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Predictors of NAFLD rapidly progression in type 2 diabetes patients

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Abstract

The goal of our case-control research was to study the associations between speed progression of NAFLD and risk factors among patients with the type 2 diabetes. 82 patients with type 2 diabetes and NAFLD took part in the study. We divided the patients into two groups: with speed (n=38) and slow (n=44) progression of fibrosis. The results of our study revealed the definitive associations between speedy progression of fibrosis and the level of insulin, ACT and alkaline phosphatase. We found the direct relations of speed fibrosis progression with the level of TC and TG. We also showed the significant influence the inflammatory mechanisms have on fibrosis progression (direct definitive relations between fibrosis and the consistence of cytokines - IL-1β (OR 1,017; p=0,035), TNF-α (OR 0,004; p=0,049) and the inverse relations between the speed progression of fibrosis and the consistence of IL-6 (OR 0,94; p=0,058).

Using the results of a step-by-step multivariate regression analysis we created the final clinical model of fibrosis speed progression among the type two diabetes patients and people affected with NAFLD, which includes six prognostic variables: TG, alkaline phosphatase, insulin, IL-6, TNF-α and adiponectin.

Keywords: diabetes mellitus type two; nonalcoholic fatty liver disease; fibrosis

Abbreviations: ALT, Alanine transaminase, AST, Aspartate transaminase, BMI, Body mass index, GGT, Gamma-glutamyl transferase, HDL-C, cholesterol of high density lipoproteins, LDL-C, cholesterol of low density lipoproteins, OR, odds ratio, TG, triglycerides, TC, total cholesterol.

Non-Alcoholic Fatty Liver Disease or NAFLD typifies by a significant variability and level of clinical aspects severity, as well as its speedy progression (1-6). However, the factors that develop NAFLD progression up to Nonalcoholic Steatohepatitis (NASH) are yet to be defined.

Aim: To study the associations between the speedy progression of the disease and the number of clinic-demographic, metabolic and pro-inflammatory factors of risk within the patients diagnosed with type 2 diabetes and NAFLD.

Material and method

82 patients with the type 2 diabetes and NAFLD took part in the case-control studies. Participants were chosen by their age over 18-years-old, the patients' consent to participate in the study, diagnosed type 2 diabetes and NAFLD. The exclusion criteria were the existence of chronic viral, autoimmune and drug-induced hepatitis, liver damage, caused by alcohol overconsumption. NAFLD was diagnosed within the recommendations of the American Gastroenterological Association (AGA) and the American Association for the Study of Liver Diseases (AASLD) [7]. The diagnosis verification was based on the analysis of the clinical progression of the disease, laboratory findings, complex liver ultrasound [8, 9].

The speedy progression of fibrosis among the type 2 diabetes patients was calculated with the use of a modification T. Poynard formula (liver fibrosis stage within the combined scale FIB-4 and NAFLD score divided by the diabetes duration, was measures in units per year (units/year).

Median rate of fibrosis progression (RPF) among the type 2 diabetes patients was 0,167 (0,05-0,5) units/year, therefore the patients were divided into two subgroups: group 1 with the slow progression of liver fibrosis (RPF≤0,167 units/year) (n=44) and the group 2 with the speedy progression of liver fibrosis (RPF>0,167 units/year) (n=38).

We analyzed the following groups of variables: biological (gender, age), behavioral (ability to stick to a healthy diet under doctor's recommendation), comorbidity, as well as laboratory findings (aminotransferase activity, GGT, alkaline phosphatase, total bilirubin level and serum albumin), carbohydrate (BMI, insulin), lipidic (TG, TC, LDL-C and HDL-C), cytokine profile (IL-6, IL-8, IL-1β, TNF-α).

The detailed analysis of the clinic-demographic criteria showed that neither gender, nor age of a patient over 65, does not associate with the speedy progression of fibrosis among the type 2 diabetes patients with the NAFLD (table 1). We have not gotten the positive relations between BMI and the speedy progression of fibrosis. Although Vilar-Gomez E. has proved there is a high prognostic value for the NASH fibrosis among the patients of such criteria as weight and age [10].

