Improvement of Fat Redistribution, Insulin Resistance and Hepatic Fatty Infiltration in HIV - Associated Lipodystrophy Syndrome by Pioglitazone : A Case Report

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Abstract

HIV-associated lipodystrophy syndrome is a syndrome occurring in HIV-infected patients who were treated with highly-active antiretroviral therapy (HAART), especially regimen containing protease inhibitors. The syndrome consists of fat redistribution, with loss of subcutaneous fat and increase in visceral fat, and metabolic disturbances, including glucose intolerance or overt diabetes and dyslipidemia. No standard treatment has been established for this syndrome. Pioglitazone is an oral antidiabetic agent that acts primarily on adipose tissue to reduce insulin resistance. The authors report a 50-year old HIV-infected woman who developed HIV-associated lipodystrophy syndrome after 3 months of HAART. She had significant weight loss with obvious loss of subcutaneous fat, together with development of hypertension, diabetes and dyslipidemia. After treatment with 30 milligrams of pioglitazone daily, her body weight increased within the first month of treatment. Subcutaneous fat loss was restored. Improvement in glycemic and lipid control was also noted. CT scan of the abdomen revealed that fatty infiltration in the liver was markedly decreased. Visceral fat as assessed by CT scan had also decreased. Pioglitazone appeared to have beneficial effects in this patient.

Key word : HIV-Associated Lipodystrophy, Pioglitazone, Insulin Resistance

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The combined use of highly active antiretroviral therapy, so-called "HAART" has become another milestone for the treatment of HIV infection. The drugs effectively reduce the viral load and markedly improve the quality of life of the patients. However, prolonged use of these agents may cause

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serious adverse effects which can be troublesome to the patients. A syndrome consisting of lipodystrophy, insulin resistance, glucose intolerance, dyslipidemia and accelerated atherosclerosis has been increasingly recognized[1-7]. The syndrome most commonly, but not necessarily, occurs with the use of anti HIV regimen containing protease inhibitors (PI)[8-13].

Pioglitazone is a novel antidiabetic agent that acts primarily by improving insulin sensitivity. The drug binds to specific nuclear receptor; the peroxisome proliferator activated receptor gamma or PPARγ and induces expression of multiple genes involving glucose and lipid metabolism[14]. PPARγ is expressed mainly in adipose tissues and activation of PPARγ causes adipocyte differentiation, fatty acid redistribution and improvement in insulin sensitivity. It is, therefore, possible that pioglitazone may have favorable effects on lipodystrophy and insulin resistance associated with the use of antiretroviral agents. The authors report a case of HIV-associated lipodystrophy and insulin resistance successfully treated with pioglitazone. Of particular interest is that the infiltration of fat in the liver commonly associated with this syndrome is also markedly diminished with the use of pioglitazone.

CASE REPORT

A 50 year-old Thai female, a housewife, was found to be HIV-seropositive. She presumably acquired the infection from her husband. She had no other medical illnesses. Her CD_4 was 472 cells/mm^3 and her HIV-RNA was more than 750, 000 copies/ml. She was prescribed HAART containing stavudine (80 mg/day), didanosine (400 mg/day) and nevirapine (400 mg/day). The regimen successfully suppressed her HIV-RNA to less than 50 copies/ml. However, after 3 months of treatment, she developed abdominal discomfort and frequent nausea and the regimen was switched to stavudine, lamivudine and efavirenze. During this time, she was found to have hypertension (blood pressure 170/110 mmHg) and was prescribed enalapril to control her blood pressure. She also complained of remarkable weight loss of 11 kg (from 95 to 84 kg) after 5 months of HAART. At the 6^{th} month, she had lost another 9 kg (from 84 to 75 kg) without any evidence of opportunistic infection. Laboratory tests revealed that her fasting plasma glucose was 265 mg/dl, serum cholesterol 302 mg/dl, triglyceride 264 mg/dl, HDL 33 mg/dl, AST 87 u/L (normal 10-37 u/L), ALT 40 u/L (normal 10-40 u/L), alkaline phosphatase 372 u/L (normal 32-150 u/L). Hepatitis B and C serology were negative. At this time, she was given glipizide and simvastatin to control her metabolic problems. However, she continued to lose another 9 kg (from 75 to 66 kg) and her metabolic derangement was still not under control. The fasting plasma glucose level was 285 mg/dl with 15 mg/day of glipizide. The cholesterol level was 261 mg/dl, and the triglyceride level was 267 mg/dl with 10 mg of simvastatin daily.

