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TRIGLYCERIDES/HDL RATIO AND RISK OF DEVELOPING DIABETES MELLITUS DURING ANTIRETROVIRAL THERAPY

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On behalf of ICONA Foundation Study Group

Introduction

The possible increased risk of diabetes in HIV-infected subjects is a matter of debate.

According to American Diabetes Association guidelines, patients with a BMI>25, HDL cholesterol level <35 mg/dl and Triglycerides(TRG)>250 mg/dl should be tested for diabetes (1). Low HDL and higher TRG were significantly associated with incidence of Diabetes in a large Cohort of HIV-infected patients (2) Triglycerides to high-density lipoprotein cholesterol (TRG/HDL) ratio is a sensitive marker of insulin resistance (3). Among HIV-infected subjects abnormal TRG and HDL levels are frequently observed particularly among those treated with Protease Inhibitors and/or Non nucleoside reverse trascriptase inhibitors (4).

Another important issue concerns the higher prevalence of non alcoholic fatty liver disease and consequent liver fibrosis in HIV-infected patients and its association with Insulin Resistance and Diabetes Mellitus (DM).

The aim of our analysis was to evaluate the incidence of DM and its association with TRG, TRG/HDL ratio and liver fibrosis (measured by FIB-4) during combination antiretroviral therapy (cART).

Methods

This analysis was conducted within the Italian Cohort of Antiretroviral-Naive Patients (ICoNA) study, an observational cohort of HIV-infected individuals who were antiretroviral naïve at enrolment. Patients from the ICONA Foundation study initiating first-line cART between 1997 and 2013 were selected and observed up to new-onset Diabetes Mellitus (DM) or last clinical follow-up.

Inclusion criteria

• Initiation of cART, including ≥3 antiretroviral drugs

Exclusion criteria

• Baseline glucose >126 mg/dL
• Previous diagnosis of Diabetes or antidiabetic treatment at baseline
• Therapy with Lipid lowering drugs at baseline

Patients were classified according to the different value of TRG:

1: ≤ 180 mg/dl
2: 181-300
3: >300

DM was defined as: first of 2 consecutive glucose>126 mg/dl, or clinical diagnosis of DM, or start of anti-diabetes treatment.

Incidence rate was calculated as number of observed DM after cART initiation divided by person years of follow-up (PYFU). Multivariable Poisson regression was used to determine factors independently associated with DM.

Two different model were used:

model A (including current TRG/HDL) and **model B** (including current TRG)

Both models were adjusted for gender, age, nationality, CD4 count before cART, CDC C stage, baseline $\log_{10}$ HIV-RNA, HCV co-infection, baseline cholesterol, current BMI, calendar year of cART start, current antiretroviral regimen and current presence of liver fibrosis (as defined by a FIB-4 score >3.25 [5]).

Results

3,546 patients [males 73.7%, median age 38 yrs [InterQuartileRange (IQR)= 33-45], median BMI 23.1 (IQR 21.1-25.2), HCV-ab positivity 22.1%] were included in this analysis. Complete patients' demographics were depicted in Table 1.

Of these, 80 persons developed DM over 13,911 PYFU, corresponding to an incidence of 5.7 per 1,000 PYFU (95%CI 4.6-7.1). Incidence of DM according to most recent TRG was 4.3/1,000 PYFU for patients with TRG <180 mg/dl vs 15.3/1,000 PYFU in patients with TRG>300 mg/dl while according to the most recent TRG/HDL incidence rate was 1.9/1,000 PYFU in the first quartile vs 8.8/1,000 PYFU in the upper quartile (See Figure 1).

Results of Univariate and Mutivariate analyses are depicted in table 2

TRG/HDL was associated with DM diagnosis at multivariate analysis (p<0.001).

Advanced liver fibrosis (defined as FIB-4 index >3.25) was also independently associated with higher risk of DM in model A but not in model B . However, the association was much stronger among patients without HCV co-infection (RR 5.28; 95%CI 1.25-22.27) than in those with positive HCV-Ab (RR 1.91; 95%CI 0.61-6.0 p-value for interaction=0.02).