Table 1 Associations between speedy progression of fibrosis and clinic-demographic characteristics among the type two diabetes patients diagnosed with NAFLD with the univariate logistic regression analysis

Characteristics	Type 2 diabetes patients with NAFLD		p	OR, (95% CI)	P value
	Group 1	Group 2			
Female gender (0 – no, 1 – yes), n (%)	26 (59,1)	19 (50,0)	0,410	0,69 (0,29-1,67)	0,410
Patients over 65 y.o. (0 – no, 1 – yes), n (%)	19 (43,2)	14(36,8)	0,560	0,77 (0,31-1,87)	0,560
Obesity BMI≥35 kg/м^2 (0 – no, 1 – yes), n (%)	26 (59,1)	28 (73,7)	0,166	1,93 (0,76-4,96)	0,167
BMI, kg/м^2, median (interquartile range)	36,16 (31,8-39,83)	37,8 (32,72-41,77)	0,123	1,05 (0,97-1,14)	0,201
Waist circumference, cm, median (interquartile range)	114,5 (101,5-125)	116 (108-127)	0,256	1,02 (0,97-1,06)	0,385
Diet violation (0 – no, 1 – yes), n (%)	6 (13,95)	14 (36,84)	0,017	3,59 (1,21-10,65)	0,021

From the number of comorbid conditions that come with speedy fibrosis progression among patients with the type 2 diabetes III-IV stage nephropathy, irritable bowel syndrome and diet violation definitely associate with the disease. To our opinion, III-IV stage nephropathy can have common pathogenetic mechanisms of fibrosis formation both in kidneys and liver.

During our study we found out the definite relations between speedy progression of fibrosis and insulin level in blood of patients with the type 2 diabetes. Our finding proves the important role of hyperinsulinemia in the progression of the mentioned condition. Also the median value of the ACT level was definitely higher among type 2 diabetes patients with the speedy progression of fibrosis. Type 2 diabetes patients from the speedy fibrosis group had significantly higher median value of the alkaline phosphatase level than the patients of the

other group. The study also proved the associations between speedy progression of fibrosis and such metabolic biomarkers as insulin, ACT, and alkaline phosphatase (table 2).

Table *2* - Associations between speedy progression of NAFLD and laboratory values of patients with the type 2 diabetes during univariate logistic regression analysis

Laboratory values	Patterns in groups median (interquartile range)		OR, (95% CI)	P value
	Group 1	Group 2		
Insulin, mkIU/ml	13,85 (9,4-18,6)	17,6 (13,4-23,9)	1,06 (0,99-1,13)	0,051
ALT, IU/L	68,65 (61,4-75)	69,7 (60-84,1)	1,00 (0,97-1,03)	0,895
ACT, IU/L	55,8 (49,15-64,8)	71,6 64,2-84,2)	1,08 (1,04-1,13)	<0,001
Bilirubin, mkmol/L	18,4 (16,6-22,2)	19,3 (17,9-21,4)	1,05 (0,94-1,17)	0,384
Alkaline phosphatase, IU/L	180 (165-210)	232,5 (210-250)	1,01 (1,00-1,03)	0,025
GGT, IU/L	53 (46-64,5)	56 (47-63)	1,01 (0,97-1,05)	0,550
TG, mmol/l	3,65 (2,7-4,36)	4,14 (3,7-4,56)	2,14 (1,21-3,78)	0,008
TC, mmol/l	6,5 (5,9-6,9)	7,15 (6,1-7,6)	1,98 (1,15-3,42)	0,014
LDL-C, mmol/l	2,65 (1,95-3,83)	2,85 (2,3-3,51)	0,95 (0,69-1,31)	0,785
HDL-C, mmol/l	1,6 (1,2-2,0)	1,3 (1,2-1,7)	0,622 (0,24-1,62)	0,330

The obtained data give us a reason to make a conclusion that inflammatory and cholestatic conditions in liver can provoke the speedy progression of fibrosis among type 2 diabetes patients.

Lipemic index study of patients with the type 2 diabetes demonstrated the patients from the speedy progression group had significantly higher levels of cholesterol and triglycerides than the patients from the slow progression group of the disease. With the help of univariate logistic regression analysis, we found the direct associations of fibrosis speedy progression with TC та TG levels among type 2 diabetes patients.

