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-Original Article-

Prevalence of impaired renal function in virologically suppressed people living with HIV compared with controls: the COCOMO study

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Renal impairment in well-treated PLWH & controls

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ABSTRACT

Objectives While renal impairment is reported more frequently in people living with HIV (PLWH) than in the general population, previous studies are generally dominated by PLWH at high renal risk.

Methods Caucasian PLWH, virologically suppressed on antiretroviral treatment, without injecting-drug use, or hepatitis C were recruited from the Copenhagen comorbidity in HIV infection study. Sex and age matched controls were recruited 1:4 from the Copenhagen General Population Study up to November 2016. We defined renal impairment as one estimated glomerular filtration rate ≤ 60 mL/min/1.73m², and assessed associated factors using adjusted logistic regression models. The impact of HIV-related factors was explored in a subanalysis.

Results Among 598 PLWH and 2,598 controls, the prevalence of renal impairment was 3.7%

[95% confidence interval, CI, 2.3-5.5] and 1.7% [95%CI 1.2-2.2], $p=0.0014$, respectively. After adjustment, HIV status was independently associated with renal impairment, odds ratio (OR) 3.4 [95%CI 1.8-6.3]. In addition, older age (OR 5.4 [95%CI 3.9-7.5] per 10 years), female sex (5.0 [95%CI 2.6-9.8]), and diabetes (2.9 [95%CI 1.3-6.7]) were strongly associated with renal impairment. The association between HIV-status and renal impairment increased with older age ($p=0.02$ for interaction). Neither current or nadir CD4 count, time with HIV or previous AIDS-defining diagnosis was associated with renal impairment among virologically suppressed PLWH.

Conclusion The prevalence of renal impairment is low among low risk virologically suppressed Caucasian PLWH, but remains significantly higher than in controls. Renal impairment therefore remains a concern in all PLWH and requires ongoing attention

Introduction

Impaired renal function is an increasingly important non-AIDS comorbidity with a reported prevalence as high as 30% in people living with HIV (PLWH) (1)(2)(3). The combination of declining renal function with age and the reduced mortality rates amongst PLWH over the last decades means that renal impairment is likely to become an even more common comorbidity in the coming years.

If renal impairment persists it is often progressive in nature despite efforts to control the underlying cause, and may subsequently result in end stage renal disease requiring dialysis or transplantation and high risk of death (4). In addition, impaired renal function may predispose to development of other common comorbidities including anemia, osteoporosis, and cardiovascular disease (5–7).

Risk factors for development of both chronic and acute renal impairment in PLWH have been well described over the past decade and include an array of traditional factors (including older age, hypertension and diabetes), HIV related factors (including impaired immune function, ongoing viremia and viral hepatitis co-infection), and the use of several nephrotoxic drugs including certain antiretrovirals used to control HIV (8–12).

Studies of renal outcomes amongst PLWH have traditionally included a relatively large proportion of individuals of African descent with a known inherent increased risk of impaired renal function (13–16). In addition, prior studies have had a relatively high proportion of individuals with injection drug use (IDU), viral hepatitis C (HCV) co-infection, or ongoing HIV replication, all potent risk factors for impaired renal function (17–20). To date, it is therefore unknown to which extent virologically suppressed PLWH are at increased risk of renal impairment, over and beyond the contribution of known confounding factors.

To directly assess the impact of HIV on renal function, we therefore designed a cross-sectional case-control study to determine if the prevalence of impaired renal function differs between

Danish general population controls and a well-characterized cohort of PLWH without common confounders of altered renal function. We also aimed to assess if, in virologically suppressed low risk population of PLWH, HIV status remains an independent risk factor for impaired renal function.

MATERIALS AND METHODS

Study design

The Copenhagen Comorbidity in HIV infection (COCOMO) study is a prospective cohort study investigating the prevalence and pathogenesis of non-AIDS comorbidity in PLWH in Copenhagen, Denmark. The COCOMO study follows 1,099 PLWH, corresponding to > 40% of PLWH in the greater Copenhagen area, details have previously been published (21).

In this cross-sectional sub-study, only individuals from Scandinavia, of Caucasian ancestry, on combination antiretroviral treatment (cART), with undetectable HIV viral load (≤ 50 copies/mL) and without HCV antibodies and current/prior IDU were included.

This population was subsequently frequency matched by sex and five-year age strata with controls recruited from the ongoing Copenhagen General Population Study (CGPS) (22). The CGPS study is a prospective cohort study which systematically collects data on the health of the Danish general population. We randomly identified four unique controls for every PLWH in each age and sex stratum. The controls did not undergo systematically HIV testing, but the expected prevalence of HIV among the general population in Denmark is very low ($\sim 0.1\%$) (23).

Ethical approval was obtained by the Regional Ethics Committee of Copenhagen (COCOMO: H-15017350; CGPS: H-KF-01-144/01).

Written informed consent was obtained from all participants.

Endpoint

The primary study endpoint was impaired renal function defined as a single estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73m². According to the KDIGO eGFR classification of renal impairment an eGFR > 90 mL/min/1.73m² is considered a normal to high renal function, whereas eGFR 69-89 mL/min/1.73m² is mild impairment, eGFR ≤ 60 mL/min/1.73m² moderate impairment, eGFR ≤ 30 mL/min/1.73m² severe impairment and eGFR ≤ 15 mL/min/1.73m² equivalent to renal failure (24). We calculated eGFR based on creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (25,26). Serum creatinine was collected and measured uniformly in all participants of both cohorts using an isotope dilution mass spectrometry (IDMS) calibrated 'Jaffe-method'. Until June 2016 measurements were done using a Konelab 60i (Thermo Scientific, Helsinki, Finland) and from June 2016 a Cobas C501 (Roche Diagnostics, Indianapolis, USA) was used. All measurements were made at Herlev University Hospital, Copenhagen, Denmark.