During this period, obvious loss of subcutaneous fat from the temporal and malar areas and over the extremities was becoming evident (Fig. 1A). Conversely, the dorsocervical fat pad and the abdomen became more prominent. CT scan of the abdomen revealed low attenuation of liver parenchyma, compared to the spleen, which was highly suggestive of fatty infiltration of the liver and increased visceral fat (Fig. 2A & 3A).

Because of her uncontrolled metabolic problems, dysfiguring lipodystrophy and continuing weight loss, the authors decided to initiate treatment with 30 mg of pioglitazone daily, in addition to her previous medications. One month after treatment, she had rapidly gained 9 kg of body weight (from 66 to 75 kg). After 5 months of treatment, her body weight had increased to 78 kg. Remarkable improvement in fat distribution over malar and temporal areas was also observed (Fig. 1B). Glycemic control also showed remarkable improvement, with fasting glucose reduced to 95 mg/dl and the dose of glipizide reduced to 2.5 mg/day. Serum cholesterol was 224 mg/dl, triglyceride 102 mg/dl and HDL 54 mg/dl 4 months after treatment. The blood pressure was 120/70 mmHg, and the dose of enalapril could be reduced from 10 to 2.5 mg daily.

Interestingly, the increase in serum AST reverted to normal after treatment with pioglitazone. The AST was 27 U/L and the ALT was 21 U/l four months after institution of pioglitazone. Follow-up CT scan at 4 months revealed reduction in liver size. Fat accumulation in the liver had markedly decreased, as evidenced by increased density in the liver parenchyma compared to the blood vessels and spleen (Fig. 2B). The reduction in visceral fat, especially in the mesenteric area was also observed (Fig. 3B).

DISCUSSION

The introduction of HAART has dramatically changed the clinical pictures of patients infected with HIV. The disease can now be regarded as a

chronic disease, with patients requiring long-term antiretroviral treatment. HIV-associated lipodystrophy has emerged as one of the most important problems in these patients. The development of lipodystrophy has a major negative impact on the quality of life of the patients. Besides, insulin resistance and metabolic complications associated with the syndrome can increase cardiovascular morbidity and mortality in this specific group of patients at a relatively young age. The syndrome has been reported most commonly with the use of PI, but other agents may be related to this syndrome as well[15,16]. In the presented patient, the HAART regimen given was PI sparing regimen (2 nucleoside reverse transcriptase inhibitors (NRTI) plus 1 non-nucleoside reverse transcriptase inhibitor (NNRTI)). The regimen could effectively control the infection, both in terms of virological and immunological profile. However, the development of lipodystrophy with marked weight loss and metabolic derangement had created a major problem to the patient. Without effective treatment, these problems can limit the use of HAART.

The etiology of HIV-associated lipodystrophy syndrome is not clearly understood. It is proposed that the syndrome may result from direct toxic effects of antiretroviral treatment or by the infection per se. Current evidence also suggests the interaction between HIV and HAART[17]. Available evidence is not conclusive whether metabolic changes precede fat redistribution or vice versa. More studies are needed

