ADVERSE METABOLIC DISORDERS DURING HIGHLY ACTIVE ANTIRETROVIRAL TREATMENTS (HAART) OF HIV DISEASE

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SUMMARY - Protease inhibitor treatment has dramatically improved rates of morbidity and mortality in HIV-infected patients. However, it has recently been shown that this medication is associated with long-term side effects characterized by metabolic, clinical and biological alterations. These modifications have been described in patients treated with highly active antiretroviral therapy (HAART), including nucleoside analogue reverse transcriptase inhibitors (NRTI) and generally (but not always) protease inhibitors (PI). Clinical alterations are characterised by a body fat redistribution syndrome or lipodystrophy, with peripheral lipatrophy and/or central fat accumulation. They are often associated with biological alterations, i.e. insulin resistance, hyperglycaemia and dyslipidaemia, which can also be observed alone. The pathophysiology of these alterations is presently unknown. The deleterious effect of PI on adipose tissue could be direct or indirect, and is probably modulated by genetic or environmental factors. NRTI could also be involved because of their mitochondrial toxicity. The purpose of the treatment is to control metabolic disturbances in order to prevent immediate complications such as acute pancreatitis and limit possible cardiovascular and diabetic complications at longer term. Studies are in progress to evaluate the possibility of therapeutic alternatives to PI when major metabolic disturbances are present.

Key-words: NRTI, protease inhibitors, lipodystrophy, insulin resistance, dyslipidaemia.

RÉSUMÉ - Les troubles métaboliques induits chez les patients VIH par les traitements antirétroviraux actifs

Les inhibiteurs de protéase ont prouvé leur efficacité dans le traitement de l’infection par le VIH. Cependant, récemment des effets secondaires à long terme à type de troubles métaboliques ont été décrits au cours de traitements antirétroviraux actifs comportant des analogues nucléosidiques et généralement des antiprotéases. Ils se présentent cliniquement sous la forme d’un syndrome de redistribution du tissu adipeux ou lipodystrophie avec lipopathie périphérique et/ou accumulation de tissu adipeux central. Ces signes cliniques sont souvent associés à des modifications biologiques : résistance à l’insuline, hyperglycémie et dyslipidémie, qui peuvent également être observés isolément. La physiopathologie de ces alterations est inconnue : le rôle délétère des inhibiteurs de protéases sur le tissu adipeux, agissant de façon directe ou indirecte, est probablement modulé par des facteurs de prédisposition génétique et environnementaux ; les analogues nucléosidiques pourraient être également impliqués du fait de leur toxicité mitochondriale. La prise en charge des patients vise à contrôler les perturbations métaboliques, pour d’une part éviter les risques immédiats tels que ceux de la pancréatite aiguë et d’autre part limiter les possibles complications cardiovasculaires et diabétiques à moyen terme. Des études sont en cours pour évaluer la possibilité d’une alternative thérapeutique aux antiprotéases en cas de survenue d’altérations métaboliques préoccupantes.

Mots-clés : analogues nucléosidiques (inhibiteurs de la reverse transcriptase), antiprotéases, lipodystrophie, insulinorésistance, dyslipidémie.

The recent use of HIV protease inhibitors (PI), in association with other antiretroviral substances such as nucleoside analogue reverse transcriptase inhibitors (NRTI), has dramatically improved the rates of morbidity and mortality for HIV infection [1]. However, these highly active antiretroviral treatments (HAART) appear to give rise to long-term side effects. Indeed, since the end of 1997, abnormalities in body fat distribution and glucose and lipid metabolism have been reported in HIV infected-patients generally under HAART, but not always including PI.

Recent studies have reported that between 30 and 80% of HIV-infected patients on HAART are affected by these metabolic alterations, and that most are being treated with PI. This wide range of variation is, at least in part, due to a lack of consensual definition of the syndrome. Moreover, the number of affected patients is rising progressively with the increasing length of PI treatment.

The aim of this review was to summarise the various clinical and biological aspects of these abnormalities. Recent hypotheses concerning the pathophysiology of these metabolic disorders will also be presented, as well as current medical recommendations for the care of affected patients.

■ ANTIRETROVIRAL TREATMENTS

The HIV replication cycle

Some notion of the different steps in the HIV replication cycle (Fig. 1) is necessary to understand the targets of currently used antiretroviral treatments.

