

Association between Duration of Protease Inhibitor Therapy and BMI in HIV Patients

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ABSTRACT

Introduction: The prognosis of HIV had changed dramatically from a deadly infectious disease into a manageable infection. Initiation of ARV, especially protease inhibitor, was thought to be associated with metabolic abnormalities. Weight gain in HIV could be a positive indicator for better prognosis. However, excessive weight gain was associated with deleterious effects. Studies regarding protease inhibitor in weight gain had different results. In this study, we intend to identify association of PI therapy duration with BMI.

Methods: We conducted a cross-sectional study in Adam Malik Hospital, Medan from August to December 2019. We recruited HIV patients above 18 years old during the outpatient with at least 6-month duration of PI therapy. During visits, patients were screened for inclusion criteria and assessed for BMI. Fasting blood glucose and insulin plasma sample were taken in the morning. Data was analysed by SPSS 22.0.

Results: Thirty-five subjects fulfilled inclusion criteria, 25 of subjects were males (71.4%). Mean age of subjects was 38.85 ± 9.7 years. Data analysis presented that there were no significant differences between two groups of treatment (24.33 ± 3.3 kg/m² vs 24.39 ± 5.0 kg/m²; $p = 0.966$). There were significant differences between two groups regarding fasting blood glucose level (84.4 ± 6.8 mg/dL vs 114.9 ± 53.6 mg/dL; $p = 0.015$) and fasting insulin level (7.28 ± 3.4 μ U/mL vs 26.01 ± 23.5 μ U/mL; $p = 0.000$).

Conclusion: BMI was not associated with duration of PI therapy in our study. Fasting

blood glucose and fasting insulin were significantly higher between groups.

Keywords: HIV, protease inhibitor, BMI, insulin, obesity, weight gain

INTRODUCTION

HIV has remained as global burden worldwide for almost five decades. [1,2] It was estimated that 38 million people living with HIV the end of 2019. [3,4] While global treatment and efforts for HIV have advanced, the number of people living with HIV (PLWH) keeps raising when receiving antiretroviral therapy. According to Joint United Nations Programme on HIV and AIDS data, 67% of adults and 53% of children living with HIV globally were receiving lifelong antiretroviral therapy (ARV) in 2019. [4] The prognosis of HIV had changed dramatically from a deadly infectious disease into a manageable infection. [5]

As the life expectancy of HIV are increasing, non-infectious comorbidity has affected PLWH. [6] Overweight and obesity has reached high number in PLWH during the last 2 decades in United States. [7] In previous study, a HIV clinic was reported to have a high proportion with the prevalence of multiple comorbidities which was associated with increased BMI (body mass index). [8] Even though weight gain in HIV could be a positive indicator for better prognosis, [9] excessive weight gain was

associated with deleterious effects in cardiovascular and metabolic parameters [10]

Instead of achieving virological control and increased global aging of PLWH population, initiation of ARV is thought to be associated with some metabolic abnormalities, such as, dyslipidemia, insulin resistance, and weight gain. [1,7,11] Previous in vitro study showed that protease inhibitors inhibited the activity of GLUT-4 (*glucose transporter-4*) and lipodystrophy in PLWH. [12] Other studies have also established the associations between PI and wide range of its adverse effects. [1,13] However, the clinical significance of these findings is still yet to be known. [14,15]

To our knowledge, studies regarding ARV therapy in weight gain had different results. [11,16,17] PI therapy was associated with weight gain in some studies. [1,11,18] Todd et al reported PI drugs were not associated with overweight or obesity. [19] Another study by Obry-Roguet et al was also failed to find this association. [20] Apart from weight gain, Noor et al reported that LPV/r (lopinavir/ritonavir) was found to induce insulin resistance in 5 days period. [21] Study by Dirajral-Fargo et al also found that atazanavir-ritonavir (ATV/r) and darunavir-ritonavir (DRV/r) were associated with insulin resistance in 4-week ARV therapy. [22] Taking into account the variabilities of available studies, we intend to identify PI therapy duration and its association with BMI.

METHODS

This cross-sectional study was performed in Adam Malik Hospital, Medan from August 2019 to December 2019. The study was reviewed and approved by Health and Research Ethics Committee of Medical Faculty University of Sumatera Utara. We enrolled HIV patients above 18 years old in outpatient clinic with at least 6-month duration of PI therapy as current treatment. Individuals with abnormal kidney function tests, history of diabetes, and taking other

drugs affecting the insulin resistance and blood glucose were excluded.

During the outpatient visits, patients were interviewed for medical history and current medications. After being screened for the inclusion criteria, informed consent was obtained for all subjects. Subjects were assessed for BMI and blood pressure. In all subjects, fasting blood glucose and insulin plasma sample were taken in the morning. Insulin plasma was measured using chemiluminescent (sandwich) immunoassay from serum/plasma added with lithium heparin or K3 EDTA or sodium citrate. BMI was classified according to Asia Pacific Classification. [23]

Data was analysed by software SPSS 22.0. Shapiro-wilk test was used to confirm normal distribution of data. For assessing comparison between duration of PI treatment and BMI, we used t-test if data was normally distributed. Mann-Whitney U test was used if data had non-normal distribution. *P* value < 0.05 was considered significant. If data was normally distributed, data were shown as mean ± standard deviation (SD).