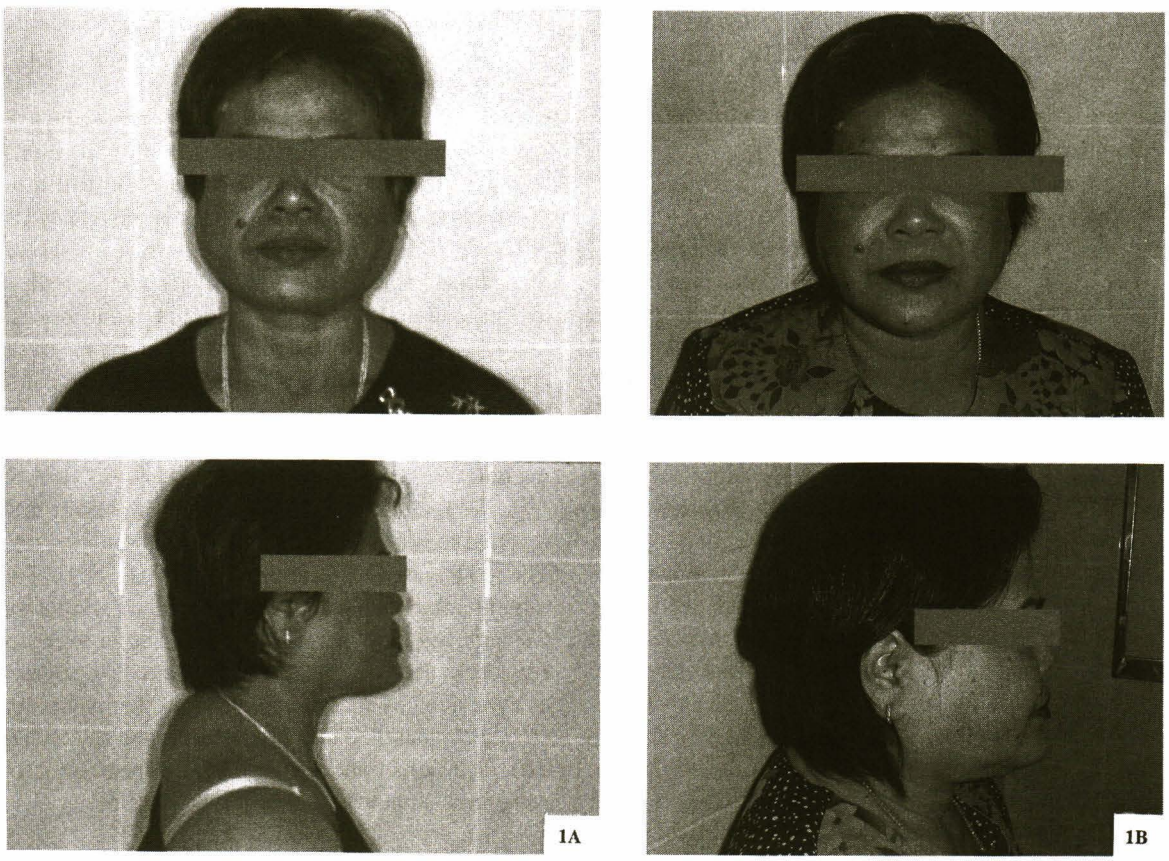

Fig. 1A & 1B. Fat distribution in the facial area of the patient before (1A) and 4 months after treatment with pioglitazone (1B).