The extracellular retrovirus binds to its target cells on specific membrane receptors (CD4 and CXCR4 and 5 co-receptors). After fusion of the viral envelope with the cellular membrane, the RNA and viral enzymes are released into the cytoplasm. Double-stranded DNA, synthesized from the RNA viral matrix by viral reverse transcriptase, enters into the nucleus of the host cell and is integrated into its genome. This provirus then uses the infected cell machinery to ensure its replication and the transcription and translation of its genetic information in proteins. The transcription of viral DNA gives rise to genomic viral RNA, which constitutes the genetic inheritance of new viral particles, as well as to several types of messenger RNAs, stemming from alternative splicing, which lead to the synthesis of regulatory or structural viral proteins. Regulating proteins determine the stages of repression (latency) or activation of viral replication. Structural proteins are synthesised in the form of three polypeptidic precursors: ENV, cleaved by a cellular protease in proteins that constitute the viral envelope; and GAG and GAG-POL, which require the specific action of viral protease for their maturation into viral proteins of the matrix, capsid and nucleocapsid and into proteins with specific viral enzymatic properties (reverse transcriptase, integrase and protease). The assembling of these different viral proteins, followed by granulation through the plasma membrane, allows the extracellular release of new infectious virions from the host cell.

Fig. 1. The HIV replication cycle. The targets of antiretroviral treatments are framed.

Targets of antiretroviral treatments

Antiretroviral treatments interrupt this viral replication cycle at different steps: Reverse transcriptase inhibitors (whether from the class of nucleoside analogues or not) inhibit viral DNA synthesis. Protease inhibitors disturb the maturation of viral proteins, leading to the formation of new virus. These synergistic medications are often used in combination.

HIV protease is a homodimeric aspartyl protease containing on each monomer the aspartate-threonine-glycine tripeptide that constitutes the active site. Its substrate, a protein precursor, is cleaved at peptidic
sites, some of which are highly specific for viral pro-
tease and insensitive to cellular proteases. This is the
case for the sequence 1-asparagine, 2-phenylalanine or
tyrosine, 3-proline. Protease inhibitors are active with-
out any metabolic transformation. They are HIV
protease substrate analogues closely associated with the
active site of the enzyme, but not hydrolysable.
Their catabolism uses the cytochrome P450 pathway.
They present no or very low-level cross-reactivity
with human monomeric aspartyl proteases such as
renin, pepsin or cathepsins D and E (review in [2]).

**METABOLIC ABNORMALITIES DESCRIBED DURING
ANTIRETROVIRAL TREATMENTS OF HIV DISEASE**

**Clinical features of the lipodystrophic (LD) syn-
drome**

Body fat redistribution syndromes (lipodystro-
phies) have been described in HIV-infected patients
since the end of 1997. They present diverse clinical
characteristics, i.e. loss of adipose tissue (lipodatroph
y) and/or fat accumulation in central areas. The estima-
tion of body fat distribution by dual-energy X-ray
absorptiometry (DEXA) or tomodensitometry allows
precise characterisation of lipodystrophies. However,
anthropometric measurements, together with specific
clinical questionnaires, provide an easier means of
detecting the presence of lipodystrophy [3-6].

Lipoatrophy concerns the face, arms, legs and but-
tocks and generally develops in a centripetal way. The
disappearance of peripheral subcutaneous fat results in
a muscular appearance with prominent veins [7, 8].
When the face is affected, cachectic features could
have important psychological consequences by sug-
gestng AIDS wasting syndrome. However, several
signs differ between the two syndromes. In wasting
syndrome, weight loss is considerable and concerns
both fat mass and non-adipose tissue, particularly
muscle mass. In LD syndrome under HAART, there
are no clinical or biological signs of denutrition, and
muscle mass is preserved. In some cases, lipoatrophy
is associated with increased central fat, particularly in
the abdomen. Weight loss, if apparent, remains modera-
t. The control of HIV disease is also very different
between these two situations. Its progression is gene-
raly poorly controlled in wasting syndrome, with a
low CD4 count and a high viral load, whereas
HAART-related lipodystrophy usually occurs in pa-
tsients with well-controlled HIV disease, as attested by
biological markers. At the metabolic level, wasting
syndrome is associated with normal or increased insul-
in sensitivity. Cholesterolasma is reduced, but hyper-
triglyceridaemia can develop secondarily to an in-
crease in hepatic lipogenesis [9]. As indicated below,
biological alterations are different for LD syndrome.
The second clinical alteration in body fat distribut-
ion observed in LD syndrome is excessive fat depo-
sition. In a few cases, a « buffalo hump » can result
from fat accumulation in the dorsocervical region [10-
13]. In many cases, visceral abdominal fat accumula-
tion [7, 8, 14], or enlargement of the breasts in women
[15, 16], is apparent.