Table 1. Characteristics of Patients

Table 1

Patients' Demographics (IQR= Interquartile Range, MSM=Men who have sex with Men, IVDU=Intravenous Drug Users, BMI= Body Mass Index)

Variables	N (%)	Median (IQR)
Male gender	2612 (73.7%)	
Age, yrs		38 (33-45)
Mode of HIV transmission		
Heterosexual contact	1513 (42.67%)	
MSM	1224 (34.52%)	
IVDU	598 (16.86%)	
Other/unknown	211 (5.95%)	
Italian nationality	3045 (85.9%)	
Years of HIV infection		1.5 (0.2-5.6)
Nadir CD4, cell/mmc		270 (170-361)
CDC stage C	355 (1.0%)	
CD4 count, cell/mmc at baseline		286 (181-384)
HIV-RNA $\log_{10}$ copies/mL at baseline		4.8 (4.2-5.2)
HCV-Ab positivity	766 (22.1%)	
HBs-Ag positivity	159 (4.5%)	
Total cholesterol at baseline, mg/dL	2943 (84. 8%)	
<200	423 (12.2%)	
201-239	104 (3.0%)	
>=240		
TRG at baseline, mg/dL		
<=180	2929 (82.6%)	
181-300	489 (13.8%)	
>=300	128 (3.6%)	
TRG/HDL at baseline		2.8 (1.8-4.5)
BMI at baseline		23.1 (21.1-25.2)

Table 2. Univariable and Multivariable Analysis (Model A+ Model B)

Table 2

- Crude and adjusted relative risk estimated by Poisson regression models. All variables included in the models are showed. (RR=relaive risk, ARR=adjusted relative risk, BMI= Body Mass Index, NRTI= Nucleoside Reverse Transcriptase inhibitors)

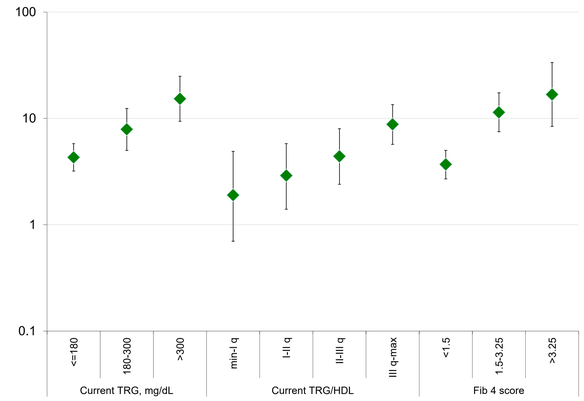
	Univariable analysis			Multivariable Model A			Multivariable Model B		
	RR	95% CI	P	ARR	95% CI	P	ARR	95% CI	P
Male gender vs female	2.42	1.31-4.47	0.005	2.09	0.91-4.79	0.083	1.81	0.89-3.65	0.099
Age (per 10 yrs older)	1.89	1.55-2.30	0.000	1.44	1.06-1.95	0.019	1.66	1.27-2.16	0.000
Italian vs not Italian	2.00	0.73-5.47	0.176	1.10	0.29-4.26	0.887	0.69	0.24-2.00	0.493
Nadir cd4 <=200 cells/mmc vs>200	2.06	1.31-3.21	0.002	1.16	0.87-1.54	0.320	1.14	0.89-1.47	0.290
CDC stage C vs A/B	2.23	1.32-3.77	0.003	1.18	0.54-2.59	0.676	1.44	0.75-2.77	0.275
HIV-RNA at baseline, $\log_{10}$ copies/mL (per 1 log higher)	1.22	0.92-1.63	0.173	1.09	0.79-1.52	0.599	1.10	0.82-1.48	0.521
HCV-Ab positive vs negative	1.62	1.01-2.60	0.047	1.70	0.88-3.25	0.112	1.83	1.04-3.23	0.037
Baseline cholesterol, mg/dL			0.068						
<200	1.00			1.00			1.00		
201-239	1.98	1.15-3.41	0.014	2.49	1.30-4.78	0.006	1.86	1.01-3.42	0.046
>=240	1.01	0.25-4.15	0.988	0.80	0.11-5.98	0.832	1.17	0.28-4.90	0.834
Current TRG/HDL (per 10 points higher)	1.17	1.10-1.26	0.000	1.63	1.32-2.01	0.000			
Current TRG, mg/dL (per 100 mg/dL higher)	1.20	1.10-1.32	0.000				1.05	0.99-1.12	0.110
Current BMI (kg/cm^2)			0.000						
<25	1.00			1.00			1.00		
25-29.99	2.36	1.38-4.02	0.002	1.64	0.87-3.10	0.126	2.06	1.17-3.61	0.012
>=30	6.76	3.78-12.10	0.000	4.92	2.42-10.00	0.000	5.73	2.95-11.13	0.000
NRTIs in the current regimen			0.014						
tdf+ftc	1.00			1.00			1.00		
tdf+3tc	0.92	0.28-3.07	0.896	1.37	0.37-5.07	0.639	1.31	0.36-4.80	0.682
abc+3tc	1.10	0.42-2.89	0.847	1.13	0.32-3.98	0.850	1.44	0.47-4.41	0.522
azt+3tc	1.39	0.77-2.54	0.277	2.16	0.84-5.54	0.110	1.87	0.76-4.58	0.173
d4t+3tc	3.92	1.82-8.48	0.001	6.31	1.95-20.40	0.002	4.74	1.60-14.02	0.005
ddi+3tc	2.55	0.88-7.37	0.084	2.09	0.44-9.90	0.352	2.83	0.76-10.55	0.121
other	1.99	1.05-3.77	0.034	2.38	0.65-8.63	0.189	3.30	1.09-9.95	0.034
Third drug in the current regimen			0.317						
efv	1.00			1.00			1.00		
nvp	0.93	0.39-2.19	0.863	1.19	0.42-3.33	0.745	0.89	0.33-2.38	0.816
lpv	1.81	0.92-3.59	0.087	1.20	0.47-3.10	0.702	1.20	0.51-2.81	0.678
atvr	1.55	0.74-3.24	0.240	3.23	1.30-7.98	0.011	2.52	1.07-5.91	0.034
fpvr	0.87	0.12-6.47	0.890	1.53	0.19-12.40	0.692	1.38	0.17-10.99	0.759
ldv-idv/r	3.13	1.26-7.79	0.014	1.25	0.26-6.16	0.780	1.70	0.59-4.85	0.324
sqv-sqv/r	3.23	0.76-13.83	0.114	-	-	0.999	3.55	0.76-16.65	0.107
nfv	1.35	0.40-4.55	0.626	1.59	0.34-7.37	0.557	1.55	0.43-5.60	0.506
only nrti	1.73	0.79-3.81	0.171	1.51	0.39-5.86	0.552	0.92	0.29-2.94	0.887
other	0.97	0.41-2.29	0.943	0.95	0.29-3.15	0.931	0.74	0.24-2.23	0.590
Current FIB 4 score			0.000						
<1.5	1.00			1.00			1.00		
1.5-3.25	3.12	1.84-5.27	0.000	1.97	1.01-3.87	0.048	1.69	0.91-3.14	0.097
>3.25	4.58	2.14-9.81	0.000	2.91	1.10-7.72	0.031	2.22	0.86-5.75	0.101
Calendar year of cART start (per 1 yr more)	0.95	0.90-1.01	0.099	1.02	0.92-1.14	0.689	1.00	0.91-1.10	0.992

