The metabolic effects of lopinavir/ritonavir in HIV-negative men

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Abstract

Background—Therapy with HIV protease inhibitors (PI) has been shown to worsen glucose and lipid metabolism, but whether these changes are caused by direct drug effects, changes in disease status, or body composition is unclear. Therefore, we tested the effects of the PI combination lopinavir and ritonavir on glucose and lipid metabolism in HIV-negative subjects.

Methods—A dose of 400 mg lopinavir/100 mg ritonavir was given twice a day to 10 HIV-negative men. Fasting glucose and insulin, lipid and lipoprotein profiles, oral glucose tolerance, insulin sensitivity by euglycemic hyperinsulinemic clamp, and body composition were determined before and after lopinavir/ritonavir treatment for 4 weeks.

Results—On lopinavir/ritonavir, there was an increase in fasting triglyceride (0.89 ± 0.15 versus 1.63 ± 0.36 mmol/l; $P = 0.007$), free fatty acid (FFA; 0.33 ± 0.04 versus 0.43 ± 0.06 mmol/l; $P = 0.001$), and VLDL cholesterol (15.1 ± 2.6 versus 20 ± 3.3 mg/dl; $P = 0.05$) levels. There were no changes in fasting LDL, HDL, IDL, lipoprotein (a), or total cholesterol levels. Fasting glucose, insulin, and insulin-mediated glucose disposal were unchanged, but on a 2 h oral glucose tolerance test glucose and insulin increased. There were no changes in weight, body fat, or abdominal adipose tissue by computed tomography.

Conclusion—Treatment with 4 weeks of lopinavir/ritonavir in HIV-negative men causes an increase in triglyceride levels, VLDL cholesterol, and FFA levels. Lopinavir/ritonavir leads to a deterioration in glucose tolerance at 2 h, but there is no significant change in insulin-mediated glucose disposal rate by euglycemic hyperinsulinemic clamp.

Keywords

HIV protease inhibitors; ritonavir; insulin resistance; body composition; cholesterol; triglycerides; lipodystrophy; HIV

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Introduction

With the advent of highly active antiretroviral therapy (HAART), the treatment of HIV has been associated with alterations in lipid metabolism, insulin resistance, and hyperglycemia [1–3]. HIV-infected patients treated with some protease inhibitors (PI) develop increased levels of triglycerides, VLDL and LDL cholesterol, but usually no change in HDL cholesterol levels [3–5]. PI treatment has also been associated with elevations in fasting glucose, insulin resistance, and impaired glucose tolerance [6–9].

It is unclear to what extent these metabolic changes are directly caused by protease inhibitor therapy, the underlying HIV disease state, immune reconstitution, or associated body composition changes [10–13]. PI induce some changes in metabolism in HIV-positive patients before the onset of body composition changes. To address these issues, our laboratory and others have studied the effects of PI on glucose and lipid metabolism in HIV-negative, healthy volunteers. We have previously found that 4 weeks of treatment with indinavir caused insulin resistance, but had no effect on lipoproteins [7]. The insulin resistance occurred in the absence of any changes in visceral or subcutaneous fat measured by computed tomography (CT) scan. In contrast, treatment of HIV-negative subjects with ritonavir for 2 weeks induced increases in triglyceride levels, VLDL, IDL, apolipoprotein B and lipoprotein (a), with a small decrease in HDL [14,15]. There was also no increase in LDL. Amprenavir, on the other hand, had no effect on lipoproteins in HIV-negative subjects [14]. However, the effects of other PI on glucose metabolism have not been studied in HIV-negative subjects.

On the basis of these observations, it appears that the effects of PI on lipid metabolism are drug specific, but there are inadequate data on the effects of PI on human glucose metabolism in the absence of the confounding effects of HIV. In-vitro data suggest that several PI block glucose uptake into cells by inhibiting GLUT4 [16,17]. To date, only indinavir has been shown to induce insulin resistance in humans. Therefore, in this study, we examined the effects of a second PI, lopinavir/ritonavir (Kaletra) on glucose and lipid metabolism in HIV-seronegative men. We found that 4 weeks of treatment with lopinavir/ritonavir increased triglyceride levels, free fatty acids (FFA), and VLDL with no effect on LDL, lipoprotein (a), or HDL. There was a small effect on glucose tolerance on the oral glucose tolerance test (OGTT), but no effect on fasting glucose and insulin or insulin resistance as measured by euglycemic hyperinsulinemic clamp.