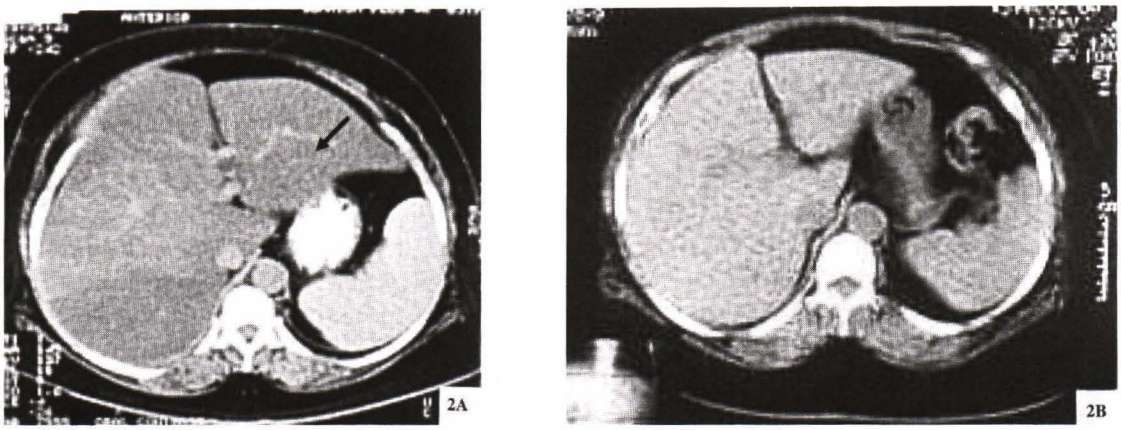

Fig. 2A & 2B. **CT scan of the liver before (2A) and 4 months after treatment with pioglitazone (2B). Note the decreased attenuation of liver parenchyma, as compared to blood vessels and spleen (Fig. 2A, arrow), indicating hepatic fatty infiltration, which improved after pioglitazone treatment.**

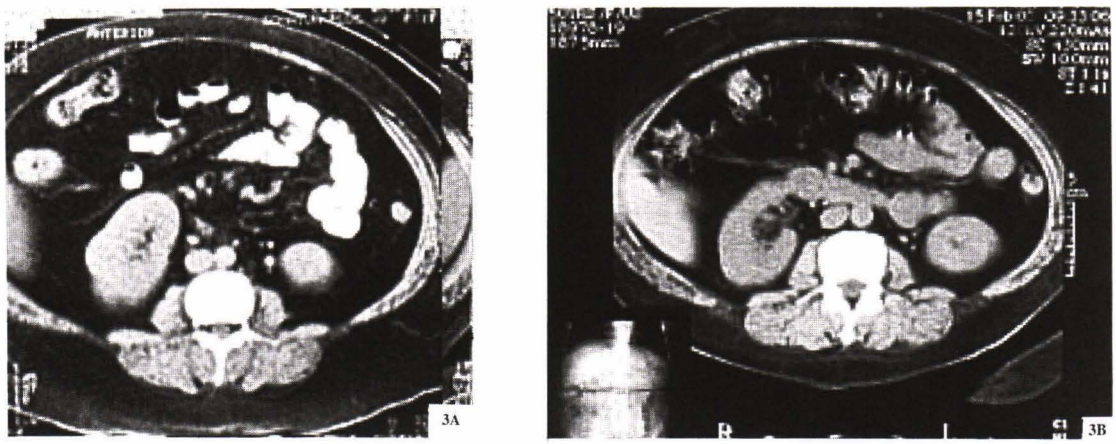

Fig. 3A & 3B. **Changes in visceral fat before (3A) and 4 months after treatment with pioglitazone (3B).**

to clarify the mechanisms and causal relationships between lipodystrophy and metabolic derangement in these patients.

PI drugs, the most common agents associated with this syndrome, have been shown to inhibit adipocyte differentiation, thereby may contribute to morphological changes[18,19]. The drug may also bind to protein homologous to HIV-1 protease such as cytoplasmic retinoic-acid binding protein type 1 (CRABP-1) and low density lipoprotein-receptor-related protein (LRP), causing alteration in lipid metabolism[20]. Other agents, particularly NRTIs, are known to be toxic to mitochondria. Mitochondrial DNA polymerase gamma is particularly sensitive to NRTIs. It is speculated that toxic effects of NRTIs on mitochondrial function and associated lactic acidosis may cause adipocyte apoptosis and lipodystrophy[21].