We assumed the patients with type 2 diabetes inflammation can be a trigger of NAFLD's speedy progression into fibrosis. We studied the associations between the speedy fibrosis progression and the level of pro-inflammatory cytokines (IL-1β, IL-8, TNF-α), as well as the level of pro-inflammatory cytokine IL-6, although the mentioned cytokine has anti-inflammatory capacity (table 3).

Table 3 - Associations between speedy progression of fibrosis and particular cytokines among the type 2 diabetes patients during the univariate logistic regression analysis

Cytokines (pg/ml)	Sign in groups, median (interquartile range)		OR, (95% CI)	p-value
	Group 1	Group 2		
IL-1β	35,9 (25,6-59,7)	47,9 (32,4-94,2)	1,02 (1,00-1,033)	0,035
IL-8	32,4 (24,4-41,9)	35,05 (25,5-46,6)	1,011 (0,99-1,034)	0,310
TNF-α	184,8 (164,3-249,7)	254,0 (184,3-317,1)	1,004 (1,00-1,008)	0,049
IL-6	13,8 (8,8-20,75)	9,8 (8,1-13,0)	0,94 (0,88-1,00)	0,058

We demonstrated the major role of inflammatory mechanisms in realization of the speedy progression of fibrosis, and that is confirmed by the existence of a associations between the following and the substance of proinflammatory cytokines - IL-1β (OR 1,017; p=0,035), TNF-α (OR 0,004; p=0,049), and inverse association between the speedy progression of fibrosis and values of pro-/anti-inflammatory cytokine IL-6 (OR 0,94; p=0,058).

Other scientists have also emphasized the role of inflammatory in fibrosis progression, but those studies were conducted among the ordinary patients, not the ones affected by type 2 diabetes. A number of authors claimed liver fibrosis is the result of a lingering healing process [11-15].

Identified risk factors found during the univariate logistic regression analysis were included into the step-by-step multivariate regression analysis. According to the results of the latter, after the correction on the number of factors type 2 diabetes patients with NAFLD had independent factors for speedy progression of fibrosis if they had high levels of TNF-α, insulin, TG, alkaline phosphatase and lower levels of adiponectin and IL-6.

Table 4- Risk factors of speedy liver fibrosis progression among patients with the type 2 diabetes and NAFLD defined during the multivariate logistic regression analysis

Risk factors	OR	95 % CI	P value	β	m
IL-6, pg/ml	0,78	0,67-0,91	0,001	-0,24	0,08
Adiponectin, mkg/ml	0,068	0,009-0,47	0,007	-2,67	0,98,
TNF-α, pg/ml	1,01	1,00-1,020	0,028	0,011	0,004
Insulin, mkIU/ml	1,14	1,01-1,28	0,031	0,131	0,061
TG, mmol/l	3,33	0,98-11,33	0,054	1,2	0,624
Alkaline phosphatase, IU/L	1,01	1,000-1,025	0,010	0,014	0,005

We detected high operational characteristics of the final clinical model, that includes six prognostic variables: TG, alkaline phosphatase, insulin, IL-6, TNF-α and adiponectin. It also has high operational characteristics, such as: sensitivity – 63,33 %, specificity– 94,59 %, positive predicative value - 90,48%, negative predicative value– 76,09% and corresponds to the criteria of a very good prognostic ability (area under ROC curve – 0,9423).

