ORIGINAL ARTICLE

Risk factors for new-onset diabetes mellitus in patients receiving protease inhibitor therapy

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BACKGROUND: Metabolic complications including diabetes mellitus (DM) have been associated with protease inhibitor (PI) therapy. Risk factors for the development of DM are not well-defined.
OBJECTIVES: To determine risk factors for the development of new-onset DM in patients initiated on PI therapy.
METHODS: A retrospective cohort study was conducted to identify predictors of developing DM in subjects started on PI therapy between January 1997 and January 2003. Diabetes cases were defined as physician documentation of DM in the outpatient medical chart and/or those subjects receiving an antidiabetic agent. Logistic regression was used to examine the relationship between new-onset DM and demographic characteristics, and between new-onset DM and total treatment days with PI therapy. Body mass index could not be entered into the model due to missing height measurements.
RESULTS: A total of 496 subjects on PI therapy were included, of which 18 (3.6%) developed DM. The mean age of the subjects was 43.4±9.4 years (range 19 to 77) and the mean duration of therapy was 3.0±1.9 years (range 0.17 to 7.9). In the multivariate model, older subjects were more likely to develop DM (OR 1.12, 95% CI 1.05 to 1.19; P=0.001). This corresponds to a 12% increased risk of DM for each one-year increase in age. Subjects that weighed more had an increased risk (OR 1.06, 95% CI 1.03 to 1.10; P=0.001), as did those belonging to a non-Aboriginal minority group when compared with Caucasians (OR 6.67, 95% CI 1.56 to 28.41; P=0.01). A longer duration of PI therapy was also significantly associated with developing DM (OR 1.52, 95% CI 1.07 to 2.17; P=0.02).
CONCLUSION: A longer duration of PI therapy is associated with an increased risk of developing DM. As with HIV-negative subjects, demographic characteristics such as age, weight and ethnicity were important predictors of developing DM in the present study.

Key Words: *Diabetes mellitus; Protease inhibitors; Risk factors*

Facteurs de risque de diabète chez des patients sous inhibiteurs de la protéas

HISTORIQUE : Des complications métaboliques, dont le diabète sucré (DS), ont été associées à la prise d'inhibiteurs de la protéase (IP). Les facteurs de risque à l'égard du développement du DS ne sont pas clairement définis.
OBJECTIF : Déterminer les facteurs de risque à l'égard du DS chez des patients qui commencent à prendre des IP.
MÉTHODES : Une étude de cohorte rétrospective a été menée afin d'identifier les facteurs de prévisibilité du DS chez des sujets qui ont commencé à prendre un traitement par IP entre janvier 1997 et janvier 2003. Les cas retenus dans le cadre de l'étude avaient été diagnostiqués par un médecin et notés dans leur dossier médical de la clinique externe, et/ou étaient sous antidiabétiques. L'analyse de régression logistique a été utilisée pour étudier le lien entre le DS d'apparition récente et les caractéristiques démographiques d'une part et le nombre total de jours de traitement par IP d'autre part. L'indice de masse corporelle n'a pas pu être intégré au modèle en raison de données incomplètes notamment quant à la taille de certains sujets.
RÉSULTATS : En tout, 496 sujets sous IP ont été inclus, dont 18 (3,6 %) ont développé un DS. L'âge moyen des sujets était de 43,4 ± 9,4 ans (de 19 à 77 ans); la durée moyenne du traitement était de 3,0 ± 1,9 ans (de 0,17 à 7,9 ans). Selon le modèle d'analyse multivariée, le risque de développer un DS était proportionnel à l'âge (RR 1,12; IC 95 %; 1,05 à 1,19; p = 0,001). Cela correspond à une augmentation de 12 % du risque de DS pour chaque année supplémentaire de vie. Les sujets qui pesaient davantage étaient aussi exposés à un risque plus grand (RR 1,06; IC 95 %; 1,03 à 1,10; p = 0,001), tout comme les sujets qui appartenaient à un groupe minoritaire non aborigène, comparativement aux sujets de race blanche (RR 6,67; IC 95 %; 1,56 à 28,41; p = 0,01). La durée du traitement par IP était également en forte corrélation avec le DS (RR 1,52; IC 95%; 1,07 à 2,17; p = 0,02).
CONCLUSION : Le risque de développer le DS est proportionnel à la durée du traitement par IP. Comme chez les sujets non infectés par le VIH, certaines caractéristiques démographiques telles que l'âge, le poids et l'origine ethnique ont été d'importants facteurs de prévisibilité à l'égard du DS dans le cadre de la présente étude.

Since the introduction of highly active antiretroviral therapy with protease inhibitors (PIs), morbidity and mortality due to HIV infection has significantly declined (1). It was soon recognized, however, that the use of PIs was associated with metabolic abnormalities including fat redistribution, hyperlipidemia, insulin resistance and hyperglycemia (2). The incidence of new-onset diabetes mellitus (DM) has ranged from 1% to 6% in retrospective studies of patients receiving PI therapy (3-5). The exact mechanism of PI-associated DM is unclear; however, insulin resistance is thought to play a major role (2,6-9). Likewise, other factors that may increase the risk of PI-associated DM are not well-described. We conducted a retrospective cohort study to identify risk factors associated with the development of new-onset DM in a patient population started on PI therapy.

