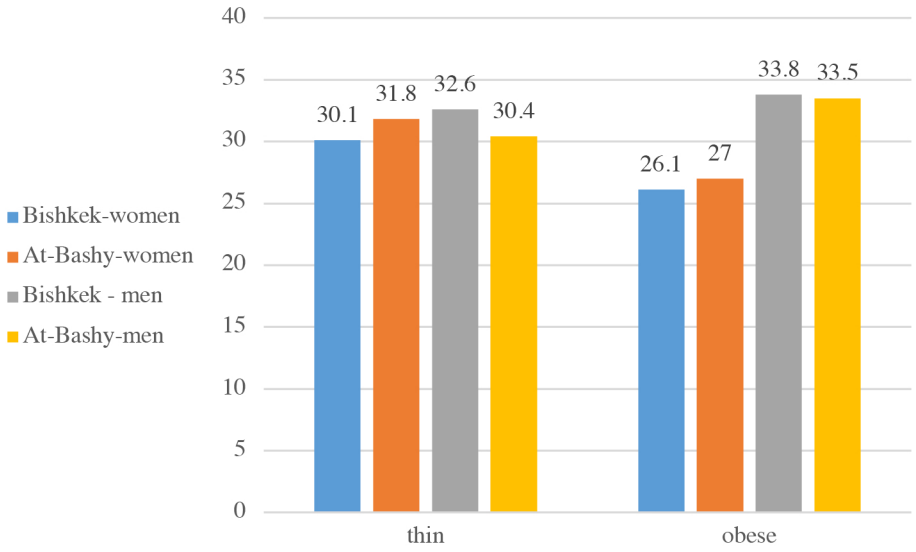

Figure 3. The fat percentage of men and women with MAFLD living in low mountains (Bishkek, n=137) and high mountains (At-Bashy village, n=201). Data are expressed in %.

heights (less than 7.0 %). Statistically low HbA1c was observed in obese highlanders with DM2 compared to residents of Bishkek. The combination of fatty liver, overweight and DM2 demonstrate high numbers of TC, TG and LDL. However, statistically significant low TC levels were found only in the overweight group without DM2 ($p<0.05$). Changes in TG and total protein were ambiguous. It is interesting to note that MAFLD with DM2 in high altitude conditions

Table 1. Blood biochemical parameters in patients of low and high mountains with MAFLD with different BMI, with and without DM2, M±m.

