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HIV-Infection: The Role of Insulin Resistance and Alternative Treatments

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1. Introduction
The impact of antiretroviral therapy (ART) on the natural history of HIV is indisputable, resulting in dramatic reductions in morbidity and mortality and improvements in quality of life. This recognition coincides with a change in view of HIV infection from a progressive fatal disease to a medically manageable chronic condition. However, the requirement for life-long therapy with ART has been associated with long-term metabolic toxicities (hyperlipidemia, insulin resistance, diabetes, and osteoporosis) and iatrogenic dysmorphias, termed lipodystrophy, that have increased the complexity of managing people living with HIV infection (PLWH), the manifestations of which include peripheral fat loss and central fat accumulation. Lipodystrophy has emerged as one of the most feared complications of ART for PLWH. The highly stigmatizing nature of this adverse event has been associated with feelings of low self-esteem, forced disclosure of HIV-status, and negative effect on antiretroviral adherence. Of more recent significant concern is the finding that the metabolic consequences of lipodystrophy and ART, as well as the inflammation caused by the virus, are strong mediators for the development of cardiovascular disease (CVD), diabetes, metabolic abnormalities, and fatty liver disease and will have important implications for the future health and survival of the PLWH. One of the possible mechanisms contributing to these metabolic abnormalities is insulin resistance (IR) that has been increasingly seen in PLWH. Interventions aimed at improving insulin sensitivity have been shown effective in alleviating some but not all of ART and/or HIV associated adverse outcomes. This chapter will review the evidence for IR as a potential mechanism involved in HIV-related complications and the role of alternative treatments in improving IR in people living with HIV infection.

2. Metabolic abnormalities associated with HIV infection
The successful introduction of highly active antiretroviral therapy (HAART), a combination of potent antiretroviral agents, including protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs), and nonnucleoside reverse transcriptase inhibitors (NNRTIs), has impacted positively on morbidity and mortality among HIV-positive patients. However, over time, HAART has been associated with a number of metabolic and anthropometric abnormalities, including dyslipidemia (1-3), hypertension (4-8) and insulin resistance (9-11), as well as subcutaneous fat loss and abdominal obesity, all included in the definition of metabolic syndrome (12) and potentially contributing to CVD risk. In a cohort of HIV-infected adults (296
participants: 217 men and 79 women) of mixed ethnicity with a mean age of 45.3 years, an appreciable prevalence of metabolic syndrome (30.0%) has been reported with the frequency increasing to 42.5% in those over 50 years of age. More women had abdominal obesity (59.5%) than men (20.7%, \( P<0.001 \)) and the frequency of elevated plasma glucose was also higher in females (37.2%) compared to males (16.9%, \( P=0.004 \)). High frequencies of decreased high-density lipoprotein cholesterol (HDLC) and elevated blood pressure were seen in both sexes. In those under 50 years of age, the 10-year Framingham coronary heart disease risk score for men was double that for women (6.2% vs. 2.7%, \( P<0.001 \)). In older participants, the risk was similar between the sexes, with a third having scores over 10 %\(^\text{13} \)).