METHODS

Subjects potentially eligible for inclusion into the present study were at least 18 years of age and were initiated on PI therapy between January 1997 and January 2003 (n=632). Individuals

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TABLE 1
Demographic and clinical subject characteristics (n=496)

Characteristic	Nondiabetes group (n=478)	Diabetes group (n=18)	P
Mean age (years ± SD)	42.1±9.2	51.6±9.6	<0.001
Male sex, n (%)	375 (79)	16 (89)	0.287
Ethnicity, n (%)			
Caucasian	316 (66)	12 (67)	0.961
Aboriginal	102 (21)	1 (6)	0.140
Other minority (non-Aboriginal)	60 (13)	5 (27)	0.073
Weight at HIV diagnosis (kg ± SD)	72.2±14.1	83.7±19.4	0.001
Hepatitis C virus infection, n (%)	173 (36)	1 (6)	0.001
Alcohol use, n (%)	113 (23.6)	1 (6)	0.073
Use of potential hyperglycemic medication, n (%)	84 (18)	4 (22)	0.540
Mean duration of PI therapy (years ± SD)	2.91±1.91	4.36±1.74	0.002

PI Protease inhibitor

TABLE 2
Crude and adjusted odds ratios for developing new-onset diabetes mellitus

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)
Weight	1.04 (1.02–1.07)*	1.06 (1.03–1.10)*
Sex (male reference)	0.46 (0.10–2.01)	2.98 (0.48–18.62)
Age	1.10 (1.05–1.15)*	1.12 (1.05–1.19)*
Ethnicity		
Aboriginal versus Caucasian	0.26 (0.03–2.01)	0.80 (0.08–7.98)
Non-Aboriginal minority versus Caucasian	2.99 (1.01–8.90)*	6.67 (1.56–28.41)*
Hepatitis C virus infection	0.07 (0.01–0.51)*	0.21 (0.02–1.81)
Alcohol use	0.19 (0.03–1.44)	0.157 (0.02–1.69)
Use of potential hyperglycemic medication	0.94 (0.27–3.31)	0.51 (0.11–2.36)
Total treatment days (PI)	1.49 (1.15–1.92)*	1.52 (1.07–2.17)*

**P<0.05. PI Protease inhibitor*

with a history of DM before PI therapy initiation were excluded (n=30). In addition, subjects were also excluded (n=106) if they were insufficiently exposed to PI therapy, which was defined a priori as less than eight weeks in duration. All subjects were identified using the database of the Northern Alberta HIV program. The database captures demographic information, medical conditions, medications, new events (eg, opportunistic infections or adverse effects) and laboratory values and is updated following each clinic visit.

Using the database, the authors identified 496 subjects initiated on PI therapy who met the inclusion criteria. From this population, subjects with new-onset DM were identified using the database records and confirmed by the medical chart. Diabetes cases were defined as physician documentation of DM in the outpatient medical chart and/or those subjects receiving an antidiabetic agent.

Demographic and clinical characteristics were collected for all subjects using the database records and were described as mean and standard deviation or proportions, as appropriate. The characteristics of the two groups under study were compared with a Student's *t* test, χ^2 test or Fisher's exact test depending on the nature of the variable.

Logistic regression models were used to examine the relationship between new-onset DM and potential risk factors, including age, sex, ethnicity, weight, alcohol use, hepatitis C virus (HCV) infection, total treatment days with PI therapy, and concurrent use of other agents known to potentially cause hyperglycemia (eg, atypical antipsychotic agents, beta-blockers, corticosteroids, diuretics, pentamidine). Body mass index (BMI) could not be entered into the model because height measurements were not systematically recorded in the database. Crude and adjusted odds ratios (ORs) and 95% CIs were calculated using logistic regression for each variable. In addition, all potentially important clinical interactions were assessed in the logistic regression models; no important or statistically significant interactions (P<0.10) were identified. All statistical analyses were performed using SPSS software (version 11.0, SPSS Inc, USA) for Windows (Microsoft Corporation, USA) using an a priori alpha of 0.05. This study was approved by the University of Alberta Health Sciences Faculties, the Capital Health Authority and the Caritas Health Group Health Research Ethics Board.

