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Review

Primary care for diabetes in HIV-infected patients

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Abstract:
Diabetes mellitus (DM) is a common disorder affecting individuals of all ages. Similar to general population, DM can also be seen in HIV infected cases. The prevalence of insulin resistance, glucose intolerance, and diabetes in the HIV-infected population has increased dramatically following the widespread use of highly active antiretroviral therapy (HAART). HIV disease being an important global problem, increasing prevalence of DM among these patients in the HAART era can be expected. Primary care for HIV-infected with reference to DM and follow up for related complications is therefore important
Key Words: HIV, Diabetes mellitus, Primary care

Diabetes in HIV-infected population:
Diabetes mellitus (DM) is a highly prevalent disorder affecting individuals of all ages.[1] Similar to the general population, impaired glucose metabolism and DM can be seen in HIV infected patients.[2] Insulin resistance is accepted as the underlying fundamental defect that predates and ultimately leads to the development of type 2 (adult-onset) DM in the general non-HIV-infected population.[3] Insulin resistance is also a major component of the metabolic syndrome that — in association with other factors such as hypertension, hypercholesterolemia, and central obesity — defines a pre-diabetic atherogenic state that leads to adverse cardiovascular events.[3] Impaired glucose tolerance in lipodystrophic HIV-infected patients relates to a failure of the beta-cells to fully compensate for decrements in insulin sensitivity despite simultaneous reduction in insulin clearance.[4] Reports of insulin resistance and the development of overt diabetes increased with the routine clinical use of antiretroviral drug. This led to the supposition that the use of this class of drugs induced hyperglycemia [5]. In the recent years, the prevalence of insulin resistance, glucose intolerance, and diabetes in the HIV-infected population has increased dramatically following the common use of highly active antiretroviral therapy (HAART).[3]

Insulin resistance, glucose intolerance and DM in HIV-infected patients:
HAART has markedly improved the prognosis of people with HIV infection for a few years.[6] However, there are long-term side effects associated with HAART. Alterations in metabolic parameters are common and these include hyperlipidaemia and insulin resistance (IR), either in isolation or as part of the lipodystrophy and metabolic syndrome.[6] An increased prevalence of insulin resistance, glucose intolerance and diabetes has been reported in HIV infection in the HAART era.[7-9] This development might be clinically significant because of its association with cardiovascular morbidity and mortality as well as the therapeutic challenges of managing polypharmacy.[7] The development of insulin resistance in the HIV-infected population is likely to be multifactorial, reflecting genetic predisposition, direct and indirect effects of both the protease inhibitor (PI) and nucleoside reverse transcriptase inhibitor (NRTI) class of antiretroviral therapy, and a possible contribution from chronic inflammatory changes induced by HIV.[10] Indirect effects of antiretroviral therapy on insulin resistance may be mediated through both the visceral adiposity and peripheral fat depletion components of lipodystrophy as well as through fatty infiltration in liver and muscle.[10] With HIV continuing to be an important global problem, the prevalence of DM is expected to increase in the HAART era. [11] Metabolic complications associated with HIV disease and its treatment — including insulin resistance and diabetes, abnormal cholesterol and triglyceride levels (dyslipidemia), and body fat gain or loss — remain a medical mystery and a topic of intense interest for AIDS researchers.[12] The optimal treatment for insulin resistance and impaired glucose intolerance in HIV-infected patients is not known, but preliminary studies

have suggested that metformin, an insulin sensitizing agent, improves insulin sensitivity, blood pressure, and waist circumference.[13] Antiretroviral drugs from new classes, as well as new drugs from existing classes with favorable resistance and side effect profiles are in various stages of development.[14] However, new tissue disorders will be certainly described in the future in patients treated with these drugs.[14]

Diabetes mellitus primary care in HIV-infected patients

Screening for DM in HIV-infected patients

Carr *et al*. [15] reported a 7% incidence of new-onset diabetes as diagnosed by a two-hour blood glucose value >200mg/dl after administration of an oral glucose tolerance test. The incidence of diabetes was reduced to a half in a study that used a random blood glucose level of 180mg/dl as the cut point for diabetes diagnosis.[16] A more recent analysis conducted in the Multicenter AIDS Cohort Study places the incidence of diabetes in HIV-infected men with HAART exposure at four times greater than that of HIV-seronegative men.[17] As a recommendation, fasting blood glucose level should be checked before initiation of HIV therapy and should be monitored every 3–6 months for patients with changes in treatment regimen or who have significant risk factors for insulin resistance.[18] For patients with impaired glucose tolerance or who have risk factors for DM, a two-hour oral glucose tolerance test should be considered.[18] HIV-infected patient with diabetes risk factors should undergo screening for DM and its complications regardless of HAART use.[19]

Hamill and Brook [20] suggested that those managing co-infected patients between HIV/HCV (hepatitis C virus) without any history of antiretroviral therapy shall pay particular attention to screening for abnormal glucose metabolism and elicit a full family history of metabolic disorders.

