RESISTIN GENE POLYMORPHISM RELATED TO WEIGHT GAIN AND PSYCHIATRIC SYMPTOMS ON InSTI

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Conflict of Interest (COI) of the Principal center:
No potential COI to disclose

BACKGROUND

- Weight gain and psychiatric symptoms (PSs) have been reported in PLWH receiving ART, especially integrase strand transfer inhibitors (INSTI).
- The interplay between the weight gain and PSs related to INSTI has remained unknown.
- Obesity and PSs are correlated with chronic inflammatory states characterized by insulin resistance.
- Some adipokines have been shown to correlate with various metabolic, inflammatory, and psychiatric diseases.
- Resistin is a pro-inflammatory adipokine and plays a key role in the insulin responsiveness of peripheral tissues and the CNS.
- A SNP at −420C>G in the promoter region of the human resistin gene (RETN-420) is correlated with serum resistin level (Fig.4) in the Japanese cohort. (GG>CG>CC).
- The aim of this study is to clarify the influence of RETN −420C>G on weight gain and PSs in PLWH receiving INSTI.

METHODS

Study population:

- Total 360 subjects who started ART between Jan 2011 and Dec 2018 with INSTI or PI were included. The participants comprised 290 PLWH with INSTI and 70 PLWH with PI, of whom 220 and 62 completed the data respectively.

Analyses:

- BMI was measured before and 6 months after starting ART.
- PSs were evaluated with the depression subscale of the Profile of Mood States, POMS or Self-rating Depression Scale, SDS.
- RETN −420C/G (rs 1862513) was investigated using PCR.
- Linear regression analysis was used to assess factors for BMI change and logistic regression analysis for PSs. We examined several variables that may affect BMI and PSs. Variables that were significant in univariate analyses were incorporated in multivariate models.
- This study was approved by KMC ethics.

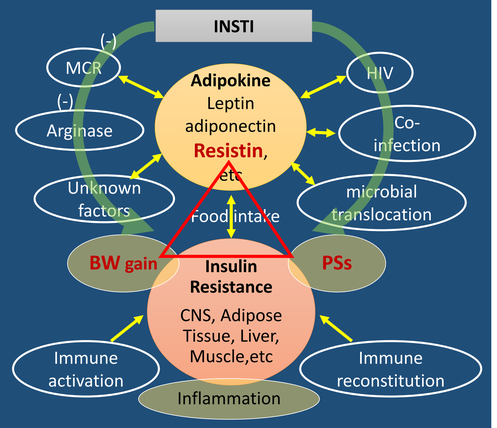
Table 1 Characteristics of the participants at baseline and the change from the baseline

	INSTI (n=220)			*PI (n=62)*		
RETN-420	CC, CG	GG	p	CC, CG	GG	p
Sex (M/F)	131/2	86/1		36/0	24/2	
Age (years)	38.1 ±11.0	40.2 ±11.0		42.3 ±6.88	45.9 ±10.2	
BW (kg)	63.8 ±11.9	65.3 ±14.1		67.7 ±14.2	62.9 ±10.2	
BMI (kg/m^2)	22.6 ±4.35	23.0 ±5.62		23.2 ±4.26	22.2 ±3.16	
Smoking (past)(Yes/No)	83/50	52/35	NS	21/15	15/11	
Smoking (current)(Yes/No)	52/81	29/58		15/21	10/16	
Key drug(DTG/EVG/RAL)	50/27/56	31/20/36		DRV	DRV	
Backbone(TDF/ABC/TAF)	56/50/27	34/36/17		26/9/1	20/5/1	
CD4+cell count (pre ART)	260 ±200	292 ±232		265 ±136	230 ±152	
HIV-RNA (log$_{10}$c/mL)	4.68 ±0.83	4.47 ±0.85	0.04	4.69 ±0.67	4.79 ±0.63	
Triglyceride (mg/dL)	162 ±134	167 ±106		133 ±91.7	110 ±49.2	*NS*
LDL-Chol (mg/dL)	93.6 ±26.1	93.7 ±36.5	NS	94.0 ±28.8	107 ±33.4	
HDL-Chol (mg/dL)	36.6 ±10.8	39.5 ±15.1		36.4 ±9.52	42.3 ±11.3	
Blood Sugar (mg/dL)	103 ±36.1	102 ±22.3		98.3 ±14.1	103 ±25.2	
Δ BW (kg)	1.27±4.34	4.17±4.82	0.0008	0.89 ±2.44	1.06 ±2.17	
Δ BMI (kg/m^2)	0.54±1.50	1.34±3.42	0.0009	0.29 ±0.85	0.37 ±0.76	
Δ CD4+cell count	168±140	186±149		194 ±124	181 ±141	
Δ Triglyceride (mg/dL)	2.87 ±112	25.4 ±122		45.1 ±169	70.9 ±96.7	
Δ LDL-Chol (mg/dL)	1.26 ±25.9	-3.11 ±31.1	NS	8.83 ±14.0	5.58 ±22.8	
Δ HDL-Chol (mg/dL)	6.0 ±11.5	2.0 ±12.0		4.54 ±11.0	-0.50 ±9.27	
Δ Blood Sugar (mg/dL)	-0.81 ±33.4	3.89 ±23.2		-1.05 ±21.5	-1.45 ±27.6	
PSs (Yes/No)	25/108	28/59	0.023	5/31	4/22	