These metabolic disturbances are of complex origin, and their development may be affected by ART as well as the underlying HIV infection \( \text{14} \)). HIV infection itself has been reported to impair triglycerides (TG) metabolism and lipoprotein-lipase (LPL) activity, and reduced plasma HDL cholesterol, Apo-B and Apo-A1, with higher LDL TG, and higher total cholesterol/HDL ratio\(^\text{1-3,15} \)). Cytokines, such as interferon alpha, may play a role in the abnormal lipid homeostasis seen in PLWH \( \text{16,17} \)). The use of PIs has been linked to further abnormalities in the serum lipid profile in PLWH \( \text{18,19} \)). Increased total cholesterol (TC), TG rich VLDL, and LDL-C are seen in PI-treated patients \( \text{19-21} \)). Data from prospective cohort studies report new-onset hypercholesterolemia and hypertriglyceridemia after 5 years of HAART in 24 and 19% of subjects, respectively \( \text{22,23} \)). Individual PIs likely have substantially different affects on the lipid profile. Data from the Swiss Cohort study suggest that ritonavir, but not indinavir or nelfinavir, is associated with increased TG levels \( \text{22} \)). Purnell\(\text{24} \) demonstrated significant effects of ritonavir on TG levels after 2 weeks in HIV-negative patients. Similarly, low dose ritonavir in combination with lopinavir over 4 weeks also increased TG levels in HIV-negative men \( \text{25} \)). The newer PI atazanavir appears to have a significantly less pronounced effect on serum lipid levels \( \text{26,27} \)). The mechanism by which PIs influence serum TG is not clear. Animal studies \( \text{28,29} \)) suggest that PIs may prevent proteosomal degradation of nascent ApoB, a principle protein component of circulating TGs, leading to increased production of VLDL particles. Furthermore, as opposed to the “traditional” metabolic syndrome, which involves high free fatty acid (FFA) levels due to the inability for appropriate storage into fat cells in the presence of IR, patients receiving HAART develop a lipotoxicity due to mitochondrial dysfunction resulting in the excess release of FFA \( \text{30} \), resulting in increased production of VLDL and small, dense LDL as well as low plasma levels of HDL. This increase in lipolysis appears to cause the characteristic subcutaneous lipoatrophy in the face, legs, and buttocks with accumulation of fat in the visceral area and the back of the neck. PIs may also induce the lipoatrophy by inhibiting sterol regulatory enhancer-binding protein (SREBP-1) \( \text{30,31} \) and peroxisome proliferator-activated receptor-\( \gamma \)((PPAR-\gamma))\(\text{32} \)), which are both involved in lipogenesis. Other antiretroviral medications may also affect serum lipids. Kumar\(\text{33} \) reported, in treatment-naïve HIV+ subjects, PI sparing regimens (zidovudine/lamivudine + abacavir) raised fasting TC and TG least in comparison with regimens containing a PI (zidovudine/lamivudine + nelfinavir) or stavudine and a PI. The DAD study \( (n=7483 \text{ patients})\(\text{34} \) reported that exposure to non-nucleoside reverse transcriptase inhibitors (NNRTIs) is also associated with modest yet significantly increased TG levels (odds ratio, 1.90; 95% confidence interval, 1.06–3.39), but not with low HDL-C or increased LDL-C. Fat redistribution has also been reported frequently in PLWH. NRTIs used to treat HIV-1 infection are particularly associated with the lipoatrophy in subcutaneous fat \( \text{35} \), whereas PIs are considered more likely to cause systemic metabolic alterations such as insulin
resistance (36). Non-nucleoside-analog reverse transcriptase inhibitors are not thought to contribute to the development of lipodystrophy, although some data have led to a reconsideration of the effects of some of these drugs on peripheral fat accumulation (37). There have been attempts to treat HIV-1-lipodystrophy using drugs of known effects against dyslipidemia (fibrates) or insulin resistance (thiazolidinediones), but results on the overall lipodystrophy syndrome have been poor (45,46).

There is a growing concern about an increased risk for cardiovascular disease (CVD) in PLWH especially those receiving ART. This risk could be related to hypertension or metabolic abnormalities such as dyslipidemia, diabetes mellitus and central fat deposition which are increasingly seen with long-term use of ART (19, 38-41). This is also supported by epidemiological studies showing an increased risk for CVD in PLWH (42-44).