Methods

Ten healthy men were recruited from the community or staff at the University of California, San Francisco (UCSF). The study protocol was approved by the Committee on Human Research at UCSF and informed consent was obtained. The subjects had no history of medical illness and had normal screening physical examinations. Hematology and chemistry results were within normal limits. All subjects had a negative HIV-1 antibody test before the study.

Exclusion criteria included a body mass index (BMI) greater than 27 kg/m^2, serum total cholesterol greater than 6.2 mmol/l, triglyceride level greater than 3.8 mmol/l, fasting glucose greater than 7.0 mmol/l, serum aspartate or alanine aminotransferases greater than 50 U/l and creatinine greater than 124 μM.

Study design

Subjects were admitted to the General Clinical Research Center (GCRC) at San Francisco General Hospital (SFGH) for 5 days and were placed on a constant calorie diet with fixed

proportions of carbohydrate, fat, and protein designed to maintain body weight and minimize dietary influences on metabolism [18]. After baseline studies, subjects were discharged, given 400 mg lopinavir/100 mg ritonavir (Kaletra; Abbott Laboratories, Abbott Park, IL, USA) to take twice a day with food, and were seen weekly for safety and adherence monitoring. They were instructed to resume their usual diet and physical activity. After 4 weeks on treatment, subjects were readmitted to the GCRC for a second 5-day period for repeat studies. To achieve adequate drug levels, lopinavir/ritonavir was given at the start of the OGTT and 40 min before the euglycemic hyperinsulinemic clamp on an empty stomach.

Euglycemic hyperinsulinemic clamp

The clamp was performed as described by DeFronzo *et al.* [19]. An antecubital vein cannulae was inserted for infusion, and a vein in the dorsum of the contralateral hand was cannulated and heated to 50–55°C for arterialized venous blood sampling. Subjects fasted overnight before the procedure. At $t = 0$ min, insulin (Humulin R; Eli Lilly, Indianapolis, IN, USA) was administered as a primed continuous intravenous infusion for 10 min, followed by a constant infusion at the rate of 40 mU/m^2 per min until $t = 180$ min. The whole blood glucose concentration was measured every 5 min. Dextrose (20%) was infused to maintain the plasma glucose concentration at 4.5 mmol/l with a coefficient of variation of less than 5% based on the negative feedback principle. Blood samples were also collected for post hoc determination of serum insulin concentrations.

Resting energy expenditure

Oxygen consumption and carbon dioxide production were measured by indirect calorimetry (DeltaTrac metabolic monitor; Yorba Linda, CA, USA). The non-protein respiratory quotient and substrate oxidation rates were calculated after correction for protein oxidation, as estimated by urea nitrogen excretion measured in the 24 h urine collection [7]. The rate of non-oxidative glucose metabolism was calculated by subtracting the rate of carbohydrate oxidation from the rate of dextrose infusion during the clamp. At the insulin levels achieved during this procedure, hepatic glucose production is completely suppressed in healthy individuals.

Fat clearance

At 08:00 hours, after a 10 h overnight fast, an intravenous fat tolerance test was performed as described previously [7]. Intralipid (Liposyn II 20%; Abbott Laboratories, Chicago, IL, USA) was infused at 0.1 g/kg body weight over 2 min, and blood samples were collected at 0, 5, 10, 15, 20, 30, 40, and 50 min for nephelometry.

Oral glucose tolerance test

At 08:00 hours, after a 10 h overnight fast, subjects received 75 g glucose orally. Blood samples were collected at 0, 30, 60, 90, 120, and 180 min and assayed from plasma glucose (sodium fluoride-containing tubes) and serum insulin. The area under the curve (AUC) for glucose and insulin were calculated by the trapezoid method. The following glucose tolerance criteria from the World Health Organization were used for clinical characterization: normal glucose tolerance (2 h glucose < 7.8 mmol/l); impaired glucose tolerance (2 h glucose 7.8–11.0 mmol/l); and overt glucose intolerance or diabetes (2 h glucose > 11.1 mmol/l) [20]. Fasting plasma glucose and fasting serum insulin levels were measured on 2 days, and the average data were used to calculate the insulin resistance index by the homeostasis model assessment (HOMA) [21].

Measurements

Fasting lipids and FFA were measured using enzymatic colorimetric methods (Sigma Diagnostics, St Louis, MO, USA and Wako Chemicals, Richmond, VA, USA). Lipoprotein and cholesterol measurements were measured by ultracentrifugation (Atherotec, Birmingham, AL, USA). Whole blood and plasma glucose and lactate were measured using a glucose analyser (YSI 2300 STAT-Plus Glucose and Lactate Analyzer; YSI Inc., Yellow Springs, OH, USA). Serum insulin levels were determined by Coat-A-Count radioimmunoassay (Diagnostic Products Corp., Los Angeles, CA, USA) with an intra-assay coefficient of variation of 7.3%, a lower detection limit of 9.3 pmol/l and 20% cross reactivity with proinsulin.