RESULTS

The mean age of the PI-treated subjects was 43.4±9.4 years (range 19 to 77) and the mean duration of PI therapy was 3.0±1.9 years (range 0.17 to 7.9). New-onset DM was identified in 18 of the 496 subjects (3.6%) who were initiated on PI therapy. The onset of DM was variable, with a mean onset of 475±301 days (range within two months up to 48 months after PI initiation). The mean age of subjects in the diabetes group was 51.6±9.6 years versus 42.1±9.2 years in the nondiabetes group (Table 1). When compared with the nondiabetes group, subjects in the diabetes group were heavier and had been on PI therapy longer (Table 1). There were no significant differences between the groups in terms of ethnicity; however, there was a higher proportion of Aboriginal subjects in the nondiabetes group, whereas subjects in the diabetes group were more likely to be members of a non-Aboriginal minority. There was a significantly higher number of subjects coinfected with HCV in the nondiabetes group.

A comparison of the demographic characteristics of individuals from the diabetes group and patients excluded from the study due to a prior history of diabetes (n=30) revealed a higher proportion of Aboriginal subjects with a prior history of diabetes (27%) and a smaller proportion of non-Aboriginal minority subjects with a prior diabetes diagnosis (7%). Thirty-three per cent of patients with diabetes before PI therapy initiation were coinfected with HCV.

In the univariate analyses, weight, age, ethnicity and a higher number of total treatment days of PI therapy were significant risk factors for developing DM (Table 2). In the multivariate model, subjects who were older were more likely to develop DM (OR 1.12, 95% CI 1.05 to 1.19; P=0.001). This corresponds to a 12% increased risk of developing DM for each one-year increase in age. In addition, subjects that were heavier had an increased risk of developing DM (OR 1.06, 95% CI 1.03 to 1.10; P=0.001), as did those belonging to a non-Aboriginal minority group (eg, African American, Hispanic, Asian) when compared with Caucasians (OR 6.67, 95% CI 1.56 to 28.41; P=0.01). Of the non-Aboriginal minority patients treated with a PI, 7.7% developed diabetes. A longer duration of PI therapy was also significantly associated with developing DM (OR 1.52, 95% CI 1.07 to 2.17; P=0.02).

DISCUSSION

We found that a higher number of total treatment days of PI therapy was associated with a substantial risk of developing new-onset DM. In addition, other independent risk factors for DM included older age, increased body weight and ethnicity (non-Aboriginal minority). Traditional risk factors for the development of type 2 DM include family history, being overweight, an age of at least 40 years, and being a member of a high-risk population (people of Aboriginal, Hispanic, South Asian, Asian or African American descent) (10). Thus, these results support a multifactorial etiology of DM in patients receiving PI therapy, where traditional risk factors play an important role.

The results from the present study are consistent with those from other studies. Palacios et al (11) conducted a case-control study of HIV-infected patients who developed DM after starting antiretroviral therapy between January 1997 and December 2001. These authors found that obesity at the start of the follow-up for HIV infection, the duration of treatment with PI and the presence of lipodystrophy were all associated with the development of DM. In a prospective study of approximately 2000 women (both HIV-infected and HIV-uninfected), Justman et al (12) found that PI use, older age and being overweight were independent risk factors for DM.

Aboriginal ethnicity was not found to be associated with the development of new-onset DM in the present study. Further analyses revealed that Aboriginal patients were, on average, five years younger than the rest of the population (both Caucasians and other minorities; $P<0.001$), which may partially explain these results. A higher proportion of Aboriginal patients had diabetes before starting PI therapy. This is not surprising, however, because Aboriginal patients are at a significantly increased risk of developing diabetes when compared with Caucasians (10). In addition, HCV infection was also not found to be associated with DM after adjusting for other risk factors. This is contrary to studies (13,14) that have found that HCV infection is associated with hyperglycemia and DM. However, on average, patients with HCV infection were younger ($P<0.01$) and had a shorter duration of PI therapy ($P<0.01$) in the present study. As well, patients with HCV infection had a lower mean body weight, although this did not reach statistical significance ($P=0.25$).

Although not a specific outcome of the present study, we also examined whether specific PI agents were associated with the development of new-onset DM. After controlling for other risk factors in the multivariate model, there was no significant difference found among the individual PIs. Importantly, however, the majority of subjects (79.3%) received indinavir or nelfinavir as their first PI therapy.

An important limitation of the present study was its retrospective design; data could not be collected for other diabetes risk factors (eg, family history), and the presence or absence of lipodystrophy could not be determined. The calculation of BMI was not possible due to missing height data for some patients; however, weight has also been associated with the development of diabetes. In addition, the case definition of diabetes may have resulted in an underestimate of DM. However, despite this, a longer duration of PI use was associated with an increased risk of developing DM.

The present study suggests that traditional risk factors play an important role in the development of new-onset DM in patients starting PI therapy. Before starting antiretroviral therapy, patients should be screened for diabetes risk factors, including family history. Given the serious, long-term health consequences of diabetes, consideration may be given to starting a non-PI regimen (or possibly atazanavir) for patients at higher risk (15). For patients initiated on PI therapy, a fasting blood glucose should be measured at baseline and regularly during PI treatment. In addition, BMI should be monitored regularly and weight loss recommended for patients who are overweight and at higher risk of developing diabetes.

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