The prevalence of lipodystrophy and metabolic syndrome associated with HIV-infection varies widely, ranging from 2-84 per cent, according to diagnostic criteria and antiretroviral agents used[3,22,23]. The management of these patients is, therefore, complicated by the wide variation in metabolic and fat distribution abnormalities experienced by each

patient. Treatments to reverse or reduce metabolic and fat distribution abnormalities must, therefore, address each patient's specific changes and health risks. A number of studies have examined various therapies for this syndrome with varying degrees of success. These include antiretroviral switch studies, anabolic steroids, growth hormone, insulin-sensitizing agents, and cosmetic surgery[24-33]. Agents that target insulin resistance may be of particular benefit in this syndrome. Metformin can be used to reduce insulin resistance in this syndrome but the patient may experience more weight loss[29]. Thiazolidinediones are a novel class of insulin sensitizing agents that are of particular interest since the drugs act directly on adipose tissues to reduce insulin resistance. The efficacy of troglitazone in the treatment of lipodystrophy syndrome has been reported but the drug has been withdrawn from the market due to hepatotoxic side effects[30]. Newer thiazolidinediones do not seem to harbor this serious side effect. Pilot studies of both rosiglitazone and pioglitazone in this syndrome have been conducted, the results of which were promising, but not yet conclusive[31-33]. The use of pioglitazone in the study from Calmy et al was in non-diabetic, glucose-tolerant patients affected with this syndrome[33]. No significant effects on metabolic profile were observed, despite a remarkable improvement in fat redistribution. To the authors' knowledge, no studies of pioglitazone have been conducted in diabetic patients with this syndrome. The authors, therefore, chose to institute pioglitazone in the presented patient. It was remarkable that pioglitazone could correct multiple abnormalities associated with this syndrome in this patient. The body weight significantly increased with regain of peripheral fat. Plasma glucose markedly decreased together with improvement in lipid profile. Of particular interest is the reduction in visceral fat accumulation, both in the omentum and the liver, as evidenced by the follow-up CT scan of the abdomen. Liver enzyme abnormalities, presumably associated with fatty infiltration were also reversed with pioglitazone treatment. These findings lead to the speculation that pioglitazone may also have beneficial effects on other diseases associated with insulin resistance and fatty liver.

The result of treatment with pioglitazone in the presented patient raised the possibility that visceral fat may be a major determinant of metabolic abnormalities in this syndrome. However, further studies are needed to confirm the efficacy of this agent. The treatment of HIV-associated lipodystrophy with pioglitazone remains speculative at this time.

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REFERENCES

1. Lo JC, Mulligan K, Tai VW, Algren H, Schambelan M. 'Buffalo hump' in men with HIV-1 infection. Lancet 1998; 351: 867-70.
2. Dong KL, Bausserman LL, Flynn MM, et al. Changes in body habitus and serum lipid abnormalities in HIV-positive women on highly active antiretroviral therapy (HAART). J Acquir Immune Dfic Syndr 1999; 21: 107-13.
3. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy and insulin resistance due to HIV protease inhibitors. AIDS 1998; 12: F51-8.
4. Miller KD, Jones E, Yanovski JA, et al. Visceral abdominal-fat accumulation associated with use of indinavir. Lancet 1998; 351: 871-5.
5. Wanke CA. Epidemiological and clinical aspects of the metabolic complications of HIV infection the fat redistribution syndrome. AIDS 1999; 13: 1287-93.
6. Mauss S. HIV-associated lipoidystrophy syndrome. AIDS 2000; 14 (Supp 13): S197-207.
7. Safrin S, Grunfield C. Fat distribution and metabolic changes in patients with HIV infection. AIDS 1999; 13: 2493-505.
8. Carr A, Samaras K, Thorisdottir A, et al. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidemia, and diabetes mellitus: A cohort study. Lancet 1999; 353: 2093-9.
9. Walli R, Herfort O, Michl GM, Demant T, et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1-infected patients. AIDS 1998; 12: F167-73.
10. Yarasheski KE, Tebas P, Sigmund C, et al. Insulin resistance in HIV protease inhibitor-associated diabetes. J AIDS 1999; 21: 209-16.
11. Yanovski JA, Miller KD, Kino T, et al. Endocrine

and metabolic evaluation of human immunodeficiency virus-infected patients with evidence of protease inhibitor-associated lipodystrophy. J Clin Endocrinol Metab 1999; 84: 1925-31.