3. Insulin resistance (IR) as one of the possible mechanisms involved

Insulin resistance a risk factor for CVD is increasingly seen in PLWH and it is often accompanied by elevated blood pressure, dysfunctional glucose homeostasis, obesity, and dyslipidemia(47,48). It has been shown (49) that the presence of dyslipidemia (i.e. hypertriglyceridemia and low plasma HDL concentration) is highly indicative of underlying IR in patients with HIV despite fasting normoglycemia. Patients with the HIV-metabolic syndrome were also found to have a redistribution of adipose tissue to the intraperitoneal compartment and have markedly elevated intrahepatic lipid content (50). Insulin resistance is also a component of the lipodystrophy syndrome, and fasting insulin levels appear to correlate with waist to hip ratio. Multivariate modeling was used to estimate an approximate 1% increase in fasting insulin level for every 1% increase in visceral fat or every 1% increase in abdominal subcutaneous fat (51). Insulin levels and IR are higher in patients with both peripheral lipoatrophy and visceral adiposity than in those who have either alone (52). Intra-abdominal fat delivers excess free fatty acids directly into the portal blood system(53) and secrete cytokines and other factors that contribute to IR, impaired fibrinolysis(54,55), and endothelial dysfunction leading to increased risk for CVD(56).

It is unclear whether IR is a direct result of HIV infection alone or it is a complication of ART. Chronic infection with HIV may contribute to glucose abnormalities among HIV-infected patients. In the Multicenter AIDS Cohort Study, insulin resistance markers were higher in all groups of HIV-infected men compared with HIV-uninfected control subjects, even among those who were not receiving ART (57), suggesting an effect of HIV infection itself. A potential factor by which HIV could induce IR is TNF-α, which is chronically released by peripheral blood mononuclear cells in PLWH. Systemic inflammation has been associated with incident of diabetes in multiple cohorts in the general population (58-60). Proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, may induce insulin resistance by binding to insulin-responsive elements in skeletal muscle (61). Among HIV-infected patients, markers of systemic inflammation decrease quickly with ART initiation (62) but do not normalize (63). It is speculated that this residual inflammation with effective ART may contribute to the pathogenesis of co-morbidities in HIV-infected patients, including diabetes (64).

Insulin resistance could also be a consequence of drug treatments in HIV. Among PLWH on ART, an IR prevalence rate of about 20-85% has been reported (9, 10, 65,66). There are differences in the pathways through which various PIs induce IR and in their propensity to do so. Certain PIs, such as indinavir (IDV), lopinavir, and ritonavir, have been shown to...
reversibly induce IR, probably by inhibition of glucose translocation through GLUT4 (67). In contrast, atazanavir had no effect on IR. The NRTIs, zidovudine and stavudine, also have direct and indirect effects on glucose metabolism (68,69). In a case-control study (70), comparing 55 previously ART-naïve individuals who developed diabetes 48 weeks after ART initiation (case subjects) with 55 individuals who did not develop diabetes during a comparable follow-up (control subjects), subjects with higher levels of high-sensitivity C-reactive protein (hs-CRP), soluble TNFR1 (sTNFR1), and sTNFR2 at 48 weeks had an increased odds of subsequent diabetes, after adjustment for baseline marker level, age, BMI at week 48, CD4 count at week 48, and indinavir use. After further adjustment for week 48 glucose, effects were attenuated and only sTNFR1 remained significant (odds ratio, highest quartile vs. lowest 23.2 [95% CI 1.28–423], \( P = 0.03 \)).

Insulin resistance, glucose and lipid metabolism were also found to be directly related to circulating adipokines suggesting that abnormalities in adipocytes may contribute to IR in patients with HIV. A known side effect of NRTIs is reduction in the production of adiponectin by lipoatrophy. Because adiponectin improves insulin sensitivity by increasing transportation/oxidation of FFAs and inhibition of hepatic glucose output, hypoadiponectinemia due to effects of NRTIs is thought to be a pathway for IR (7). Serum adiponectin level has been shown to inversely correlate with fasting insulin concentration and with hepatic fat content (71). Adiponectin also has anti-inflammatory properties. It suppresses inflammatory cell infiltration of the vascular intimal space (72-74), and deficiency of adiponectin up-regulates endothelial adhesion molecules (73). In a study by Cade et al(74) who performed adipose tissue biopsies in a cohort of HIV-infected patients, he found that the use of PIs is associated with down-regulation of adiponectin mRNA in appendicular adipocytes. These findings suggest a mechanistic link between PI use and development of dyslipidemia and IR. They also found that patients with HIV-metabolic syndrome have blunted insulin-mediated suppression of protein breakdown, unlike patients with type 2 diabetes. These findings imply a shared signalling defect in patients with HIV-metabolic syndrome that affects lipid, glucose and protein metabolism.