Data are means ± SD, Δ : Subtraction of the data of baseline from the data of 6M after starting ART.
P-values :determined by Mann-Whitney test or χ^2 test, NS: not significant; p>0.05

Objective: To clarify the influence of RETN −420C>G on weight gain and psychiatric symptoms (PSs) in PLWH receiving INSTI.
Study population: Participants were PLWH who started ART with INSTI (n=220) or PI (*n*=62).
Results:
RETN −420C>G was associated with weight gain and PSs in PLWH with INSTI, but not with PI.

Conclusions:
Our data suggests ***the potential role of resistin to modulate and link weight gain and PSs on INSTI.***
The influence of other adipokines also needs to be examined to elucidate the mechanisms of INSTI-related symptoms.



Changes of BMI 6 months after initiation of ART

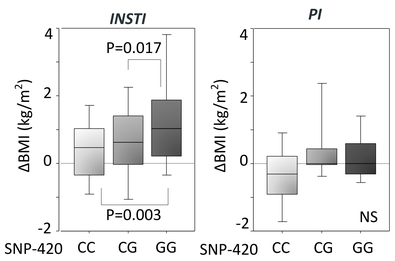


Fig.1 Box plot of ΔBMI (the change from the baseline)
p values :determined by *Bonferroni Dunn test,vs.CC*

Percentage of participants with Psychiatric symptoms

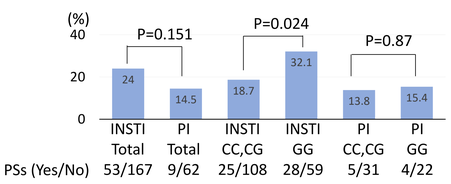


Fig.2
PSs were evaluated with the depression subscale of the POMS or SDS.
The 245 participants were evaluated with POMS and the 136 participants were with SDS. The 96 participants were evaluated with both POMS and SDS, of whom the 78 participants (81.3%) were obtained the same assessment.
p values :determined by *χ2 test.*

Table 2 Factors associated with Body weight change

	INSTI				*PI*			
Linear regression	simple		multiple		simple		multiple	
	r	P-value	r	P-value	r	P-value	r	P-value
Age	0.165	0.018	0.163	0.032	0.108	0.54		
BW before ART	-0.224	0.002	-0.196	0.013	-0.257	0.12		
BMI before ART	-0.120	0.135			-0.343	0.035	-0.235	0.17
Smoking (PH)*	0.140	0.072			0.06	0.71		
CD4 before ART	-0.268	0.0001	-0.133	0.098	-0.359	0.027	-0.359	0.27
HIV-RNA (log)	0.114	0.109			0.205	0.18		
Use of FTC/TAF*	0.243	0.0005	0.219	0.004	0.117	0.44		
PSs*	0.151	0.043	0.114	0.125	0.236	0.13		
RETN-420C>G*	0.230	0.001	0.181	0.018	0.049	0.77		