Lopinavir levels were measured by liquid chromatography, tandem mass spectrometry at the Drug Research Unit, SFGH. The method has a lower detection limit of 105 ng/ml, inter and intra-assay coefficient of variations ranging from 6.0 to 9.9 and 3.3 to 6.4%, respectively.

Studies of body composition

BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). CT was performed on a helical HiSpeed CTI Scanner (General Electric Medical Systems, Milwaukee, WI, USA) as previously described [7,22]. A single 7 mm slice obtained at the level of the L4–L5 intervertebral disc space was used for the quantification of visceral and subcutaneous fat. All images were analysed in a matrix of 512×512 pixels by one investigator, with a coefficient of variation less than 1% on repeat analysis.

Total and regional body composition was measured by dual-energy X-ray absorptiometry (DEXA; Lunar model DPX, Madison, WI, USA, software version 3.65). An analysis of scans was performed as previously described [7,22,23], with a coefficient of variation for repeated regional analysis of trunk, arm, and leg fat at 1.0, 2.7, and 1.4%.

Bioelectric impedance analysis was performed using a tetra polar BIA101 Quantum (RJL Systems Inc., Clinton Township, MI, USA). Body cell mass was calculated using software version 3.1b.

Adherence

Subjects were instructed to take 400 mg lopinavir/100 mg ritonavir twice a day with water. Adherence was monitored at each weekly visit by three methods: (i) self report/direct questioning; (ii) electronic pill counts using a medication event monitoring system (Aprex Corp., Union City, CA, USA) for quantification of adherence rate and dosing intervals; and (iii) measurement of plasma lopinavir trough levels.

Statistical analysis

Data were analysed using Sigma Stat version 2.03 (SPSS, Inc., San Rafael, CA, USA). Paired *t*-tests were used for normally distributed data. Data are presented as mean ± SEM. *P* values are two-tailed.

Results

Ten male subjects ranged in age from 29 to 66 years (mean 43.8 ± 4.5); one subject was Hispanic whereas the other nine were Caucasian. The average therapeutic coverage measured by the medication event monitoring system was 94.4 ± 1% (range 87–99). All subjects had detectable lopinavir levels that were within two standard deviations of the expected level. Average weekly lopinavir levels were 13.4 ± 7.3 μmol/l. Before the euglycemic hyperinsulinemic clamp, lopinavir levels were 10.5 ± 1.2 μmol/l at $t_{0 \text{ min}}$ and

increased during the study to 12.5 ± 1.5 μmol/l at $t_{180 \text{ min}}$. Peak therapeutic lopinavir levels have been shown to average 8.49 ± 5.4 μmol/l in HIV-infected patients [24]. The most common reported adverse effects were loose stools (four subjects) and diarrhea (two subjects); one subject had a single episode of nausea and vomiting. No one complained of dry skin or mouth. There were no abnormalities in electrolytes, white blood cell counts, or liver function tests. All 10 subjects completed the study.

After 4 weeks of lopinavir/ritonavir treatment, fasting triglyceride levels increased nearly twofold, whereas VLDL cholesterol levels increased by 33% (Table 1). Eight out of 10 subjects showed an increase in triglyceride levels (Fig. 1). There were no changes noted in fasting LDL, HDL, IDL, lipoprotein (a), total cholesterol, or HDL. Among the VLDL subclasses, $VLDL_2$ levels significantly increased and there was a smaller trend in $VLDL_3$ levels. A small decrease in LDL subspecies cannot be ruled out. FFA increased by 30% after lopinavir/ritonavir treatment. Eight out of 10 subjects showed an increase in FFA levels (Fig. 1). The clearance time of triglyceride levels as measured by an intravenous fat tolerance test showed a trend towards a small 14% delay in fat clearance (Table 1).

In contrast to what we found with 4-week treatment with indinavir, fasting glucose, insulin, and insulin resistance index by HOMA did not change after 4 weeks of treatment with lopinavir/ritonavir (Table 2). Likewise, insulin resistance as measured by euglycemic hyperinsulinemic clamp was not significantly altered. During the euglycemic hyperinsulinemic clamp, a steady state insulin level of approximately 360 pmol/l was achieved after 30 min and maintained until 180 min. Steady-state glucose levels of approximately 4.5 mmol/l were achieved at 60 min and were maintained to 180 min. The insulin-mediated glucose disposal rate per unit of insulin (M/I) from 120 to 180 min remained unchanged with lopinavir/ritonavir treatment (15.9 ± 2.1 mg/kg per min per μU/ml at baseline versus 16.2 ± 2.3 at 4 weeks; $P = 0.81$).