Thus, three main forms of LD syndrome can be
clinically described: a lipoatrophic one, a form with
increased central fat, and a more characteristic mixed
form with redistribution of adipose tissue, which is
reduced in subcutaneous regions (peripheral lipodatroph
y) and increased in visceral areas, with total fat
mass generally unaltered [7, 14].

Some authors have reported that peripheral lipoa-
trophy could be more frequent in men than women
[17, 18]. Buffalo hump is a rare condition that occurs
almost exclusively in men. Some clinical aspects of
lipodystrophies in patients treated with PI are indica-
d in *Figure 2."

In most cases, patients have been treated by PI, but
cases of LD syndrome in patients under HAART,
including NRTI but without PI, have been reported by
several authors. Lo *et al.* described 4 cases of LD
patients treated with nucleoside analogues alone [10],
and in the cohort studied by Gervasoni *et al.* [15] 12
of 32 women with fat redistribution did not take any
PI. Similar cases were presented at the 6th Conference
on Retroviruses and Opportunistic Infections held in
Chicago in February 1999 [3, 16, 19, 20]. Interestin-
vely, very recent reports [15, 21, 22] suggest that LD
syndrome occurring under NRTI without PI could
present different features, particularly at the biological
level. NRTI-related LD syndrome is relatively uncom-
mon (6.5% of men and 26% of women after a mean
therapy period of 2 years in one study [21]). It has
been described as slowly progressive fat loss in men,
whereas breast enlargement could be frequent in af-
fected women [15, 21, 22].

**Biological alterations**

**Altered glucose tolerance and insulin resistance**

Several medications used for the treatment of HIV
infection, such as ddI and ddC, two nucleoside analo-
gues which inhibit HIV reverse transcriptase, or pen-
tamidine used for prevention or treatment of pneumo-
cylostosis, have a toxic effect on the pancreas. Some
cases of diabetes have been reported during such the-
rapies [23-26]. Megestrol acetate, an androgenic pro-
estogen used to stimulate appetite, has also been
shown to be responsible for diabetes [27, 28].

The Food and Drug Administration warned Ameri-
can physicians in June 1997 of the possibility of
hyperglycaemia in PI-treated patients. Five cases of
diabetic ketoacidosis were reported. This first study evaluated the frequency of diabetes at less than 1 per cent [29, 30]. Several subsequent reports concerned clinical cases of patients presenting with diabetes between 2 weeks and one year after initiation of antiprotease treatment [31-34]. In general, patients had non-ketotic diabetes, and a family history of diabetes was frequently reported. Four cases of glycaemic normalisation after treatment interruption (with for one patient reappearance of hyperglycaemia following reintroduction of PI) argue for a causative link between diabetes and PI treatment [31, 33, 34]. A recent observation [34] illustrates the particularities of this form of diabetes and the variability of its course: Three months after initiation of treatment with ritonavir, major hyperglycaemia and hypertriglyceridaemia appeared, without ketosis. After brief insulin therapy and discontinuation of ritonavir, a satisfactory control of glycaemia was obtained with diet alone, and triglyceridaemia was normalised by fibrate therapy. The same metabolic alterations occurred again one year after the onset of indinavir and were again controlled by diet alone, PI being replaced by a non-nucleoside reverse transcriptase inhibitor. However, poststimulative hyperglycaemia persisted (glycaemia at 15 mmol/l at 120 min during an oral glucose tolerance test). Elevated insulinemia showed that insulin resistance was present. No overweight condition or family history of diabetes was noted. This case is an example of major hyperglycaemia secondary to different PI. Glycaemic variations are probably related to environmental factors, particularly diet, but do not seem to be associated with advanced stages of HIV infection.