RESULT

Demographic of Subjects

Thirty-five subjects fulfilled inclusion criteria (Table 1). There were 25 males (71.4%) and 10 females (28.6%). Mean age of subjects was 38.85 ± 9.7 years, with the oldest was 64 years old and the youngest was 18 years old. Mean systolic blood pressure was 110.57 ± 10.2 mmHg and diastolic blood pressure was 74.57 ± 7.4 mmHg. All of the subjects had normal blood pressure.

Table 1. Characteristics of Subjects

Subject Characteristic	Mean
Age (years)	38.85 ± 9.7
Male (%)	25 (71.4%)
Body Mass Index (kg/m ²)	24.35 ± 3.9
Systolic Blood Pressure (mmHg)	110.57 ± 10.2
Diastolic Blood Pressure (mmHg)	74.57 ± 7.4
Fasting Blood Glucose (mg/dL)	96.6 ± 36.8
Fasting Insulin (µU/mL)	14.77 ± 17.4
Duration of treatment	
6-12 months (%)	15 (44.1%)
> 12 months (%)	19 (55.9%)

Duration of treatment using PI-type of ARV drugs in this study was divided into two groups, which was six to 12 months and more than 12 months. Nineteen subjects had already been on the treatment of more than 12 months.

Comparison of Body Mass Index and The Duration of Treatment

Mean BMI of subjects were $24.35 \pm 3.9 \text{ kg/m}^2$, with the highest BMI was 33.06 kg/m^2 and the lowest BMI was 14.72 kg/m^2 . Most of the subjects had normal weight (13.27%) (Table 2). There was one (2.9%) underweight subject, seven (20%) overweight subjects, 11 (31.4%) obese I subjects, and three (4.6%) obese II subjects.

Table 2. Distribution of Body Mass Index of Subject

Body Mass Index	n	%
Underweight	1	2.9%
Normal	13	37.1%
Overweight	7	20%
Obese I	11	31.4%
Obese II	3	4.6%

Distribution of BMI data was analyzed using Shapiro-Wilk and had normal distribution ($p = 0.424$). Comparison of BMI and duration of treatment showed no significant difference between two groups ($24.33 \pm 3.3 \text{ kg/m}^2$ vs $24.39 \pm 5.0 \text{ kg/m}^2$; $p = 0.966$) (Table 3).

Table 3. Comparison of Body Mass Index, Fasting Blood Glucose, Fasting Insulin Level and Duration of Treatment

Variables	6-12 months	> 12 months	p
Body Mass Index (kg/m^2)*	24.33 ± 3.3	24.39 ± 5.0	0.966
Fasting Blood Glucose (mg/dL)**	84.4 ± 6.8	114.9 ± 53.6	0.015
Fasting Insulin ($\mu\text{U/mL}$)**	7.28 ± 3.4	26.01 ± 23.5	0.000

*Unpaired-t-test; **Mann-Whitney U test

Comparison of Fasting Blood Glucose and Fasting Insulin Level with Duration of Treatment

Mean fasting blood glucose of subjects was $96.6 \pm 36.8 \text{ mg/dL}$. Distribution of fasting blood glucose data was analyzed using Shapiro-Wilk and has non-normal distribution ($p = 0.000$). The analysis showed significant difference between two groups of treatment (84.4 ± 6.8

mg/dL vs $114.9 \pm 53.6 \text{ mg/dL}$; $p = 0.015$) (Table 3).

Mean fasting insulin level was $14.77 \pm 17.4 \mu\text{U/mL}$. Distribution of fasting insulin data was analyzed using Shapiro-Wilk and has non-normal distribution ($p = 0.000$). Compative analysis of fasting insulin level and duration of treatment presented significant difference between two groups of treatment ($7.28 \pm 3.4 \mu\text{U/mL}$ vs $26.01 \pm 23.5 \mu\text{U/mL}$; $p = 0.000$) (Table 3).