During the OGTT, glucose levels were increased at 2 h after 4 weeks of treatment (Fig. 2 and Table 2). Eight out of 10 subjects showed an increase in 2-h glucose levels and one subject developed impaired glucose tolerance (2 h glucose of 10.1 mmol/l) (Fig. 3). The AUC for glucose showed a trend towards an increase (Table 2). There was a trend towards a decrease in insulin levels early in the OGTT (30 min), and insulin levels also increased slightly by 2 h (Fig. 2). FFA were suppressed to the same level both before and during treatment with lopinavir/ritonavir (Table 2).

After 4 weeks treatment with lopinavir/ritonavir, there were no significant changes in body composition, including weight, BMI, body cell mass by bioelectric impedence analysis, lean body mass, bone mineral content, or fat mass by DEXA, or visceral or subcutaneous fat by CT (Table 3).

Discussion

The most notable effect of 4 weeks of lopinavir/ritonavir treatment on HIV seronegative men was the 83% increase in triglyceride levels with the greatest increase seen in VLDL particles. These results are similar to but quantitatively less than the threefold increase in triglyceride levels seen in HIV-negative subjects treated with ritonavir for 2 weeks [15]. Ritonavir is the likely agent causing the increase in triglyceride levels in the lopinavir/ritonavir combination. The effect of lopinavir cannot be studied in isolation, as ritonavir is needed as a pharmockinetic booster by blocking cytochrome CYP 3A4; therefore, one cannot determine whether lopinavir alone contributes to the elevation in triglyceride levels seen in this study.

One postulated mechanism for the elevation in triglyceride levels is an increase in VLDL production. Our results support this hypothesis over a delay in lipoprotein clearance for several reasons. First, the small 14% decrease in triglyceride level clearance seen during the intravenous fat tolerance test cannot explain the nearly twofold elevation in triglyceride levels. Second, we did not see the appearance of increased IDL cholesterol levels or remnants. Finally, others have shown that lipoprotein lipase and hepatic lipase levels remained unchanged after ritonavir treatment, thus excluding the hypothesis of the decreased lipolysis of lipoproteins as a cause of triglyceride elevation [15]. In-vitro studies have suggested several cellular mechanisms for the increase in VLDL production. Ritonavir has been shown to inhibit apolipoprotein B degradation, resulting in an increased secretion of apolipoprotein B from cultured hepatoma cells [25]. Others have suggested the involvement of activated sterol regulatory element binding proteins (SREBP) in the liver [26]. Further work is needed on the mechanism of increased VLDL cholesterol production induced by ritonavir and lopinavir/ritonavir.

In contrast to the effects on VLDL and triglyceride levels, lopinavir/ritonavir did not increase LDL cholesterol levels. Increases in LDL have been observed in HIV-positive patients on HAART with several PI [15,27,28]. However, HAART with a non-nucleoside reverse transcriptase inhibitor (NNRTI), such as nevirapine, raises LDL cholesterol to similar levels as indinavir, ritonavir, nelfinavir and saquinavir [3,5,29]. In contrast, the treatment of HIV-negative individuals with four different PI: ritonavir [15], indinavir [7], amprenavir [14], and lopinavir/ritonavir (this study), did not lead to an increase in LDL levels. These data suggest that PI therapy does not directly cause alterations in LDL metabolism. Whether these changes in LDL levels seen in HIV-positive patients on PI and NNRTI represent a restoration to health, or an interaction between HAART and HIV remains to be determined. Preliminary data indicate that atazanavir does not increase LDL in HIV-positive patients [30]. Therefore, multiple mechanisms for alterations in LDL levels may be involved.