A state of insulin resistance has been clearly demonstrated by several studies, which showed increased basal insulinemia [6, 7, 35] or used more
precise study [37], we showed that 11 patients among 14 with clinically marked facial lipoatrophy treated with indinavir had insulin resistance (as assessed by glycaemic and insulinaemic measurements during an oral glucose tolerance test) or diabetes associated with hypertriglyceridaemia. Results obtained from a systematic study of more than 600 patients treated with PI for more than 3 months at Rothschild Hospital confirmed the high frequency of altered glucose tolerance (diabetes was found in 7% and impaired glucose tolerance or impaired fasting glucose in 27% of patients) or of isolated insulin resistance in patients with normal glucose tolerance (18% of patients) [38].

Dyslipidaemia

The presence of hypertriglyceridaemia during HIV infection has been previously described, particularly in advanced stages of the disease [39]. Hepatic lipogenesis resulting in VLDL synthesis was shown to be stimulated in these patients [9], and increased production of interferon α may correlate with decreased clearance of triglycerides [40]. Concerning cholesterol, decreased HDL levels have been described early in HIV infection, whereas LDL levels were decreased later [97]. The use of PI induces an increase in the frequency of dyslipidaemia, with predominant hypertriglyceridaemia as well as hypercholesterolaemia [6, 7, 14, 36, 41]. The possible association under PI treatment of hyperglycaemia, which activates lipogenesis, and insulin resistance, which impairs lipoprotein lipase activity in adipose tissue, could also increase triglyceridaemia, which can be sufficiently high to result in acute pancreatitis. Clinicians must be very vigilant with regard to this risk, particularly when PI are prescribed together with medications toxic for the pancreas.

Concerning cholesterol, increased levels of total as well as LDL cholesterol have been reported in patients on PI, while HDL cholesterol was not significantly changed. Therefore, on the basis of epidemiological data, the major risk for coronary artery disease relates to the low level of HDL seen in HIV infection, with an even greater risk due to increased VLDL and LDL levels through the use of PI [97].

Biological alterations in LD syndrome occurring under NRTI

The main biological alterations are related to the mitochondrial toxicity of these drugs, resulting in an increased lactate level and altered hepatic functions [22]. Conversely, lipid and glycaemic parameters, as well as insulin levels, are altered minimally as compared to non-LD patients under NRTI [19, 21, 22], indicating the absence of major biological metabolic alterations associated with NRTI-related LD syndrome.

Association of lipodystrophy, insulin resistance, hyperglycaemia and hypertriglyceridaemia in patients treated with PI

Several studies have clearly shown that clinical features are associated with biological alterations in many patients treated with PI, even though such alterations can be observed independently in some patients [7, 36-38]. Compared to patients with no alteration in fat distribution, a significantly higher number of those with LD present with insulin resistance, impaired glucose tolerance, diabetes or hyperlipidaemia [6, 7, 38].

The chronology of appearance of the different signs has not been evaluated in large prospective studies. Some authors suggest that insulin resistance, increased glycaemia and hypertriglyceridaemia could occur after a few months in patients treated with PI, preceding any clinically apparent lipodystrophy [42, 43]. Generally, lipodystrophy occurs after about one year of HAART, with predominant increased central adiposity at first and then peripheral lipodystrophy [44], which frequency increases with the length of treatment with PI [38]. Insulin resistance seems to worsen during the course of the disease [45]. A recent study by Carr et al. [6] evaluated the natural course of PI-associated LD syndrome in 113 PI-treated patients examined twice at 8-month intervals. The severity of lipodystrophy was progressive in most cases, and its assessment by a questionnaire including patients’ ratings was in good agreement with DEXA measures. The length of both PI therapy and HIV infection as well as triglyceride and fasting C-peptide concentrations were positively correlated, whereas HDL-cholesterol level was negatively correlated with a greater severity of lipodystrophy. Diabetes and impaired glucose tolerance were found respectively in 7 and 16% of these normal-weight patients (mean body mass index : 23.4) under PI therapy for a mean 21 months. It is noteworthy that most abnormalities in glucose tolerance were found in 2-h post-OGTT values but not in basal values in this study. This characteristic, already observed in the Rothschild cohort and found to be associated with high insulin levels [38], is consistent with a state of insulin resistance at the peripheral level in these patients.

PATHOPHYSIOLOGICAL HYPOTHESES

The pathogenesis of PI-associated metabolic adverse effects is still unknown.