12. Hadigan C, Corcoran C, Stanley T, et al. Fasting hyperinsulinemia in human immunodeficiency virus-infected men: relationship to body composition, gonadal function, and protease inhibitor use. J Clin Endocrind Metab 2000; 85: 35-41.
13. Tsiodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: A 5-year cohort study. Arch Intern Med 2000; 160: 2050-6.
14. Day C. Thiazolidinediones: A new class of antidiabetic drugs. Diabet Med. 1999; 16: 179-92.
15. Saint-Marc T, Partisani M, Poizot-Martin I, et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. AIDS 1999; 13: 1659-67.
16. Madge S, Kinloch-de-Loes S, Mercy D, Johnson MA, Weller IV. Lipodystrophy in patients naïve to HIV protease inhibitors. AIDS 1999; 13: 735-7.
17. Leow MKS, Addy CL, Mantzoros CS. Human Immunodeficiency virus/highly active antiretroviral therapy-associated metabolic syndrome: Clinical presentation, pathophysiology, and therapeutic strategies. J Clin Endocrinol Metab 2003; 88: 1961-76.
18. Zhang B, MacNaul K, Szalsowski D, Li Z, Berger J, Moller DE. Inhibition of adipocyte differentiation by HIV protease inhibitors. J Clin Endocrinol Metab 1999; 84: 4274-7.
19. Wentworth JM, Burris TP, Chatterjee VK. HIV protease inhibitors block human preadipocyte differentiation, but not *via* the PPAR-gamma/RXR heterodimer. J Endocrinol 2000; 164: 407-10.
20. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease-inhibitor-associated peripheral lipodystrophy, hyperlipidemia, and insulin resistance. Lancet 1998; 351: 1881-3.
21. Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. Lancet 1999; 354: 1112-5.
22. Carter VM, Hoy JF, Bailey M, et al. The prevalence of lipodystrophy in an ambulant HIV-infected population: It all depends on the definition, HIV Med 2001; 2: 174-80.
23. Martinez E, Mocroft A, Garcia-Viejo MA, et al. Risk of lipodystrophy in HIV-1 infected patients treated with protease-inhibitors: A prospective cohort study. Lancet 2001; 357: 592-8.
24. Martinez E, Conget I, Lozano L, Casamitjana R, Gatell JM. Reversion of metabolic abnormalities afterswitching from HIV-I protease inhibitors to nevirapine. AIDS 1999: 13: 805-10.
25. Saint-Marc T, Touraine JL. The effects of discontinuing starvudine therapy on clinical and metabolic abnormalities in patients suffering from lipodystrophy. AIDS 1999; 13: 2188-9.
26. Torres RA, Unger KW, Cadman JA, Kassous JY. Recombinant human growth hormone improves truncal adiposity and 'buffalo humps' in HIV-positive patients on HAART. AIDS 1999; 13: 2479-81.
27. Mauss S, Wolf E, Jaeger H. Reversal of protease inhibitor-related visceral abdominal fat accumulation with recombinant human growth hormone. Ann Intern Med 1999; 131: 313-4.
28. Wanke C, Gerrior J, Kantaros J, Coakley E, Albrecht M. Recombinant human growth hormone improves the fat redistribution syndrome (lipodystrophy) in patients with HIV. AIDS 1999; 13: 2099-103.
29. Hadigan C, Corcoran C, Basgoz N, et al. Metformin in the treatment of HIV lipodystrophy syndrome. A randomized controlled trial. JAMA 2000; 284: 472-7.
30. Arioglu E, Duncan-Morin J, Sebring N, et al. Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. Ann Intern Med 2000; 133: 263-74.
31. Gelato MC, Mynarcik DC, Quick JL, et al. Improved insulin sensitivity and body fat distribution in HIV-infected patients treated with rosigliytazone: A pilot study. J Acquir Immune Defic Syndr 2002; 31: 163-70.
32. Sutinen J, Hakkinen AM, Wesrebacka J, et al. Rosiglitazone in the treatmen of HAART associated lipodystrophy (HAL): A randomized, double-blind, placebo-controlled study. Program of the Ninth Conference on Retroviruses and Opportunistic Infections, Seattle WA 2002 (Abstract LB13).
33. Calmy A, Hirschel B, Hans D, Karsegard VL, Meier CA. Glitazones in lipodystrophy syndrome induced by highly active antiretroviral therapy. AIDS 2003; 17: 770-2.