*For categorical variables, "No" was scored 0, and "Yes" was scored 1. Variables found to be important in simple regression analysis were used in multiple regression model.
r: Regression coefficient

Variables associated with PSs in Logistic Regression

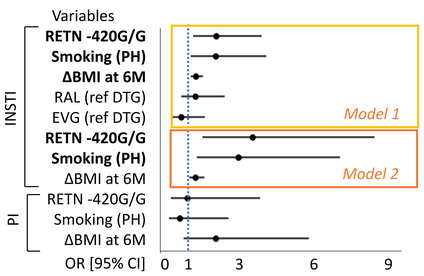


Fig.3 Logistic Regression Analysis to determine the factors associated with PSs
Model 2 was simplified by using variables which were significant (p<0.05) in Model 1

RESULTS

- BMI increased by 0.86 kg/m^2 (p<0.001, paired *t*-test) in the INSTI group and 0.33 kg/m^2 (p=0.04, paired *t*-test) in the PI group.
- In the INSTI group, BMI increased significantly in RETN-420 GG genotype compared with CC and CG genotype, but in the PI group, the difference was not significant (Fig.1).
- In INSTI, BMI increase was significantly associated with elder age, low body weight and low CD4 counts before ART, use of TAF, PSs, and RETN-420G allele in simple regression analysis, and age, low body weight, use of TAF, and RETN-420G allele in adjusted multiple linear regression analysis (Table2).
- In PI, BMI increase was significantly associated with low BMI and CD4 counts before ART only in simple regression analysis (Table 2).
- 24% of the INSTI group and 14% of the PI group showed PSs (Fig.2).
- PSs was significantly associated with weight gain, smoking and the RETN −420G in model 1, and smoking and the SNP −420G in model 2 in logistic regression analyses. In the PI group, no factors were associated with PSs (Fig3).

CONCLUSIONS

- Inflammation and insulin resistance are known to underlie the pathophysiology of depression as well as MetS.
- Resistin regulates insulin sensitivity, and it links between inflammation and its metabolic consequences. It is also involved in the pathogenesis of psychiatric symptoms.
- The mechanisms of weight gain and PSs associated with INSTI might be multifactorial and its precise mechanism remains unknown.
- INSTI-containing regimens could be their faster virologic control compared to PI, that might alter the inflammation level (immune reconstitution) and adipokine network.
- DTG is reported to inhibit melanocortin 4 receptor (MC4R), which regulates caloric intake or stress responsiveness by modulating adipokine (leptin) signaling in the CNS.
- Direct interaction between MCR and resistin has not been reported, but inhibition of MCR has been reported to increase resistin expression.
- Our data showed RETN −420C>G was associated with weight gain and PSs in PLWH on INSTI. These results suggest weight gain and PSs shared the common pathway, and resistin plays a potential role to link INSTI-related weight gain and PSs. So, Individuals with weight gains should be screened for the presence clinically significant psychiatric symptoms, and vice versa.

Limitations

- The influence of other adipokines also needs to be examined to elucidate the precise mechanisms of INSTI related weight gain and psychiatric symptoms.
- Frequency of RETN genes varies with ethnicity (G alleles; JPN 0.33, Caucasian 0.33, African American 0.45, Chinese 0.41)
- This was a small study, and larger studies are warranted to confirm this finding.

Proposed model for the induction of Type 2 diabetes mellitus

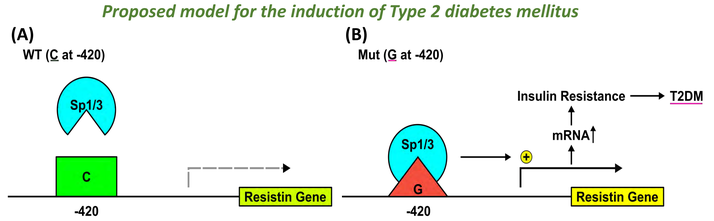


Fig.4 (A) Sp1/3 cannot bind to C at RETN −420 and the promoter is not activated. (B) Sp1/3 can bind specifically to G at −420, which activates the promoter. (*Ref. Osawa H,et al, Am. J. Hum. Genet., 2004)*