DISCUSSION

The most age range of subjects were 34-49 years old. Most of the subjects were men, which contribute to 71.4% of subjects. Based on the study on 18,669 subjects, most of HIV patients are men with mean age of 47.5 years. [24] Other study by Fiseha et al showed that mean age in their study were 37 years old. [25] This result is similar to our studies, as it shows most patients tend to be infected in their teen or early adult years. Saktina et al stated that most people infected in 12 to 35 years old which may be caused by the productive groups tend to do high risk sexual activities these days. These activities included multiple sexual partners and negligence use of condoms. They also are more likely to use and share intravenous drugs. [26]

All subjects had normal blood pressure with mean systolic blood pressure $110.57 \pm 10.2 \text{ mmHg}$ and mean diastolic blood pressure $74.57 \pm 7.4 \text{ mmHg}$. In terms of hypertension, men are more likely to have it than women. The prevalence of hypertension was higher in older patients that in their younger counterparts. Other factors associated with hypertension in HIV patients are longer duration of HIV infection, family history of hypertension, high BMI, low CD4 count, DM comorbidity, and impaired renal function. [25] HIV infected adults on ARV have higher prevalence of hypertension when compared with HIV-uninfected individuals. Several virological and treatment-related factors have been implicated in pathophysiology of

hypertension in HIV infection, such as chronic inflammation, immune reconstitution and lipodystrophy. All of these will activate renin-angiotensin-aldosterone system (RAAS).^[27] Study by Fiseha et al found that duration of ARV was associated with hypertension.^[25] However, the findings were different with study by Hatleberg et al stated. In their study, they failed to find evidence for any association between any ARV drugs and the risk of hypertension.^[28] Our results were aligned with Hatleberg et al that we did not find high blood pressure subjects. In this case, few considerations should be considered, as we only measure blood pressure at one occurrence and look up to previous medical record. Blood pressure were not repeatedly measured as recommended by Indonesian Society of Hypertension Guideline,^[29] no confounding comorbidity, such as DM that would contribute to hypertension. Further investigations regarding this matter are still needed.

Mean BMI of subjects were $24.35 \pm 3.9 \text{ kg/m}^2$, with the highest BMI was 33.06 kg/m^2 and the lowest BMI was 14.72 kg/m^2 . Study by Araujo et al also stated mean BMI on HIV-patient with ARV were 23.9 kg/m^2 .^[30] We found that there was no significant difference of BMI between two groups of treatment ($24.33 \pm 3.3 \text{ kg/m}^2$ vs $24.39 \pm 5.0 \text{ kg/m}^2$; $p = 0.966$). This result was aligned with study by Tshikuka et al. Tshikuka et al conducted a 12-year cohort study to assess ARV regimens that predicts overweight, obesity, and other factors associated with BMI changes among ARV recipients. In their study, first-line, second-line and third-line of ARV and duration of treatment did not have significant effect on BMI. Factors contributed to increased BMI in HIV patients are gender, CD4 count, and DM-related comorbidity.^[31] This explains the lack of association of treatment duration and non-diabetic subjects in our study leading to no significant difference of BMI between two groups of treatment.

We found significant difference of fasting blood glucose and fasting insulin

between two groups of treatment ($p = 0.015$; $p = 0.000$). Regarding duration of treatment, toxicity of ARV usually appears after 6-18 months duration of treatment. ARV could cause metabolic disorder, such as hyperlipidemia, lipid accumulation, insulin resistance, diabetes and osteopenia.^[32] Dirajlal-Fargo et al. stated that PI and NNRTI were both associated with higher risk of DM.^[22] This result supported with study by Carr et al. Carr et al stated that PI could significantly raise blood glucose, especially in patient with and predisposed DM. This is due to metabolic effect of PI.^[33] Normal limit of fasting blood glucose is less 100 mg/Dl ^[34] and fasting insulin is less than $13 \text{ } \mu\text{U/ml}$.^[35] Subjects receiving more than 12 months of PI have had higher than normal fasting blood glucose and fasting insulin.

PI affecting blood glucose metabolism, by selectively inhibits Glucose Transporter Type 4 (GLUT4).^[36] GLUT4 is part of a family of glucose transporter proteins containing 12-transmembrane domains. It is expressed primarily in skeletal muscle and adipose tissue. It is responsible in insulin signalling. Transportation of glucose across cell membrane occurs via GLUT4's mechanism of Adenosine Triphosphate (ATP)-independent facilitative diffusion. If insulin or exercise presents, GLUT4 storage vesicles will undergo exocytosis to the plasma membrane where it acts as glucose transport. Once insulin is absent, GLUT4 will enter the cell and glucose transport stops. Inhibition of GLUT4 will cause defective intracellular signalling, therefore glucose transportation is inhibited and resulted in higher blood glucose. At last, higher blood glucose will stimulate higher insulin levels in blood.^[37]

There are few limitations regarding this study. First, we acknowledged the limited timeline for monitoring. Blood glucose and insulin examination are better measured regularly with longer period of monitoring as it will better represent blood glucose control of patient. Alternatively,

HbA1c can replace blood glucose regarding this matter. Second, as we did not use HbA1C as an indicator to diagnose DM type 2 in subjects, DM could be missed and may affect our result.

CONCLUSION

BMI was not associated with duration of PI therapy in our study. Fasting blood glucose and fasting insulin were significantly higher in patients receiving ARV for more than 12 months than for six to 12 months. Further investigation regarding other factors affecting blood glucose control is still needed.

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