Although lopinavir/ritonavir had marked effects on triglyceride, FFA and VLDL cholesterol metabolism, less dramatic effects were seen on glucose metabolism and insulin resistance. Unlike indinavir, lopinavir/ritonavir had no effect on fasting glucose, fasting insulin, or HOMA, an assessment of fasting insulin resistance. No difference in insulin sensitivity or the induction of insulin resistance was seen in 10 patients using the euglycemic hyperinsulinemic clamp. However, there was a small, but significant, decrease in glucose tolerance at 120 min of OGTT. A similar impairment in glucose tolerance during OGTT, but with little insulin resistance by the minimal model, was found with amprenavir treatment of HIV-positive patients [31]. We also previously found an increase in insulin and glucose at 120 min with indinavir 4-week treatment of healthy normal volunteers [7]. There are several potential explanations for the different effects of lopinavir/ritonavir on glucose metabolism compared with amprenavir and indinavir. First, the changes seen during the OGTT may be independent of GLUT4 blockade, and may be caused by impaired first and second-phase insulin secretion. Woerle *et al.* [32] showed in 13 HIV-infected patients starting various PI including lopinavir/ritonavir and indinavir that first-phase insulin secretion was decreased by 25% during the hyperglycemic clamp. Second-phase insulin secretion did not decrease, but was inappropriately reduced in the setting of peripheral insulin resistance, as reflected in a decreased disposition index. Lopinavir/ritonavir may thus impair both first and second-phase insulin secretion more than peripheral resistance, resulting in impaired glucose tolerance on OGTT, with little evidence of impaired insulin-mediated glucose disposal on euglycemic hyperinsulinemic clamp. The decreased insulin levels at 30 min during the OGTT are consistent with impaired first-phase insulin secretion. An effect on insulin clearance is less likely, as levels during the clamp were not affected. Alternatively, the 10% decrease induced by lopinavir/ritonavir in glucose tolerance by AUC during the OGTT is

small, and it is possible that a small change may have been missed on euglycemic hyperinsulinemic clamp or fasting glucose and insulin levels. The finding that 2 h insulin levels on OGTT increased in those with the largest increase in glucose supports this hypothesis. Although insulin levels at 120 min are elevated, second-phase insulin secretion may not be adequately increased in the setting of insulin resistance. A combination of mild insulin resistance coupled with impaired secretion preventing an adequate compensatory increase in insulin is therefore likely. Although we have not performed a randomized trial of lopinavir/ritonavir versus indinavir, it is of note that on lopinavir/ritonavir one patient developed impaired glucose tolerance, whereas on indinavir, one developed diabetes and two developed impaired glucose tolerance. The clinical significance of the small impairment of glucose tolerance on lopinavir/ritonavir is uncertain.

The lack of significant insulin resistance seen with lopinavir/ritonavir treatment during the clamp differs from the current in-vitro data on PI. Indinavir, amprenavir, and ritonavir have been shown to inhibit glucose uptake in 3T3-L1 adipocytes, and indinavir has been shown to inhibit glucose uptake by the acute blockade of GLUT4 transporters in a *Xenopus laevis* oocyte GLUT4 expression system. Of note, the effect of lopinavir on GLUT4 *in vitro* remains to be studied. One consideration in comparing the in-vivo effects of indinavir with other PI is the lower protein binding of indinavir. Whereas indinavir is only 60–65% protein bound, ritonavir and lopinavir are over 98% protein bound. The in-vitro studies of PI did not use normal concentrations of serum proteins, and therefore may have had higher free drug levels that do not account for the possible in-vivo effects of protein binding seen with lopinavir and ritonavir. Indinavir may thus achieve higher serum unbound drug concentrations *in vivo* than other PI.

Another difference between indinavir and lopinavir/ritonavir treatment was their effects on the FFA level. Four-week treatment with indinavir did not increase FFA, whereas lopinavir/ritonavir raised FFA by 30%. Although the stimulation of lipolysis with elevated FFA could be considered a mechanism for the insulin resistance of PI, this is not likely to be the case for several reasons. First, treatment with indinavir induced more insulin resistance than lopinavir/ritonavir by euglycemic hyperinsulinemic clamp, and yet did not increase fasting FFA levels, but tended to decrease them. Second, both indinavir and lopinavir/ritonavir showed FFA suppression during the OGTT. Third, indinavir acutely induced insulin resistance during a euglycemic hyperinsulinemic clamp with normal suppression of FFA. Finally, lopinavir/ritonavir induced a robust increase in fasting FFA without inducing insulin resistance. Although some have speculated that insulin resistance in HIV infection occurs secondary to the increased release of FFA, such studies demonstrate an uncoupling of FFA release and an induction of insulin resistance.

Likewise, it might be postulated that PI-induced insulin resistance might be the cause of the observed hypertriglyceridemia after lopinavir/ritonavir treatment. However, indinavir induced insulin resistance without increasing triglyceride levels, and lopinavir/ritonavir increased triglyceride levels without inducing significant insulin resistance. These data demonstrate that the effects of the drugs on each metabolic pathway are independent. They also emphasize the need to study other PI drugs on multiple metabolic pathways.

