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Role of fatty acids in pathogenetic mechanisms of NAFLD progression among 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 the level of fatty acids among patients with the type 2 diabetes. All patients were divided into two groups: with speed (n=38) and slow (n=44) progression of fibrosis. We studied the level of saturated, monounsaturated and polyunsaturated fatty acids and their rate. Our study showed higher median value of sum of saturated fatty acids level in the group of patients with speed progression of fibrosis (51,6% and 45,75%, p=0,001) and lower median value of arachidonic acids than in the group of patients with slow progression of fibrosis (10,5 and 11,5 in the group of slow fibrosis progression, p=0,049). In the group of patients with speed fibrosis progression saturated fatty acids prevailed unsaturated fatty acids (Me=1,02). According to our data, the risk factor of speed progression of fibrosis among patients with type 2 diabetes and NAFLD, is the rate of saturated and unsaturated fatty acids. We found the significant associations between the rate of saturated and unsaturated fatty acids and the speed progression of fibrosis (OR 77,3; p=0,004).

Abbreviations: BMI, body mass index, IR, insulin resistance, NAFLD, nonalcoholic fatty liver disease, OR, odds ratio, FFA, free fatty acids, FA, fatty acids, LDL, low density lipoproteins, RPF, median rate of fibrosis progression, TG, triglycerides

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

Nonalcoholic fatty liver disease is the most common chronic liver disease and is characterized by excess TG accumulation within the liver. It is associated with obesity, type 2 diabetes and dyslipidemia, and commonly occurs in the setting of insulin resistance (IR) [1]. NAFLD encompasses a spectrum of liver histopathologies from simple hepatic steatosis, often referred to as non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), which hepatic steatosis is accompanied by inflammation, cell death and fibrosis [2]. Although multiple factors lead to hepatic steatosis, circulating FA are the main source of hepatic lipids in NAFLD [3]. In the setting of overnutrition and obesity, hepatic fatty acid metabolism is altered, commonly leading the accumulation of triglycerides within hepatocytes.

The overflow of FA derived from excessive lipolysis in the adipose tissue contributes to the pathogenesis of insulin resistance in mice and humans [4], leading to both type 2 diabetes [5] and NAFLD [6, 7].

Under normal circumstances on a daily basis, the liver processes large quantities of FA, but stores only small amounts in the form of TG, with steady state TG contents of less than 5% [8]. This is because the rates of acquisition of FA by uptake from the plasma and from *de novo* synthesis within the liver are balanced by rates of FA oxidation and secretion into plasma as TG-enriched very low-density lipoprotein (VLDL-TG). The relatively small quantities of TG stored within the liver are localized in cytoplasmic lipid droplets.

A variety of endogenous and exogenous sources provide fatty acids that can be assembled into to triglycerides within the liver in health and disease [9, 10].

Multiple hepatocellular mechanisms regulate fatty acid uptake, synthesis, transport, and oxidation [11].

The findings, mentioned higher, prove that different persons can change the basic processes, that regulate homeostasis of FA in different way, and have different chances for NAFLD progression [12], as well as for fibrosis later.

Aim: To define the role of fatty acids in pathogenic mechanisms of speed progression of fibrosis in NAFLD among patients with the type 2 diabetes.

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) [13]. The diagnosis verification was based on the analysis of the clinical progression of the disease, laboratory findings, complex liver ultrasound [14, 15].

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 \leq 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 studied the level of saturated fatty acids (myristic, palmitic, heptadecanoic, stearic and the sum of saturated fatty acids), monounsaturated acids (palmitooleic, oleinic and their sum), polyunsaturated fatty acids (linoleic, eicosatetraenoic, arachidonic acids and their sum), as well as rate of saturated to desaturated fatty acids by the gas-liquid chromatography method. We calculated the median (Me) and quartiles (Q). In order to prove the associations between the speed progression of fibrosis and the consistence of fatty acids we used the logistic regression analysis, calculated the odds ratio (OR) and their 95% confidence intervals (CI). Statistic processing of the results was made with the help of STATA Version 12 for Windows software application program (StataCorp, Texas, USA).

Results and evaluation. We have presented the main demographic and cliniclaboratorial characteristics of patients with speed and slow progression of liver fibrosis in a table 1.

The groups of patients with slow and speed progression of liver fibrosis happened to be identical as of age, sex, BMI. Patients with the liver fibrosis F_0 - F_2 (79,65% and 65,79%, respectively) dominated both groups. However, the F_3 - F_4 liver fibrosis was more frequently registered among the patients of the group 2.

The study showed that type 2 diabetes patients from the group of speed fibrosis progression had higher median value of certain saturated fatty acids (myristic, palmitic, stearic) than patients from the group of slow fibrosis progression (table 2).

The univariate logistic regression analysis showed that the content of the mentioned acids was significantly associated with the speed progression of fibrosis.