4. Treatment challenge

Because HIV infection frequently occurs in young individuals, long-term HAART is necessary and, thus, risk-factor modification is increasingly important to prevent the development of CVD. There is no single pharmacologic agent available with effects on multiple targets. The efficacy and safety of combining anti-inflammatory, antihypertensive, hypoglycemic and lipid lowering agents and their interactions with ART must be considered and favourable effects on reversing these abnormalities have not been uniformly reported.

For example, dyslipidemia is common in HIV-infected patients, but treatment outcomes are often unsatisfactory. In one study (75) responses to lipid-lowering therapy were compared between 829 HIV-infected patients and 6941 uninfected controls, all with laboratory evidence of dyslipidemia. The HIV-infected patients had significantly smaller LDL declines in response to statins therapy than their HIV-negative counterparts (reduction, 25.6% vs. 28.3%); within the HIV population, pravastatin was less effective than other agents (simvastatin, lovastatin, or atorvastatin). This drug is cited in current guidelines as a preferred agent because it has fewer interactions with ART than do other statins. The various classes of ART respond to lipid-lowering therapy differently; for example, PIs blunted response to fibrate therapy, but NNRTIs did not (75).
There have also been attempts to treat HIV-1-lipodystrophy using drugs of known effects against dyslipidemia (fibrates) or insulin resistance (thiazolidinediones), but results on the overall lipodystrophy syndrome have been poor \cite{45,46}. Therefore, drug treatment needs to be balanced against the potentially significant drug–drug interactions.

Until definitive data are available on the efficacy of these medications, the primary focus of treatment should be on lifestyle modification, including diet, exercise since they are shown to improve IR and CVD risk in the general population. As well, patients with HIV infection have been shown to have inadequate dietary intake and suboptimal levels of various micronutrients some of which play an important role in regulating insulin function and CVD risk \cite{76-78}. Therefore, addressing nutritional deficiencies and modifiable risk factors such as smoking, obesity, and sedentary lifestyle can have a far greater impact on IR and CVD than changes in antiretroviral therapy.

5. Dietary factors, physical activity and insulin resistance

The identification of dietary factors that influence energy and lipid metabolism is an important research field of nutrition science and has become a growing requirement in the context of the HIV/AIDS epidemic in an attempt to attenuate the metabolic abnormalities and CVD risk associated with antiretroviral therapy.

Consumption of energy-dense / high fat diets is strongly and positively associated with the overweight state, that in turns induces IR, particularly when the excess body weight is located in the abdominal region \cite{79,80}. In patients with HIV infection, we collected 7-day food diary from 60 males who also had metabolic abnormalities \cite{77}. We estimated their energy, macro- and micronutrient intakes and compared it to the Dietary Reference Intakes for Canadians. A large proportion (41.5% and 63.1%) of subjects had intakes of fat and saturated fat exceeding the recommended levels of intake. None of the subjects met the recommended level of intake for fiber and 90.8% did not meet the recommended levels of intake for vitamin E. These findings have also been confirmed in other studies \cite{79,81}.