Indicator	Bishkek, 750-800 m. (n=69)		At-Bashy district, 2046-2300 m. (n=137)		Bishkek, 750-800 m. (n=68)		At-Bashy district, 2046-2300 m. (n=64)		p-value
	MAFLD				MAFLD with DM 2				
	BMI≤23	BMI >23	BMI ≤23	BMI >23	BMI ≤23	BMI >23	BMI ≤23	BMI >23	
	n=10	n=59	n=29	n=108	n=13	n=55	n=5	n=59	n=33
	1	2	3	4	5	6	7	8	8
Fasting blood glucose mmol/L	4.53±0.03	5.28±0.09	4.45±0.16	4.88±0.16	9.27±1.7	10.2±0.45	8.0±0.1	8.71±0.41	P1-2 <0.001 P1-3 >0,05 P2-4 <0.05 P5-7 >0,05 P6-8 <0.05
HbA1c %	5.8±0.1	6.17±0.5	5.9±0.2	5.8±0.3	6.51±0.6	9.65±0.31	6.3±0.3	8.4±0.42	P1-3 >0.05 P2-4 >0.05 P5-7 >0.05 P6-8 <0.05
TC mmol/L	4.09±0.01	5.38±0.13	4.15±0.2	4.4±0.1	4.95±0.37	5.56±0.17	5.0±0.1	5.15±0.16	P1-3> 0.05 P2-4< 0.001 P6-8> 0.05
TG mmol/L	1.07±0.1	1.82±0.11	0.82±0.16	1.4±0.25	1.73±0.18	2.49±0.26	2.31±0.11	1.68±0.29	P1-2 <0,001 P1-3 >0.05 P2-4 >0.05 P5-7 <0.05 P6-8 <0.05
HDL mmol/L	1.0±0.1	1.1±0.03	1.2±0.11	1.6±0.28	1.0±0.14	1.22±0.09	1.2±0.08	1.32±0.13	P1-3 >0.05 P2-4 >0.05 P3-7 >0.05 P4-8 >0.05
LDL mmol/L	1.59±0.1	3.72±0.19	2.57±0.18	4.32±0.38	3.0±0.41	3.61±0.24	2.8±0.12	2.86±0.23	P1-2 <0,001 P1-3 <0.001 P2-4 >0.05 P1-5 <0.05 P6-8 <0.05
Total bilirubin μmol/L	14.7±0.3	13.4±1.05	15.08±1.57	12.8±0.42	11.7±2.5	15.47±1.2	16.5±0.43	13.04±0.7	P1-3 >0.05 P2-4 >0.05 P3-7 >0.05 P4-8 >0.05
Total protein g/L	70.0±0.1	71.3±2.1	62.7±1.6	65.0±1.3	55.4±1.3	69.4±1.5	63.1±0.25	68.2±3.2	P1-3 <0.05 P2-4 <0.05 P5-7 <0.05 P6-8 >0.05
ALT U/L	36.0±0.1	40.2±3.1	31.1±4.07	33.5±2.8	28.4 ±6.3	38.9±3.5	32.0±7.0	34.7±2.8	P1-3 >0.05 P2-4 >0.05 P3-7 >0.05 P4-8 >0.05
AST U/L	30.0±0.1	35.0±3.0	33.4±4.1	30.5±1.5	33.9±3.7	36.3±3.1	43.3±11.0	31.4±1.9	P1-3 >0.05 P2-4 >0.05 P3-7 >0.05 P4-8 >0.05
FIB-4	0.73±0.1 Low risk	1.12±0.09 Low risk	1.09±0.13 Low risk	1.46±0.13 Intermediate risk	2.13±0.3 Intermediate risk	1.62±0.19 Intermediate risk	2.37±1.2 Intermedi-ate risk	1.66±0.2 Intermedi-ate risk	P1-2 <0,05 P1-3 <0.05 P2-4 <0.05 P1-5 <0.001 P5-7 >0.05
Creatinine mmol/L	52.7±0.2	80.08±4.5	87.7±312.8	91.7±3.3	85.6±12.3	86.0±2.8	61.2±1.2	94.4±4.4	P1-3 <0.05 P2-4 <0.05 P5-7 >0.05 P6-8 >0.05
GFR	91.8±1.2	80.4±3.4	70.2±9.5	68.0±3.7	85.6±6.7	73.3±2.6	81.4±12.0	66.0±3.4	P1-3 <0.05 P2-4 <0.05 P5-7 >0.05 P6-8 >0.05

is represented by lower LDL values ($p<0.05$). There were no significant differences in the level of ALT and AST between the regions, although lower values were noted among residents of the highlands. The combination of MAFLD and DM2 increased the risks from low to intermediate. However, the highest FIB-4 numbers were noted in the group of lean patients in both regions. MAFLD among residents of highlands was distinguished by statistically significant low GFR with $p<0.05$.

In our patients with MAFLD, there was a statistically significant direct strong relationship between BMI and SMM ($r = 0.918$, $p<0.001$) (Figure 4). There was a statistically significant inverse strong relationship between SMM and fat percentage ($r = -0.973$, $p<0.001$) (Figure 5). A moderate positive relationship was found between FIB-4 and FINDRISC ($r = -0.319$, $p<0.001$) and a moderate negative relationship between FINDRISC and fat percentage ($r = -0.467$, $p<0.001$).

Patients with MAFLD have shown a significantly increased risk of developing chronic kidney disease (CKD), arterial hypertension (AH), type 2 diabetes mellitus (DM2), cardiovascular disease (CVD), multiple sclerosis, hyperuricemia, and even COVID-19 (3,9-14). In non-obese people with MAFLD, the severity of metabolic disorders is also significantly higher than in people without MAFLD (9). A hallmark of the adipose tissue of MAFLD in non-obese individuals is high metabolic activity. These patients are more predisposed to insulin resistance (IR), abnormal glucose metabolism, and a higher risk of developing diabetes (15-17). It has been established that fatty degeneration of the liver increases the risk of developing diabetes in men with normal body weight (BMI 20–22.9 kg/m^2), while in women the risk of developing DM2 is associated with increased weight (18). The results of the body composition analysis highlight the importance of assessing the balance between skeletal muscle mass and body fat percentage, and not just assessing BMI. A low BMI and a high-fat percentage increase the risk of developing sarcopenia, especially in patients with concomitant DM2 (19). Sarcopenia may also independently associate with the development of fibrosis in these patients (20).