Some genetic syndromes of severe insulin resistance, in the absence of HIV infection, are also associated with total or partial lipodystrophies, hyperglycaemia and hypertriglyceridaemia [46]. The most studied form is lipotoxic diabetes with generalised lipodystrophy, which can be either congenital with a recessive mode of transmission (Berardinelli-Seip...
syndrome) or acquired in infancy or adulthood (Lawrence syndrome) [47]. In the congenital form, characteristic signs associate complete lipatrophy at birth with hypertriglyceridaemia in infancy and often diabetes diagnosed at puberty. Resistance to insulin is constant. At the clinical level, hyperandrogenism, muscular hypertrophy and acanthosis nigricans are commonly observed together with hepatomegaly due to steatosis, which can progress to cirrhosis in young adulthood. Severe hypertriglyceridaemia can be complicated by acute pancreatitis. At the genetic level, the recessive mode of transmission would seem to incriminate a gene (when altered on both alleles), accounting for changes in adipose tissue differentiation (lipoatrophy) as well as metabolism [48].

The recent description of murine models of these diseases has directed hypotheses concerning pathogenesis towards primary alterations in adipogenesis : In transgenic mice, the alteration of transcription factors involved in adipose tissue differentiation has led to an association involving complete disappearance of white adipose tissue, major insulin resistance and hypertriglyceridaemia [49, 50].

With respect to Lawrence syndrome, which generally occurs in infancy after an acute illness, a possible association with auto-immune diseases and/or altered levels of some complement fractions suggests a deleterious role of the immune system for adipocytes.

Other lipodystrophy syndromes have been described. In particular, the two types of Köberling-Dunnigan syndrome are transmitted as dominant autosomal diseases and characterized by partial lipoatrophy, with either conserved (type I) or increased (type II) adipose tissue in the neck and face. At the biological level, insulin resistance is associated with alterations in glycaemia and dyslipidaemia [51]. Interestingly, in type II Dunnigan syndrome, a small genetic region in lq21-22 has been shown to be implicated in affected patients, suggesting that an altered allele of the responsible gene induces modifications in glucose and lipid metabolism with insulin resistance at the biological level, and both partial lipoatrophy and accumulation of adipose tissue at the clinical level [52].

Our knowledge of human adipose tissue metabolism is partial. However, major differences with respect to anatomical site have been indicated. Some of these differences could explain how the same stimulus could be responsible for simultaneous decreased fat mass in one anatomical site and increased adiposity in another. In fact, the hormonal sensitivity of adipose tissue to insulin, epinephrine and cortisol is different in visceral and subcutaneous fat [53, 54]. Otherwise, small and large adipocytes respond in opposite ways to thiazolidinediones, i.e. insulin sensitiser medications which bind to the adipose transcription factor PPARγ2. Treatment of rats with troglitazone, a thiazolidinedione, resulted in an increased number of small adipocytes, whereas apoptosis of large adipocytes was stimulated [55]. Troglitazone has also recently been shown to induce a redistribution of body fat, involving a decrease in intra-abdominal fat and/or an increase in subcutaneous fat in Type 2 diabetes [56] and severe insulin-resistant, non HIV-infected, LD patients [57]. Moreover, adipose tissue distribution is highly dependent on genetic- and gender-related factors, diet composition (high fat or high carbohydrate), exercise and age. The same PI molecule can modify fat distribution differently when these factors vary [58].

In addition to congenital forms, some human acquired partial lipodystrophies, in the absence of any HIV infection, are associated with membranoproliferative glomerulonephritis and/or a decrease in the level of complement C3 factor. In some cases, the nephritic factor, an autoantibody activating the alternative complement pathway, is present [59]. The pathogenesis of these acquired partial lipodystrophies is still unknown.

Otherwise, protease inhibitor-related LD syndrome is close to the very common metabolic syndrome described by Reaven [60], which is of unknown cause and represents a major cardiovascular risk.

Finally, alterations in body fat have been observed in multiple symmetric lipomatosis or Launois-Bensaude syndrome, which is characterized by the development of large subcutaneous fat masses in the upper body and frequent peripheral neuropathy. Alterations in mitochondrial DNA, resulting in altered function of the respiratory chain, have been reported [61, 62]. A mitochondrial dysfunction documented after treatments with NRTI is probably due to the inhibition of DNA polymerase γ, which is required for mt DNA replication. Therefore, it is possible that the LD syndrome occurring under NRTI is due, at least in part, to mitochondrial toxicity [63, 64].