**Dietary fat quality**: IR is also independently affected by the type of dietary fat. In animal studies, saturated fat increases whereas omega-3 polyunsaturated fatty acids (PUFA) from fish and seafood reduce IR \cite{82,83}. Several human studies \cite{84-91} have also shown that saturated fat is significantly associated with worsening of IR, independent of body fat, while monounsaturated and PUFA improves IR. Based on fatty acid composition in plasma and muscle, studies also consistently show that increased unsaturated fat intake is associated with improved insulin sensitivity \cite{91-94}. Reports from systematic reviews \cite{95,96} also concluded that omega-3 PUFA reduce IR and serum triglycerides. Based on this, the American Diabetes Association \cite{97} and American Heart Association \cite{98} have recommended the consumption of 2-3 servings of fish/week. In one of our ongoing study (unpublished data) in males with HIV infection (n=27) who were found to have non-alcoholic fatty liver disease and several metabolic abnormalities, the omega-3 index (a combination of 2 long-chain omega-3 PUFA, Eicosapentaenoic acid and Docosahexaenoic acid) in the red blood cells was significantly lower when compared to HIV-negative male subjects (n=6) with minimal findings in their liver biopsies (3.44±0.35 vs. 6.20±1.15; P=0.022). This was accompanied with a significantly higher omega-6 to omega-3 PUFA ratio in HIV-infected group (5.58±0.57 vs. 3.40±0.31; P=0.028) in favor of inflammatory processes in the body.

The levels of the omega-3 PUFA in the blood and in the tissues are determined by diet and probably also by a genetic component. Changes in the levels of omega-3 PUFA are expected

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in a given individual after a change in diet and during treatment with omega-3 PUFA. In a study (99) of 54 persons with HIV and elevated serum triglycerides (>150 mg/dL) and/or abnormal Quantitative Insulin Sensitivity Check Index values (<0.35 but >0.30) in which total fat, type of fat, fiber, and glycemic load were controlled along with supplementation with n-3 fatty acids to achieve an intake of 6 g/d, serum triglycerides in the intervention group decreased from a median of 180 mg/dL to 114 mg/dL from baseline to 3 weeks, whereas they remained stable in the control group (P = 0.003). Serum phospholipid fatty acids indicated a decrease in de novo lipogenesis and a decrease in arachidonic acid in the intervention group. At 3 weeks, the insulin area under the curve decreased but not significantly.

In another randomized placebo-controlled trial (100), 51 patients with HIV infection received either 2 capsules of Omacor (an omega-3 PUFA supplement) twice daily or 2 capsules of placebo. Plasma triglycerides were reduced in the n-3 PUFA group by 0.14 mmol/l after 12 weeks of treatment (n=26), while plasma triglycerides increased by 0.36 mmol/l in the control group (n=25). There was a significant increase in leukotriene B5 (LTB5) and LTB5/LTB4 ratio in the omega-3 PUFA group compared to the control group, inducing anti-inflammatory effects by increasing formation of anti-inflammatory LTB5.

**Calcium:** The importance of dietary calcium in the regulation of body weight and lipid metabolism has been the object of scientific investigations throughout the years. This relationship was first studied by Zamel et al (101-103), and today it continues to be an object of scientific interest (104, 105). Some epidemiological studies show that, in the general population, a high calcium and dairy product intake were associated with less fat accumulation and higher insulin sensitivity. It also presents an inverse relationship with metabolic syndrome components, especially hypertension (106, 107). On the other hand, the results of other investigations have indicated that calcium supplementation (1500 mg day$^{-1}$) did not induce changes in body weight or lipid metabolism (108). It has been proposed that low calcium intake inhibits lipolysis and stimulates de novo synthesis, reducing fat oxidation, which results in an increased waist circumference. Through these mechanisms, a low dietary calcium intake leads to weight gain, whereas a high dietary calcium intake exerts the opposite effects (104). Another hypothesis suggests that calcium may have a modulating effect on the faecal excretion of fats (109). Reports from dietary assessments in the HIV infected patients have shown suboptimal intake of calcium (77, 79, 81). In these studies, over 90% of the patients did not meet the recommended level of intake of 1000 g/day of calcium. In one study, patients who had dietary calcium intake below 700 mg day$^{-1}$ had greater waist circumference and body mass index (BMI) (81). Dairy food consumers (>2 servings per day) showed lower BMI ($P < 0.01$), waist circumference ($P = 0.05$), systolic and diastolic blood pressure, all components of the metabolic syndrome (81).