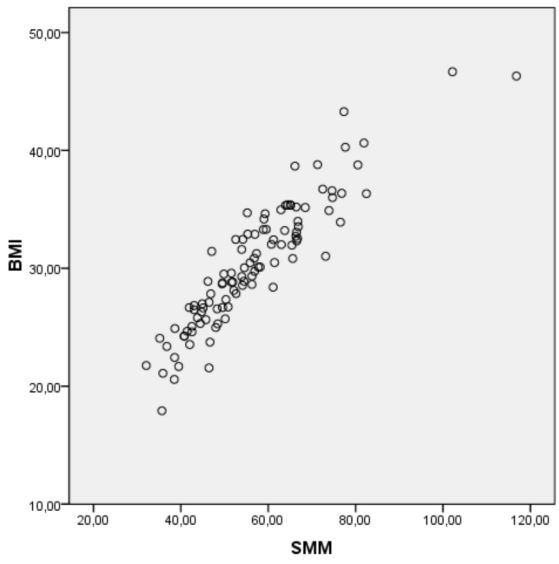

Figure 4. Correlation between BMI and SMM (skeletal muscle mass) residents of low mountains (Bishkek, n=137) and high mountains (At-Bashy village, n=201) ($r = 0.918$, $p<0.001$).

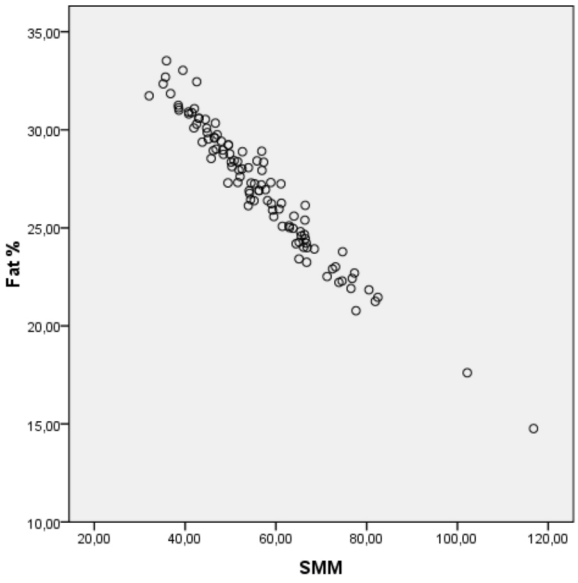

Figure 5. Correlation between fat percentage and SMM (skeletal muscle mass) residents of low mountains (Bishkek, n=137) and high mountains (At-Bashy village, n=201) ($r = -0.973$, $p<0.001$).

Mountains occupy almost 27 % of the earth's land surface, 15 % of the world's population lives in mountainous regions. The main factor affecting the health of the population in high mountains is hypoxia. The state in Central Asia - the Kyrgyz Republic has more than six million people, and 41 % of the population lives at an altitude of more than 1000 m above sea level (21). Therefore, the study of the course of MAFLD in people living in high mountains is relevant (4).

There are no publications on the characteristics of the course of MAFLD in humans under conditions of high-mountain hypoxia, and there are few experimental studies of fatty liver in conditions of chronic hypoxia (22). The evidence indicates that high-altitude hypoxia increased expression of genes associated with mitochondrial biogenesis, mitochondrial respiratory function, and mitochondrial DNA content in a group of C57BL/6J mice on a high-fat diet at 4,300 m altitude compared to animals on the same diet, kept at an altitude of 50 m. A significant increase in antioxidant activity and a decrease in the production of reactive oxygen species were also found. It has been hypothesized that chronic hypoxia in high altitude conditions may have a protective effect against the development non-alcoholic fatty liver disease (22). In our studies, this assumption takes place in low numbers of TC and LDL in highlanders.

Directions for further research's

The study of MAFLD in people living at different altitudes is carried out for the first time, which clearly dictates the expediency of further prospective studies of the course of MAFLD in the high mountain population.

CONCLUSION

Residents of the high mountains with MAFLD had a lower BMI compared to the lowlanders. Low blood glucose and HbA1c levels are observed in patients with high BMI living in high-altitude areas compared with lowlanders, especially in combination with T2DM. In the group of obese patients with MAFLD living in highlands, low TC, LDL, and GFR are observed. A high risk of fibrosis was noted in the group of lean patients in both regions.