การรักษาการกระจายตัวของไขมันที่ผิดปกติ, ภาวะดื้อต่ออินสุลินและภาวะไขมันสะสมที่ตับในผู้ป่วย HIV-associated lipodystrophy syndrome โดยใช้ยา pioglitazone : รายงานผู้ป่วย 1 ราย

วิศิษฏ์ ประสิทธิศิริกุล, พบ, พงศ์อมร บุนนาค, พบ***

HIV-associated lipodystrophy syndrome เป็นกลุ่มอาการที่อาจพบได้ในผู้ป่วยติดเชื้อเอ็ชไอวี ที่ได้รับการรักษาด้วยยาต้านไวรัสหลายตัวร่วมกัน (highly active antiretroviral therapy; HAART) โดยเฉพาะสูตรยาที่มี protease inhibitors ร่วมด้วย กลุ่มอาการนี้ประกอบด้วยการหายไปของไขมันใต้ผิวหนังร่วมกับการเพิ่มขึ้นของไขมันในช่องท้องและการเปลี่ยนแปลงทางเมตะบอลิสม ได้แก่ความผิดปกติของระดับน้ำตาลและไขมัน ในปัจจุบันยังไม่มีการรักษาที่เป็นมาตรฐานสำหรับกลุ่มอาการนี้ ยา pioglitazone เป็นยาลดระดับน้ำตาลในเลือดที่ออกฤทธิ์ในการแก้ไขภาวะดื้อต่ออินสุลินที่เซลล์ไขมันโดยตรง จึงอาจแก้ไขความผิดปกติที่พบในโรคนี้ได้ คณะผู้วิจัยได้รายงานผู้ป่วยหญิงอายุ 50 ปี 1 รายซึ่งติดเชื้อเอ็ชไอวี และเกิด HIV-associated lipodystrophy syndrome ภายหลังได้ HAART ประมาณ 3 เดือน โดยผู้ป่วยมีน้ำหนักตัวลดลง 20 กิโลกรัม และมีไขมันใต้ผิวหนังลดลงอย่างเห็นได้ชัด นอกจากนี้ ยังตรวจพบโรคเบาหวาน, ความดันโลหิตสูงและไขมันในเลือดผิดปกติร่วมด้วยการทำ CT scan พบมีไขมันสะสมที่ตับ ภายหลังการรักษาด้วยยา pioglitazone ในขนาด 30 มก ต่อวัน พบการเปลี่ยนแปลงในทางที่ดีขึ้นทั้งในเรื่องไขมันใต้ผิวหนังที่หายไปและปัญหาทางด้านเมตะบอลิก การทำ CT scan ซ้ำที่เวลา 4 เดือนภายหลังการรักษา พบว่าปริมาณไขมันทั้งที่ตับและในช่องท้องลดลง ยา pioglitazone จึงเป็นยาที่อาจช่วยแก้ไขความผิดปติที่พบในผู้ป่วยที่เป็น HIV-associated lipodystrophy syndrome ได้

คำสำคัญ : การกระจายตัวของไขมันผิดปกติในผู้ป่วยเอ็ชไอวี, ไพโอกลิตาโซน, ภาวะดื้ออินซูลิน

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