**Chromium:** The metabolic abnormalities reported in PLWH are very similar to the abnormalities seen in patients with Type 2 diabetes and in those with chromium (Cr) deficiency. Chromium is a nutrient that potentiates insulin action and thus is an essential element for glucose and lipid metabolism (110-116). Improvements in glucose tolerance (117-128), plasma TG, total and HDL-cholesterol (128-131) after Cr supplementation is well documented in humans and in animals. In Type 2 diabetic patients, Cr supplementation resulted in an improvement in insulin sensitivity (132-134) and other metabolic parameters (135,136). Studies involving patients on total- parenteral- nutrition (TPN) led to conclusive documentation of the essential role of Cr in human nutrition (117, 123,124). These patients developed diabetic symptoms including glucose intolerance, weight loss, impaired energy utilization, and...
nerve and brain disorders that were refractory to insulin. After adding Cr to TPN fluids, diabetic symptoms were alleviated, and exogenous insulin was no longer required. Furthermore, children, the elderly and people with type I and II diabetes mellitus have all been shown to display positive effects on blood glucose and lipids in response to supplemental Cr (128,129, 136, 137). Finally, in a meta-analysis of 41 randomized trials involving 1198 participants, Cr supplementation significantly improved glycemia and dyslipidemia among patients with diabetes but had no effect in those without diabetes (138).

The metabolic abnormalities including IR documented in PLWH may be related to suboptimal chromium status. We were the first to show (139) that the blood level of Cr was significantly lower and the urinary excretion was higher in antiretroviral-treated PLWH when compared with healthy control subjects. In a subsequent randomized, double blind, placebo-controlled trial (140), 50 HIV-positive subjects with evidence of body fat redistribution, elevated lipids or glucose and who were found to have IR based on the calculation of homeostatic model of assessment (HOMA= (fasting blood glucose x fasting insulin) / 22.5) were randomized to receive either 400 ug of Cr-nicotinate or placebo for a period of 16 weeks. For inclusion, the HOMA had to be > 2.5. Body weight and medication profile remained stable throughout the study period for both groups. Cr supplementation resulted in a significant decrease in blood insulin, blood triglycerides and HOMA. Blood glucose, C-peptide, total cholesterol, LDL and HDL cholesterol and Hb A1c remained unchanged. Biochemical parameters did not change in the placebo group except for LDL cholesterol that increased significantly post supplementation with placebo. In subjects supplemented with Cr, those who had body fat redistribution, had a more pronounced drop in blood triglycerides (-0.70±0.29 mmol/l) than those without (0.02 ±0.20 mmol/L) (P=0.056). The severity of IR at baseline determined the response to Cr supplementation as there was a strong correlation between baseline insulin level and the post-supplementation drop in blood: insulin (r=-0.852, p=0.0001), triglycerides (r=-0.602, p=0.001) and c-peptide (r=-0.401, p=0.065).

Analysis by dual energy X-ray absorptiometry (DEXA) scan also showed a significant decrease in total body fat mass (kg) in the Cr-supplemented group. This was accompanied by a significant reduction in percent total body fat mass and a significant increase in percent total lean body mass. Further analysis of the regional fat distribution showed a significant decrease in percent trunk fat mass as well as percent fat mass in the arms and legs. In the Cr-supplemented group, the change in trunk fat mass was much more pronounced in subjects with body fat redistribution (-654.6 ±233.7 g) compare to those without this abnormality (-33.66 ±218.2 g) (P=0.068). As well, in subjects with body fat redistribution, Cr supplementation resulted in a decrease in trunk fat mass (-654.6 g ±233.7 g) whereas in the placebo group, trunk fat mass increased (1803±356 g). The difference between the two groups was statistically significant (P=0.05). Trunk fat mass correlated significantly with waist circumference (r=0.854, p=0.0001), and HOMA at baseline (r=0.275, p=0.036).