Acknowledgments

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REFERENCES

1. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020;73(1):202-209.
2. Yamamura S, Eslam M, Kawaguchi T, Tsutsumi T, Nakano D, Yoshinaga S, et al. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. Liver Int. 2020;40(12):3018-3030.
3. Lin S, Huang J, Wang M, Kumar R, Liu Y, Liu S, et al. Comparison of MAFLD and NAFLD diagnostic criteria in real world. Liver Int. 2020;40(9):2082-2089.
4. Toktogulova N, Tuhvatshin R. Features of the course of non-alcoholic fatty liver disease in experimental animals at high altitudes. Open Access Maced J Med Sci. 2021;9(A):1092-1096.
5. World Health Organization. Obesity: preventing and managing the global epidemic (Internet). Geneva: World Health Organization; 2000. Available from: https://apps.who.int/iris/handle/10665/42330
6. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves JW, Hill MN, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005;45(1):142-161.
7. Fukuoka Y, Narita T, Fujita H, Morii T, Sato T, Sassa MH, et al. Importance of physical evaluation using skeletal muscle mass index and body fat percentage to prevent sarcopenia in elderly Japanese diabetes patients. J Diabetes Investig. 2019;10 920:322-330.
8. Martirosov EG, Nikolaev DV, Rudnev SG. Technologies and methods for determining the

composition of the human body. Moscow: Nauka, 2006.

9. Sun DQ, Jin Y, Wang TY, Zheng KI, Rios RS, Zhang HY, et al. MAFLD and risk of CKD. Metabolism. 2021;115:154433.
10. Lim GEH, Tang A, Ng CH, Chin YH, Lim WH, Tan DJH, et al. An observational data meta-analysis on the differences in prevalence and risk factors between MAFLD vs NAFLD. Clin Gastroenterol Hepatol. 2021;S1542-3565(21)01276-3.
11. Guerreiro GTS, Longo L, Fonseca MA, de Souza VEG, Álvares-da-Silva MR. Does the risk of cardiovascular events differ between biopsy-proven NAFLD and MAFLD? Hepatol Int. 2021;15(2):380-391.
12. Lee H, Lee YH, Kim SU, Kim HC. Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: a nationwide cohort study. Clin Gastroenterol Hepatol. 2021;19(10):2138-2147.
13. Chen YL, Li H, Li S, Xu Z, Tian S, Wu J, et al. Prevalence of and risk factors for metabolic associated fatty liver disease in an urban population in China: A cross-sectional comparative study. BMC Gastroenterol. 2021;21(1):212.
14. Sharma P, Kumar A. Metabolic dysfunction associated fatty liver disease increases risk of severe Covid-19. Diabetes Metab SynDr. 2020;14(5):825-827.
15. Choi JH, Rhee EJ, Bae JC, Park SE, Park CY, Cho YK, et al. Increased risk of type 2 diabetes in subjects with both elevated liver enzymes and ultrasonographically diagnosed nonalcoholic fatty liver disease: A 4-year longitudinal study. Arch Med Res. 2013;44(2):115-120.
16. Succurro E, Marini MA, Frontoni S, Hribal ML, Andreozzi F, Lauro R, et al. Insulin secretion in metabolically obese, but normal weight, and in metabolically healthy but obese individuals. Obesity. 2008;16(8):1881-1886.
17. Sinn DH, Kang D, Cho SJ, Paik SW, Guallar E, Cho J, et al. Lean non-alcoholic fatty liver disease and development of diabetes: A cohort study. Eur J Endocrinol. 2019;181(2):185-192.
18. Narisada A, Shibata E, Hasegawa T, Masamura N, Taneda C, Suzuki K. Sex differences in the association between fatty liver and type 2 diabetes incidence in non-obese Japanese: A retrospective cohort study. J Diabetes Investig. 2021;12(8):1480-1489.
19. Seo DH, Lee YH, Park SW, Choi YJ, Huh BW, Lee E, et al. Sarcopenia is associated with non-alcoholic fatty liver disease in men with type 2 diabetes Diabetes Metab. 2020;46(5):362-369.
20. Sung MJ, Lim TS, Jeon MY, Lee HW, Kim BK, Kim DY, et al. Sarcopenia is independently associated with the degree of liver fibrosis in patients with type 2 diabetes mellitus. Gut Liver. 2020;14(5):626-635.
21. Aidaraliev A, Jangaracheva M, Shanazarov A, Shuler M, Namazbekov B, Abylgazieva A, et al. National human development report. Human development in mountain regions of Kyrgyzstan (Internet). Bishkek: National centre for mountain regions development in the Kyrgyz Republic; 2002. Available from: https://hdr.undp.org/system/files/documents//kyrgyzstan2002en1pdf.pdf
22. Song K, Zhang Y, Ga Q, Bai Z, Ge RL. High-altitude chronic hypoxia ameliorates obesity-induced non-alcoholic fatty liver disease in mice by regulating mitochondrial and AMPK signalling. Life Sci. 2020;252:117633.