There are several potential limitations to the current study. There were no significant changes in body composition after 4 weeks of treatment with lopinavir/ritonavir. There was a trend towards a small decrease (4%) in visceral fat by CT scanning, but no decrease in subcutaneous fat, or total fat by DEXA. We cannot rule out the possibility that this small decrease in visceral adipose tissue may have dampened the induction of insulin resistance, but it might also have dampened the increase in FFA and triglyceride levels. The lack of

increase in visceral adipose tissue suggests that changes in lipid and glucose metabolism seen with lopinavir/ritonavir are independent of increased central fat accumulation.

The drug combination of lopinavir/ritonavir limits the ability to identify which of the individual drugs or whether the combination of both are the causative agents of the effects on glucose and lipid metabolism. However, the combination is currently used to treat HIV patients and may be more relevant clinically [33]. Four-week treatment with lopinavir/ ritonavir may not have been taken long enough to induce significant changes in body composition. Only men were enrolled in the current study, and pre and postmenopausal women may have different metabolic outcomes.

In summary, 4-week treatment with lopinavir/ritonavir increased plasma triglyceride levels and worsened glucose tolerance during OGTT; however, insulin sensitivity as measured by the euglycemic hyperinsulemic clamp was not impaired. These results contrast with those seen with indinavir, which had little effect on lipid metabolism but significantly increased insulin resistance. The metabolic effects of PI thus appear to be drug specific and not class specific. Individual PI need to be studied with respect to their effects on lipid and glucose metabolism *in vivo* and in the presence and absence of HIV. As of yet, no PI has been shown to increase LDL significantly in HIV-negative individuals. Further exploration of the mechanism of altered lipid metabolism with PI may lead to a better understanding of lipoprotein production, and long-term studies may offer a better insight into the risk of coronary artery disease in patients with HIV infection.