Concerning metabolic alterations which develop during treatment of HIV infection, some of the hypotheses which were first set forth have now been invalidated : Inhibition of the synthesis of mature insulin as the result of a cross-reactivity of PI with the proteases which process proinsulin is very unlikely in the absence of hyperproinsulinaemia in patients [37]. A systemic hypersecretion of glucocorticoids has been excluded by measurements of urine free cortisol levels and serum cortisol after dexamethasone suppression tests [10-12, 37, 65]. However, some authors have suggested the possibility of a local excess of, or an enhanced sensitivity to, cortisol in visceral adipose tissue, which could result in enhanced central fat accumulation [10, 65-68]. The C3 complement factor, which can be decreased in non HIV-associated partial lipodystrophies, has not been found to be decreased in these patients [7, 37]. The role of cytokines must be considered since several have been reported to be increased in HIV infected-patients and could modulate adipocyte metabolism. In particular, TNFα, which is
produced by adipose tissue, induces an insulin-resistant state in these cells [69].

Carr et al. [70] proposed a pathogenic hypothesis based on a partial sequence homology between the catalytic site of HIV protease, the C-terminal region of CRABP1 (cytoplasmic retinoic-acid binding protein type 1) and the binding domain for lipids of LRP (low density lipoprotein-receptor-related protein). Binding of PI to these proteins could alter their function, inducing metabolic consequences. CRABP1, in conjunction with P450 3A cytochrome, plays an important role in the synthesis of 9cis retinoic acid, which is involved in the activation of RXR, a partner of PPARγ2 in the induction of adipocyte differentiation, mainly in peripheral sites [71]. On the one hand, PI could inhibit retinoic acid synthesis by their interaction with CRABP1 and their impairment of cytochrome P450 availability, and then disturb the differentiation of peripheral adipose tissue. On the other hand, LRP acts on hepatic uptake of chylomicrons and, as a complex with lipoprotein lipase, on triglyceride hydrolysis in the vascular endothelium. PI-induced inhibition of LRP could lead to hypertriglyceridaemia, insulin resistance by substrate competition [72] and distribution of fat toward visceral adipose tissue, the only site available for storage. Diabetes would occur when hyperinsulinaemia could no longer compensate for insulin resistance, as in common Type 2 diabetes. However, these hypotheses have not been verified experimentally [73], and inactivation of the hepatic LRP gene in normal mice has not led to lipodystrophy or dyslipidaemia [74].

Only a few studies have concerned the in vitro effects of PI. An increase in adipocyte differentiation was reported in the murine preadipocyte 3T3-L1 cell line treated with indinavir [75]. Conversely, adipocyte differentiation of mesenchymal stem cells was blocked by various PI [76]. Insulin receptor expression was shown to be decreased in vitro by PI and in vivo in muscles of HAART-treated insulin-resistant patients [77], while insulin signaling was not affected by indinavir in rat muscles [78].

These discrepant results require further studies to assess the effects of PI in vitro. Together with data from transgenic mice lacking adipose tissue, they may support the hypothesis for an interaction between PI and transcription factors involved in adipocyte differentiation, which could be responsible for lipodystrophy and secondarily for metabolic disturbances. They could also suggest an alteration in the insulin receptor signalling pathway since insulin controls several adipose-specific proteins required for maintenance of the differentiated phenotype.

Otherwise, the dramatic improvement in the immune responses which follows PI use has been proposed as a possible factor responsible for the development of autoimmune diseases [79]. The involvement of immune reconstitution in the appearance of metabolic changes should also be studied. However, the relationship between the immune improvement attested by CD4 level and the HIV viral load and the clinical and biological signs of lipodystrophy is not accepted by all authors [20, 80, 81].

All these hypotheses are not exclusive, and several alterations could be required for lipodystrophy to occur. It may be postulated that, in an altered metabolic background, HAART induces some additional factors resulting in LD syndrome. The hypothesis that both NRTI and PI induce LD by different mechanisms is interesting. A genetic predisposition may play a role, but the very high frequency of lipodystrophy in patients under HAART (above 50% in recent studies [6, 7, 38]), suggests that these genetic variants could be relatively common in the population. Environmental factors, particularly diet, are probably important in the severity of metabolic biological disturbances.