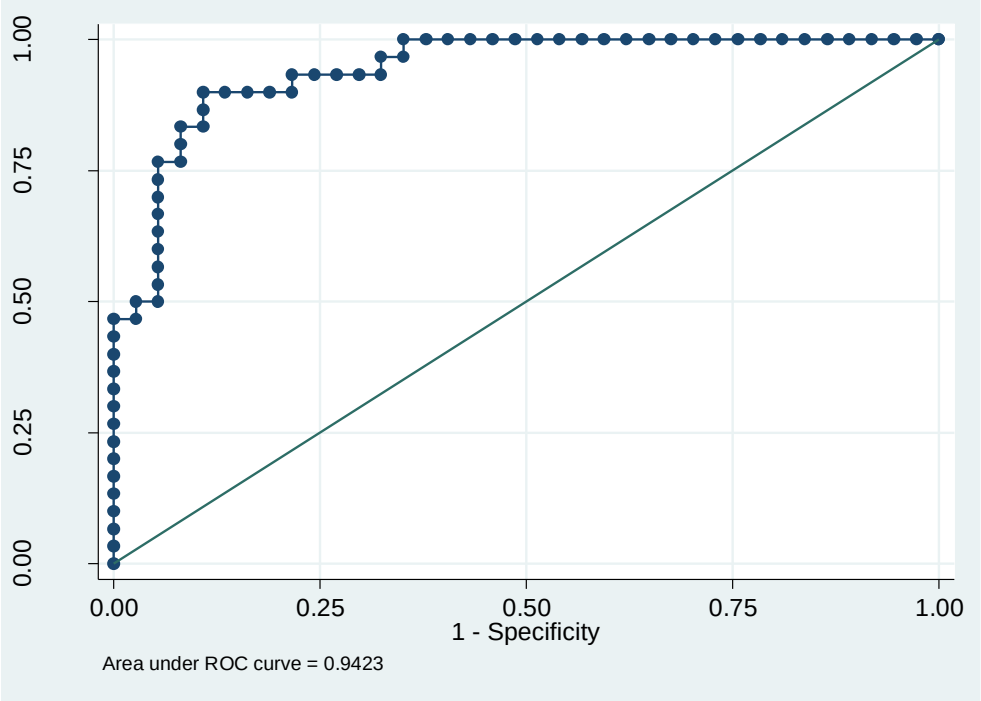

Fig. 1. ROC-curve of the prognostic model of liver fibrosis speedy progression among patients with type 2 diabetes

Thus our study showed the use of the proposed prognostic model on practice will give doctors the ability to predict the prevalence of liver fibrosis speedy progression among the type 2 diabetes patients, and define the priority order of medicines and preventive actions prescription.

References

1. Noureddin M, Vipani A, Bresee C, Todo T, Kim IK, Alkhouri N, Setiawan VW, Tran T, Ayoub WS, Lu SC, Klein AS, Sundaram V, Nissen NN. NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications For Liver Transplant and Ethnic and Gender Variances. Am J Gastroenterol. 2018;113:1649-59.

2. Suzuki A, Diehl AM. Nonalcoholic Steatohepatitis. Annu Rev Med. 2017;68:85-98.

3. Setiawan VW, Stram DO, Porcel J, Lu SC, Le Marchand L, Noureddin M. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multiethnic cohort. Hepatology. 2016;64:1969-77.

4. Younossi ZM. Non-alcoholic fatty liver disease - A global public health perspective. J Hepatol. 2019;70:531-44.

5. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, Sebastiani G, Ekstedt M, Hagstrom H, [et al]. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology. 2017;65(5):1557-65. doi: 10.1002/hep.29085. Epub 2017 Mar 31.

6. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018;24:908-22.

7. 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;64:1388–402.

8. Bugianesi E. Non-alcoholic steatohepatitis and cancer. Clinics in Liver Disease. 2007;11(1):191–207.

9. Tarantino G, Conca P, Pasanisi F, Ariello M, Mastrolia M, Arena A, Tarantino M, [et al.]. Could inflammatory markers help diagnose nonalcoholic steatohepatitis? Eur J Gastroenterol Hepatol. 2009; 21(5):504-11. doi: 10.1097/MEG.0b013e3283229b40

10. Vilar-Gomez E, Yasells-Garcia A, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, et al. Development and validation of a noninvasive prediction model for nonalcoholic steatohepatitis resolution after lifestyle intervention. Hepatology 2016;63:1875–87.

11. Popov Y, Schuppan D. Targeting liver fibrosis: Strategies for development and validation of antifibrotic therapies. Hepatology 2009;50:1294–306.

12. Friedman SL, Sheppard D, Duffield JS, Violette S. Therapy for fibrotic diseases: nearing the starting line. Sci Transl Med 2013;5:1–17.

13. Rockey DC, Bell PD, Hill JA. Fibrosis–a common pathway to organ injury and failure. N Engl J Med 2015;372:1138–49.

14. Friedman SL, Trautwein C, Schuppan D, Pinzani M. Hepatic fibrosis: Concept to treatment. J Hepatol 2015;62:S15–24.

15. Fallowfield JA. Future mechanistic strategies for tackling fibrosis–an unmet need in liver disease. Clin Med (Lond) 2015;15:83–87.