Following up DM treatment in HIV-infected patients

Follow up of DM for complication in HIV-infected patients can be similar to that of the general population. According to Polgreen *et al*. [21], persistent differences in blood glucose and glycosylated hemoglobin (HbA1C) measurements were observed in four HIV positive patients with diabetes mellitus, all of whom were taking drugs associated with hemolysis, which interferes with the reliability of HbA1C levels. They suggested that the determination of fructosamine level was a more accurate alternative for measuring average glycemic control in these patients.[21] Diop *et al*. also contend that HbA1C should be interpreted with caution in HIV-infected patients.[22] Its underevaluation of mean fasting glycaemia could be a result of hemolysis, associated with lamivudine treatment.[22]

Urinary microalbumin levels have been correlated with CD 4 T-cell and white blood cell counts, tumor necrosis factor α and β2-microglobulin levels, suggesting an association between AIDS progression and microalbuminuria.[23] By monitoring urinary microalbumin levels, those patients susceptible to the development of nephrotic syndrome could be identified and prophylactic measures initiated.[23]

Complications in HIV and non-HIV diabetic populations

There is no systematic evaluation on comparison between prevalence of the complications in HIV and non-HIV diabetic populations. However, the HIV diabetic population tend to have more chance for development of complications. For example, diabetic foot can easily occur in HIV infected patients. There are many underlying opportunistic infections in HIV that have common dermatologic manifestation on the foot such as fungal nail infections that can

increase the chance of diabetic foot.[24] The underlying opportunistic infections in retina such as cytomegalovirus retinitis can increase the chance of developing diabetic retinopathy in HIV infected patients.[25] The control of opportunistic infections might help reduce these diabetic complications in HIV cases. With increasing importance of non-HIV-associated diseases, especially for DM, attention should be focussed on prevention and control of those disorders in HIV-positive individuals.[26] Interventions targeting modifiable risk factors, including overweight and physical inactivity, are warranted.[19]

Primary care for HIV-infected patients with Diabetic complications

Diabetic foot

Quarterly foot examinations are recommended for HIV-infected patients with DM.[27] Due to the immune impairment, severe infection as consequence of diabetic foot can be expected. The early recognition of infection, particularly osteomyelitis, is paramount in the management of diabetic foot disease. Careful clinical appraisal remains the cornerstone of the assessment.[28] Hematologic, biochemical, and radiological investigations are important aids in assessing the severity of infection.[28] Microbiological assessment, particularly in more severe infection, requires good quality samples, combined with rapid transport in an appropriate medium and effective communication with the laboratory.[28]

Diabetic retinopathy

In a series of 200 AIDS patients evaluated clinically, AIDS retinopathy was present in 66.5% with 64% having cotton-wool spots, and 12% having intraretinal hemorrhages.[29] Increased risk for diabetic retinopathy is reported in HIV infected patients with DM.[30,31] Regular visual check is therefore required for all HIV-infected patients with DM.

Nephropathy

HIV-associated nephropathy (HIVAN) is now the third leading cause of end-stage renal disease in African Americans between the ages of 20 and 64 years. [32] Atta *et al*. [33] proposed that HIV patients with nephrotic-range proteinuria warranted a kidney biopsy because the presence of nephrotic-range proteinuria, even in the presence a low CD4 count, did not establish the diagnosis of HIVAN. The Association of the Infectious Diseases Society of America recommends screening for chronic kidney disease in HIV-infected patients; screening tests should be similar to those for patients with DM to detect early renal involvement.[32] In seropositive patients with renal disease, renal biopsies should be performed to confirm the diagnosis and determine the true incidence.[34] Special attention should be directed toward understanding the underlying cause of HIVAN.[34]

Conclusion

With the global presence of HIV infection and increasing use of HAART, it is prudent to expect an increasing prevalence of DM among these patients. The general physician in primary care should pay particular attention for their HIV infected patients with DM.

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