Clinical management of metabolic disturbances

The medical management of metabolic disturbances is not currently well-modified because of a lack of precise data on their pathogenesis. The psychological consequences of various abnormalities in the distribution of body fat can compromise adherence to treatment, including PI. The risk/benefit ratio needs to be carefully evaluated at the individual level before a patient is switched from PI to other HAART regimens. The recent availability of non-nucleoside reverse transcriptase inhibitors could be beneficial in maintaining adequate suppression of viral replication without PI therapy. The first clinical evaluations of such treatment changes are conflicting and still preliminary. The switch from one PI to another does not seem to be useful [82] since metabolic alterations and lipodystrophic signs are observed in patients regardless of the PI used [6, 83, 84]. However, recent reports suggest that indinavir could cause more deleterious effects on insulin sensitivity [85] and that ritonavir and saquinavir could increase hypertriglyceridaemia [6, 80]. Preliminary data obtained when PI were replaced by another medication or even stopped are conflicting. The replacement of PI by non-nucleosidic RTI has recently been studied. When patients were switched to nevirapine [31, 40, 86-88], clinical alterations partly resolved and laboratory alterations were improved. Conversely, a switch to efavirenz did not lead to significant differences in clinical and metabolic abnormalities after 6 months [89, 90].

The most important immediate risk in these patients is acute pancreatitis due to major hypertriglyceridaemia (above 10 mM). This situation, which should be considered as a therapeutic emergency, justifies a fat-free diet, normalization of glycaemia (diabetes being frequently associated), and biological and ultrasound tests to detect possible acute pancreatitis. Apart from acute situations, major hypertriglyceridaemia re-
quires dietary measures, regular physical exercise, and possibly fibrate therapy. In cases of minor hypertriglyceridaemia or mixed dyslipidaemia, the problem of long-term cardiovascular risk should be considered. This risk has been emphasized [91], but is still controversial [92-94]. Clinical studies are required to evaluate the efficiency and safety of lipid-lowering medications in combination with HAART. In particular, statins, because of their interference with the cytochrome P450 metabolic pathway in the liver, should be used with due caution in association with PI, despite interesting preliminary data [95].

Blood glucose needs to be measured in the fasting state, but also in the postprandial state, in order to detect alterations in glucose tolerance. The current strategy in treating hyperglycaemia is close to that proposed for Type 2 diabetes: diet and exercise should be encouraged first. Other cardiovascular risk factors should also be evaluated and treated. Oral hypoglycaemiant are prescribed in second intention, and sulphonylureas have been used in most reported observations. Insulin therapy is justified in cases of ketosis, ineffectiveness of other measures, or major glycaemic disturbances. Some studies have tried to evaluate the treatment of insulin resistance with metformin and troglitazone, which have been shown to increase insulin sensitivity. Metformin [96] is able to decrease visceral fat and insulin resistance moderately, and troglitazone [45, 77] improves insulin sensitivity and signs of lipodystrophy but, due to its hepatic toxicity, cannot be proposed for use in HIV-infected patients.

CONCLUSION

Observations over 18 months have revealed clinical and biological metabolic alterations in HIV-infected patients treated with HAART. Alterations related to the use of PI have been defined as an LD syndrome associating modifications in body fat distribution with resistance to insulin, hyperglycaemia and dyslipidaemia. NRTI may also induce lipodystrophy involving minor biological metabolic alterations and liver dysfunction. PI-related abnormalities are frequent, of varying severity, and associated differently in patients. They show important similarities with genetic or acquired syndromes of extreme insulin resistance and justify the systematic management of blood lipids and fasting plus postprandial glycaemias in patients on HAART. The involvement of PI is likely but could be indirect. Environmental factors (particularly diet), immune markers, or genetic predispositions could play an important role in triggering these alterations. In the absence of experimental data on the pathogenesis of these anomalies, a pragmatic therapeutic attitude, based initially on diet and exercise, should be adopted to avoid acute pancreatitis secondary to major hypertriglyceridaemia, and chronic hyperglycaemia. The problem of long-term complications is important since HIV infection is becoming a chronic disease because of the efficiency of antiretroviral therapies. Studies of the efficiency and safety of different associations of antiretroviral medications and of the pathogenesis of these metabolic alterations are necessary to understand, avoid and treat these adverse effects.

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