Table 1

Characteristics	Type 2 diab	р	
	1 Group	2 Ggroup	
	(n=44)	(n=38)	
Age, years (M±m)	61,4±1,35	$60,5\pm7,9$	0,525
Sex, abs. number (%):			0,506
men	18 (40,9)	19 (50,0)	
women	26 (59,1)	19 (50,0)	
BMI $\kappa g/m^2$, Me (Q ₁ -Q ₂)	36,16 (31,8-39,5)	37,9 (32,72-41,8)	0,067
Liver fibrosis ratio, n (%):			
$\leq F_2$	35(79,6)	25 (65,8)	0,123
F ₃ -F ₄	9 (20,4)	13 (34,2)	

Medico-demographic profile of patients from the defined groups

Table 2

-					
Fatty acids, %	FA content in groups,		р	OR	р
	Me (Q ₁ -		(95%CI)		
	1 Group	2 Group			
Myristic 14:0	8,3	10,1	0,025	1,23	0,031
	(7,3-11,2)	(8,5-12,9)		(1,02-1,48)	
Palmitic 16:0	29,7	35,4	0,018	1,11	0,017
	(28,1-34,6)	(28,4-39,1)		(1,02-1,22)	
Heptadecanoic17:0	0,5	0,5	0,376	2,63	0,283
	(0,4-0,7)	(0,4-0,8)		(0,45-15,41)	
Stearic 18:0	6,1	7,2	0,017	1,51	0,049
	(5,3-6,8)	(6,3-7,7)		(1,00-2,28)	
Sum of saturated FA	45,75	51,6	0,001	1,02	0,140
	(40-49,2)	(44,5-54,9)		(0,99-1,04)	

fatty acids among the patients with type 2 diabetes and NAFLD

Associations between speed progression of fibrosis and the content of saturated

As for the monounsaturated fatty acids, we did not get the significant discrepancy in content of the studied fatty acids among patients of the studied groups, because the median value of oleic and palmitoleic acids content, as well as median value of their sum among the patients of both groups, were the same (table 3).

At the same time, we have got the clearly lower median value of arachidonic acid content among the patients with type 2 diabetes and NAFLD from the group of speed progression of fibrosis than among the patients with type 2 diabetes and NAFLD from the group of slow progression of fibrosis. Along with that the higher concentration of mentioned fatty acid was lowering a type 2 diabetes patient's chances to have speed progression of fibrosis (OR 0,86).

Associations between speed progression of fibrosis and content of unsaturated

Fatty acids	FA content in groups,		р	OR	р		
	Me $(Q_1 - Q_3)$			[95% CI]			
	1 Group	2 Group					
Monounsaturated FA, %:							
Palmitoleic16:1	1,5	1,7	0,2161	2,19	0,153		
	(1,4-1,9)	(1,5-2,1)		[0,75-6,4]			
Oleic 18:1	14,5	14,9	0,387	1,12	0,416		
	(12,9-15,6)	(13,4-15,8)		[0,85-1,48]			
Sum of monounsaturated	16,1	16,7	0,232	1,21	0,205		
FA	(14,9-17,2)	(14,9-17,6)		[0,89-1,63]			
Polyunsaturated FA, %:							
Linoleic C 18:2	23,4	22,8	0,659	0,97	0,602		
	(18,4-25,9)	(18,7-25,6)		(0,89-1,07)			
Eicosatrienoic C 20:3	1,4	1,4 (0,9-	0,432	0,68 (0,341-	0,324		
	(1,1-2,1)	1,9)		1,42)			
Arachidonic C 20:4	11,5	10,5	0,049	0,86	0,036		
	(9,5-13,4)	(7,2-12,3)		(0,74-0,99)			
Sum of polyunsaturated FA	37,3	33,7 (27,9-	0,094	0,94	0,087		
%	(32,2-40,2)	38)		(0,87-1,00)			
Sum of unsaturated FA,%	53,6	48,9	0,212	0,95	0,141		
	(47,3-55,6)	(43,8-55,3)		(0,88-1,012)			
Ratio of saturated FA to	0,93	1,02	0,001	77,3	0,004		
unsaturated FA	(0,79-1,01)	(0,95-1,2)		(4,01-148,9)			

fatty acids among the type 2 diabetes and NAFLD patients

As for linoleic acid, we did not get clear discrepancies in its concentration among the patients of studied groups. However, according to the scientists' data, conjugated linoleic acid plays an important part in liver fat deposition and IR development [16] – the main link between NAFLD, diabetes and obesity.

Median value of the polyunsaturated fatty acids sum among the patients with type 2 diabetes from the speed fibrosis progression group, was also lower than among the patients from the low progression of fibrosis group. However, this discrepancy was on a statistical margin (p=0,087) level.

However, the median value of the unsaturated fatty acids sum (mono- and poliunsaturated) in both groups was almost equal - 48,9% among the patients with type 2 diabetes from the speed fibrosis progression group, and 53,6% among the patients with type 2 diabetes from the slow fibrosis progression group.

But the more significant risk factor of speed progression of fibrosis among the type 2 diabetes and NAFLD patients, according to our data, was the ratio of saturated FA to unsaturated FA. Thus, the ratio was higher than one (Me=1,02) in the group of patients with speed progression of fibrosis, namely saturated FA content was significantly higher than the content of unsaturated FA. In the group of patients with the low progression the mentioned ratio was smaller than one (Me=0,93). We found the definitive associations between the ratio of saturated fatty acids to unsaturated fatty acids and the speed progression of fibrosis (OR 77,3; p=0,004).

Conclusions. So the results of our studies demonstrate the important role of fatty acids in pathogenetic mechanisms of speed progression of fibrosis during NAFLD affected patients with the type 2 diabetes.

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