Acknowledgments

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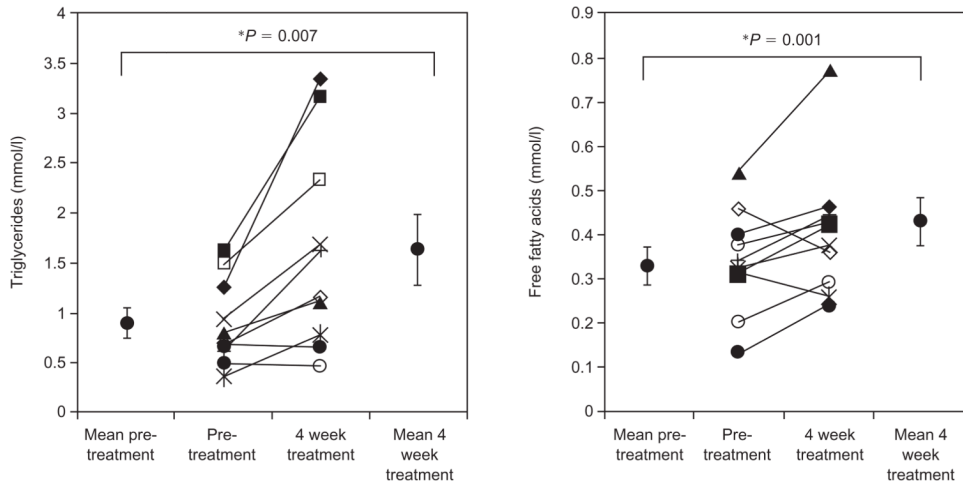
Fig. 1.
Fasting triglyceride and free fatty acid levels at baseline and after 4 weeks of treatment with lopinavir/ritonavir.
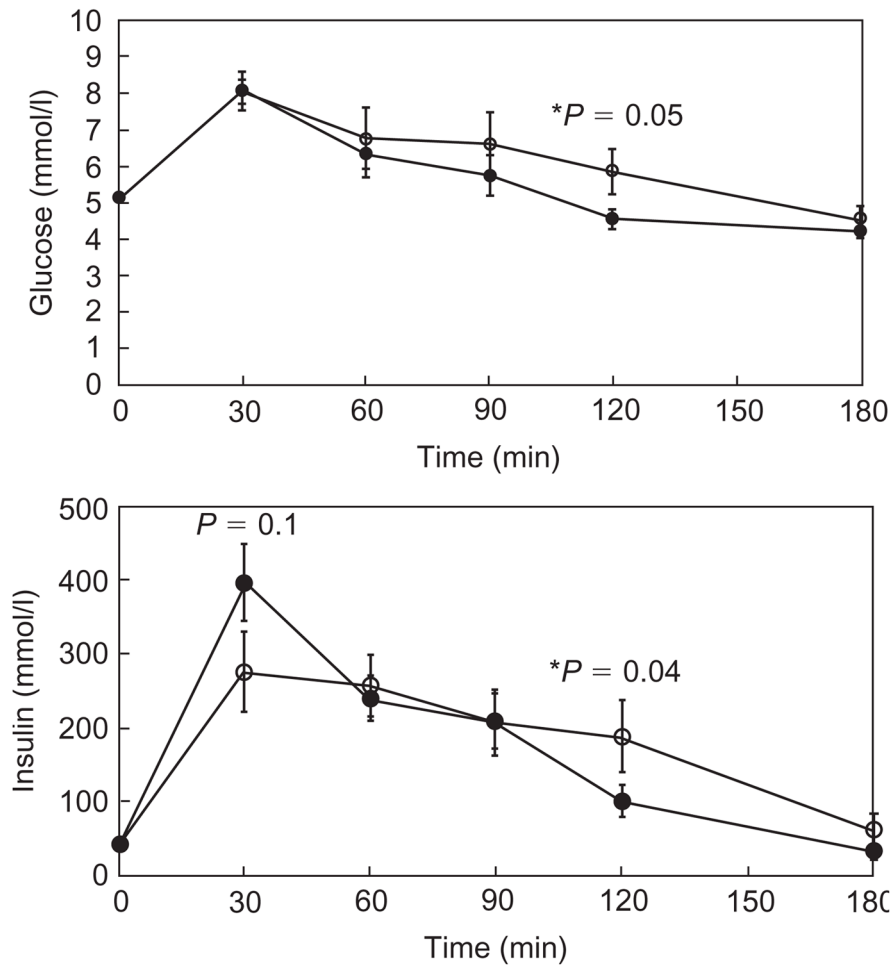
Fig. 2. Glucose and insulin levels during oral glucose tolerance test at baseline and after 4 weeks of treatment with lopinavir/ritonavir
—●— Pre-treatment; —○— 4 weeks of treatment.
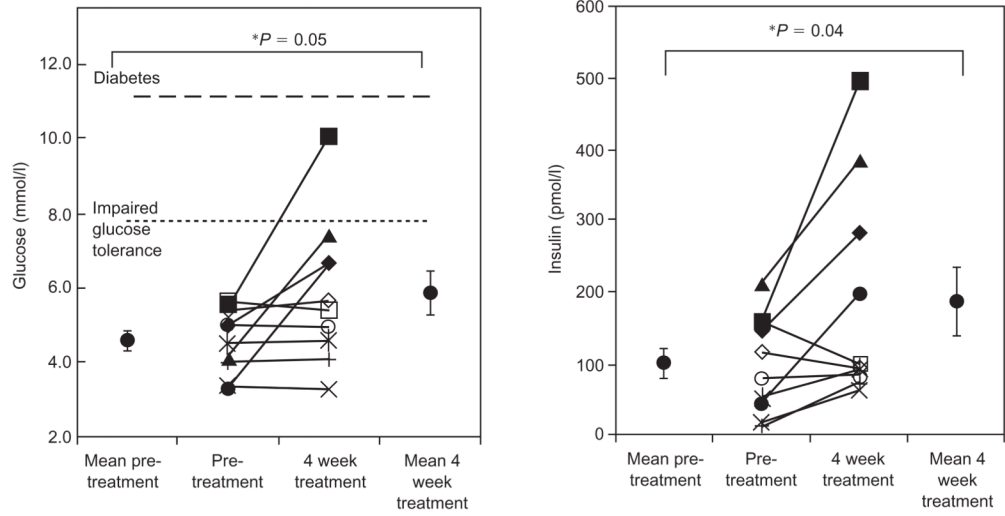
Fig. 3.
Glucose and insulin levels at 120 min during oral glucose tolerance test before and after 4 weeks of treatment with lopinavir/ritonavir.

Table 1

Lipoproteins and lipids at baseline and after 4 weeks of treatment with lopinavir/ritonavir.