A detailed understanding of the molecular action of Cr is lacking; several lines of evidence point to enhancement of insulin action. Chromium increases insulin-stimulated glucose uptake in cultured muscle cells (141) and adipocytes (142). Chromium may increase insulin binding to cells, insulin receptor number, and insulin receptor tyrosine kinase activity (143). The enhancement of insulin action by Cr is associated with phosphorylation of insulin receptor substrate-1 (IRS-1) (141) and phosphatidylinositol 3-kinase (PI 3-kinase) (144) and is inhibited by wortmannin, an inhibitor of PI 3-kinase. Activation of these proteins in the insulin-signalling transduction pathway leads to translocation of glucose transporters from

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the cytosol to the plasma membrane. Indeed, Cr-picolinate supplementation was shown to significantly enhance the membrane-associated Glut-4 content of skeletal muscle and rate of glucose disappearance in obese rats after insulin stimulation\(^{(145)}\). In a follow-up study it was reported that improved glucose disposal rates in Cr-fed, obese, insulin-resistant animals were attributable to enhanced insulin-stimulated IRS-1 and PI 3-kinase activity in skeletal muscle\(^{(146)}\).

The form or availability of Cr in specific foods is generally not known. A balanced diet will provide Cr with an average availability of 1-2\%\(^{(147,148)}\). Processed meats; liver; whole-grains including some ready-to-eat bran cereals; some pulses, such as dried beans; some vegetables, including broccoli and mushrooms; and spices are some of the best sources of Cr. Dairy products, and most fruits and vegetables, contain low amounts of Cr. Rice and sugar are poor sources.

The suggested safe and adequate intake for Cr is established at 50-200\(\mu\)g/day for adolescents and adults, and 10-120\(\mu\)g/day for infants and children\(^{(149)}\). It is reported that Cr intake by even healthy subjects consuming average Westernized diets is suboptimal\(^{(150)}\) and is below the recommended level of 50\(\mu\)g. One third of the diets, designed by a nutritionist to be well-balanced and to contain the recommended daily intake of vitamins and minerals (except chromium) contained less than the minimal safe and adequate intake of 50\(\mu\)g of Cr\(^{(151)}\). Anderson and Kozolovsky\(^{(152)}\) measured the daily Cr intake of 22 female and 10 male subjects for 7 days. Not a single subject had a mean daily Cr intake of 50\(\mu\)g or more. On the other hand, consuming less than 50\(\mu\)g/d of Cr does not mean that one would eventually become Cr deficient. For example, in one study\(^{(152)}\), 11 elderly women had an average intake of 20.1\(\mu\)g/day and 11 elderly men had an average intake of 29.8\(\mu\)g per day; the range of intakes was 13.6-47.7\(\mu\)g among the 22 subjects. Of these, 16 maintained equilibrium, 4 exhibited positive balances, and 2 exhibited slight and one exhibited severe negative balance. The intake at which Cr is low enough to induce changes responsive to Cr supplementation is not well established. Moreover, because other substances in the diet influence absorption and metabolism of Cr, the point at which Cr intake becomes inadequate depends in part on the other foods consumed, medical conditions and medication profile.

Chromium chloride, chromium nicotinate, and chromium picolinate are commonly used formulations of trivalent chromium in the supplements. The studies that reported positive effects of supplemental chromium on people with diabetes usually involve 400\(\mu\)g or more of Cr. Chromium supplements are inexpensive\(^{(153)}\), and the limited safety data suggest that Cr is safe even at high doses\(^{(154)}\). Therefore, Cr supplementation would be an attractive option for management of diabetes and for control of insulin and lipid concentration of PLWH. The role of Cr supplementation in conjunction with the initiation of HAART should be studied prospectively as a cost-effective approach to reducing CVD.