Multivariabl analyses controlled for gender, age, nationality, CD4 count before cART, CDC C stage, log10 HIV-RNA, HCV-coinfection, baseline cholesterol, current BMI, calendar year of cART start, current antiretrovial regimen

Figure 1. Incidence Rate of Diabetes

Figure 1

- Crude incidence rate of DM stratified by current TRG, current ratio TRG/HDL and current fib 4 score categories.



TRG/HDL ratio: I quartile=1.7; II quartile=2.7, III quartile=4.5

Discussion

In our cohort of HIV-infected patients incidence of Type II diabetes did not differ significantly from the incidence among HIV-negative subjects in Italy, according to literature's data (5.7 /1000 PYFU between 33-45 years vs 5.1/1000 PYFU in patients between 30-49 years) (6).

Classical risk factors for diabetes' onset such as age and BMI were confirmed in our study.

TRG/HDL ratio predicts better than TRG alone the onset of diabetes probably because TRG/HDL represents better the grade of Insulin Resistance that is the driving force to development of Diabetes (7).

High TRG and abnormal HDL levels, often associated with cART, particularly with PIs and NNRTIs use (4), represent a condition conferring an actual increased risk of DM. Such alterations should, therefore, drive to early screening strategies for DM.

Advanced liver fibrosis was associated with diabetes.

This association could be explained by the higher prevalence of non alcoholic fatty liver disease (NAFLD) in diabetic patients and the by drug-induced steatosis. FIB-4 >3.25 could be a surrogate marker of abnormal metabolism as a result of drug induced steatosis and NAFLD especially in those with non HCV related liver damage.

Conclusion

High TRG/HDL ratio predicted the risk of new-onset DM, independently of other traditional risk factors. The use of this simple marker as predictor of the risk of DM merits to be further explored. Advanced hepatic fibrosis estimated using FIB-4 score might be an additional predictor for DM, especially in those with non HCV related liver damage.

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