	Baseline	4 weeks' treatment	*P* value
Total cholesterol (mmol/l)	4.5 ± 0.3	4.4 ± 0.4	0.74
Triglycerides (mmol/l)	0.89 ± 0.15	1.63 ± 0.36	0.007
Free fatty acids (mmol/l)	0.33 ± 0.04	0.43 ± 0.06	0.001
LDL cholesterol (mmol/l)	3.0 ± 0.2	2.8 ± 0.2	0.31
LDL-A (mmol/l)	1.1 ± 0.2	1.0 ± 0.1	0.05
LDL-B (mmol/l)	1.3 ± 0.3	1.2 ± 0.2	0.59
HDL cholesterol (mmol/l)	1.13 ± 0.1	1.12 ± 0.1	0.85
HDL_2 cholesterol (mmol/l)	0.21 ± 0.03	0.22 ± 0.03	0.49
HDL_3 cholesterol (mmol/l)	0.92 ± 0.08	0.90 ± 0.07	0.63
VLDL cholesterol (mmol/l)	0.39 ± 0.07	0.52 ± 0.09	0.05
$VLDL_2$ cholesterol (mmol/l)	0.19 ± 0.04	0.27 ± 0.05	0.03
$VLDL_3$ cholesterol (mmol/l)	0.2 ± 0.04	0.26 ± 0.03	0.11
IDL cholesterol (mmol/l)	0.35 ± 0.04	0.39 ± 0.04	0.39
Lipoprotein (a) (mmol/l)	0.20 ± 0.04	0.19 ± 0.03	0.60
Half-life fat clearance (min)	21.3 ± 3.6	24.2 ± 3.5	0.07

Table 2

Glucose metabolism at baseline and after 4 weeks of treatment with lopinavir/ritonavir.

	Baseline	4 weeks' treatment	*P* value
Fasting plasma glucose (mmol/l)	4.8 ± 0.1	4.8 ± 0.1	0.91
Fasting serum insulin (pmol/l)	40.9 ± 8.3	36.4 ± 5.3	0.51
Fasting serum insulin/fasting plasma glucose (pmol/mmol)	8.5 ± 1.7	7.5 ± 1.1	0.51
Homeostasis model assessment insulin resistance	1.2 ± 0.3	1.1 ± 0.2	0.52
Lactate (mmol/l)	0.77 ± 0.08	0.78 ± 0.07	0.85
Insulin-mediated glucose disposal (mg/kg/min)	7.4 ± 0.6	7.1 ± 0.7	0.27
Insulin-mediated glucose disposal (mg/kg/min per μU/ml insulin)	15.9 ± 2.1	16.2 ± 2.3	0.81
Oxidative component of total glucose disposal (mg/kg/min)	1.8 ± 0.2	1.6 ± 0.2	0.18
Non-oxidative component of total glucose disposal (mg/kg/min)	5.6 ± 0.6	5.2 ± 0.5	0.27
Glucose 2 h (OGTT) (mmol/l)	4.6 ± 0.3	5.9 ± 0.6	0.05
Insulin 2 h (OGTT) (pmol/l)	99.6 ± 21.9	187.6 ± 48.4	0.04
AUC glucose (OGTT) (mmol/h/l)	16.9 ± 0.8	18.6 ± 1.4	0.07
AUC insulin (OGTT) (pmol/h/l)	523 ± 12.8	552 ± 73.6	0.63
Free fatty acids 2h (OGTT) (mmol/l)	0.13 ± 0.03	0.1 ± 0.02	0.18

AUC, Area under the curve; OGTT, oral glucose tolerance test.

Table 3

Body composition and energy expenditure at baseline and after 4 weeks of treatment with lopinavir/ritonavir.

	Baseline	**4 weeks' treatment**	*P* value
Weight (kg)	78.6 ± 3.8	78.2 ± 3.8	0.21
Body mass index (kg/m^2)	24.6 ± 0.7	24.4 ± 0.6	0.13
Abdominal adipose tissue by CT scan			
Subcutaneous (mm^2)	17 629 ± 2025	16 922 ± 2371	0.29
Visceral (mm^2)	8950 ± 1933	8560 ± 2094	0.11
Visceral + subcutaneous (mm^2)	26 579 ± 3177	25 482 ± 3638	0.16
DEXA scan			
Total fat tissue (kg)	16.8 ± 1.9	16.6 ± 1.2	0.31
Appendicular fat (kg)	8.5 ± 0.7	8.4 ± 0.7	0.60
Trunk fat (kg)	7.6 ± 1.3	7.4 ± 1.4	0.38
Total lean tissue (kg)	57.3 ± 3.3	57.0 ± 3.4	0.23
Appendicular lean (kg)	27.9 ± 2.2	27.9 ± 2.2	0.83
Trunk lean (kg)	26.1 ± 1.3	25.9 ± 1.2	0.47
Bone mineral content	3.1 ± 0.2	3.1 ± 0.3	0.14
Body cell mass (kg)	30.5 ± 0.2	30.4 ± 0.2	0.77
Energy expenditure during clamp (kcal/day)	2095 ± 106	2055 ± 92	0.41
Non-protein respiratory quotient			
Fasting	0.85 ± 0.03	0.82 ± 0.02	0.16
Clamp	0.91 ± 0.01	0.88 ± 0.02	0.15

CT, computed tomography; DEXA, dual-energy X-ray absorptiometry.