**Physical activity:** At the present time, overweight and obese individuals constitute a much larger segment of the HIV-infected population than patients with wasting syndrome\(^{(155)}\). As with individuals in the general population, an obese patient with HIV should be advised about the benefits of weight loss and regular physical activity; this is applicable not only to patients with high risk of diabetes but also to individuals who have already developed glucose intolerance or frank diabetes. There is considerable evidence that lifestyle changes, including changes in diet (eg, calorie restriction and reduction in intake of carbohydrates, saturated fats, and cholesterol) and increased physical activity can help reverse the
progression to type II diabetes and improve glycemic control in individuals already diagnosed with the condition (156-159). In a randomized study, aggressive lifestyle modification was more effective than metformin in preventing the development of diabetes in individuals with elevated fasting glucose (160); however, adherence to lifestyle changes is difficult to maintain over time. The expected improvement in Hb A1C levels in individuals who are able to follow lifestyle modification recommendations is 1%-2%, similar to goals that are attainable with some drug regimens. Clear evidence has established that adults who engage in regular physical activity and/or exhibit high cardiorespiratory fitness have a reduced risk of developing type II diabetes (161). Furthermore, the beneficial effects of a physically active lifestyle seem to hold true for normal-weight, overweight, and obese individuals alike. It is hypothesized that the mechanisms underlying this protective effect may be due, at least in part, to the insulin-sensitizing properties of physical activity on skeletal muscle. From controlled studies, exercise training is associated directly with improved insulin sensitivity (162-165). Hughes et al (166) showed that exercise training of between 50% and 75% of maximal capacity can improve insulin sensitivity in individuals with impaired glucose tolerance. From community studies, increased levels of overall habitual physical activity have been positively associated with surrogate measures of insulin sensitivity among individuals without diabetes (167-168) and among those with impaired glucose tolerance (169), independent of obesity. In another study (170), including 1467 men and women of African American, Hispanic, and non-Hispanic white ethnicity, aged 40 to 69 years, with glucose tolerance ranging from normal to mild non-insulin-dependent diabetes mellitus, increased participation in non-vigorous as well as overall and vigorous physical activity was associated with significantly higher insulin sensitivity. However, questions remain regarding the nature and amount of physical activity required to have a sustained, beneficial impact on glucose and insulin metabolism at the individual and the community levels. The Centers for Disease Control and Prevention (CDC), and the American College of Sports Medicine (ACSM), have recently recommended that every US adult should accumulate at least 30 minutes of moderate-intensity physical activity (3 to 6 metabolic equivalents [METs]) on most, preferably all, days of the week (171). The same recommendation was put forth by a 1996 National Institute of Health Consensus Statement (172).

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HIV Infection in the Era of Highly Active Antiretroviral Treatment and Some of Its Associated Complications


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HIV-Infection: The Role of Insulin Resistance and Alternative Treatments


Human immunodeficiency virus (HIV) infection is a complex illness affecting the immune system. Acquired immunodeficiency syndrome (AIDS) is an advanced form of HIV infection in which the patient has developed opportunistic infections or certain types of cancer and/or the CD4+ T cell count has dropped below 200/µL. More than 40 million persons around the world are infected with HIV, with approximately 14,000 new infections every day. The disease causes 3 million deaths worldwide each year, 95% of them in developing countries. Optimal management of human immunodeficiency virus requires strict adherence to highly active antiretroviral treatment (HAART) regimens, but the complexity of these regimens (e.g., pill burden, food requirements, drug interactions, and severe adverse effects) limits effective treatment. However, more patients with HIV are surviving longer today because of these drugs. This allows further study of commonly associated adverse effects. These may affect all body systems and range from serious toxicities to uncomfortable but manageable events. This book reviews some of HAART-related metabolic and neurological complications.

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