Covariates

Details on data collection and establishment of the COCOMO biobank have been described elsewhere (21). Information on socioeconomic status and lifestyle factors were obtained through identical questionnaires in both cohorts. Educational level was defined as education obtained after high school and grouped as: none, short (≤ 3 years), vocational, medium length (≥ 3 years, e.g. nurse, teacher) and university degree. Smoking status was classified as never smoker, former smoker or current smoker. For smokers, smoking intensity was reported as cumulated pack years; number of packs of 20 cigarettes smoked per day multiplied by the number of years the person had smoked. A physical examination including body weight, and blood pressure (BP) were measured uniformly in all participants. Body mass index (BMI), was defined as the weight divided by the square of the height and was fitted as a continuous variable with ascending values. BP was measured after five minutes rest and with the subject in sitting position, using an automatic Digital Blood Pressure Monitor. Hypertension, was defined as having BP of either ≥ 140 mmHg/ ≥ 90 mmHg, ≥ 140 mmHg/ < 90 mmHg, ≤ 140 mmHg/ ≥ 90 mmHg and/or use of

antihypertensive medication. Diabetes mellitus was defined as non-fasting venous plasma glucose ≥ 11.1 mM, or HbA1c ≥ 48 mM or being treated with antidiabetic drugs.

HIV-related variables were obtained from patient records and included information about: mode of HIV transmission: men who have sex with men (MSM), heterosexual or other; current, median and nadir CD4 count (cells/mm³); HIV viral load (copies/mL); time since HIV diagnosis in years and history of AIDS defining diagnoses.

Statistical analysis

PLWH and controls characteristics were compared using Student's t-test or Mann Whitney U test for continuous data with respectively normal or non-normal distribution, and X² for categorical data. A p-value of 0.05 or lower was used to infer statistical significance.

Uni- and multivariate logistic regression analyses were performed on the full dataset containing both cohorts (PLWH and controls). The variables included in the model were based on factors previously shown to adversely impact renal function and included age, sex, ethnic origin, HIV status, BMI, smoking, diabetes, hypertension and educational level (11,13,20,27–30).

In a separate model, we further assessed whether various HIV-related factors were independently associated with impaired renal function among PLWH.

An a priori planned investigation of interactions ($p < .05$) between age, diabetes and hypertension with HIV status on the risk of having eGFR ≤ 60 mL/min/1.73m² was carried out. All statistical analyses were performed using SAS version 9.4, USA.

RESULTS

Inclusion

Of 1,099 persons under follow-up in the COCOMO study, 677 persons (61.7%) fulfilled the inclusion criteria of Caucasian origin, being on cART with fully suppressed viremia and no HCV or IDU. A total of 79 persons were excluded due to lack of eGFR data, leaving 598 persons for

analysis (88.3%, Figure 1). From the general population cohort, 2,598 of 2,708 (95.9%) age and gender matched individuals were included in the analysis.

Baseline Characteristics

Demographics and clinical characteristics are presented in table 1. Most participants were males (89%) with a median age of 51.2 (interquartile range, IQR, 46.0-62.3) years. PLWH tended to have lower median BMI (24.3 vs 26.1, $p < 0.001$), but also a lower prevalence of hypertension (46.0% vs 56.8%, $p < 0.001$), while the prevalence of diabetes was similar in the two groups (4.6% vs 3.9%, $p = 0.4$). Smokers in the PLWH group further had longer median cumulative exposure to tobacco than smokers among the controls (19.0 vs 15.0 pack years, $p < 0.001$). Finally, a larger proportion of PLWH had education of shorter duration or no education compared to the controls (46.0% vs 56.8%, $p < 0.001$).

For the HIV-specific characteristics, the most common mode of HIV transmission was via MSM (76.4%). A total of 16.9% had a previous AIDS defining diagnosis. The median CD4 count was 700 (IQR 521-900), while the median duration of HIV was 169 (IQR 87-263) months. Prior use of the potential nephrotoxic antiretrovirals tenofovir disoproxil fumarate (TDF), atazanavir (ATV) and lopinavir (LPV) was seen in 16.7%, 14.9% and 12.2% of the participants respectively, while 63.4%, 11.4% and 0.3% were currently on these drugs (Table 3). Among those currently on TDF and ATV the median exposure was 3.8 (IQR 1.7-6.3) and 8.1 (IQR 5.1-9.8) years respectively, while only two participants were currently on LPV.

Prevalence of renal Impairment

The prevalence of impaired renal function was 3.7% [95% confidence interval CI 2.3-5.5] and 1.7% [95%CI 1.2-2.2] in PLWH and controls ($p = .001$), respectively.

In addition, more controls (54.0%) had a normal eGFR (> 90 mL/min /1.73m²) than PLWH (48.7%, $p = 0.001$), and there were no one with severely impaired renal function (≤ 30 mL/min /1.73m² amongst the controls (0 vs 0.17%, $p = .001$) (Table 1).

Predictors of renal impairment, full cohort

In univariate models including both PLWH and controls, increasing age, female sex, higher BMI, more cumulated pack years, diabetes, hypertension, lower educational level and HIV-positive status were all associated with $eGFR \leq 60 \text{ mL/min/1.73m}^2$ (Table 2).

After adjustment, HIV-positive status remained significantly and independently associated with impaired renal function (odds ratio, OR, 3.4 [95%CI 1.8-6.3]). Besides HIV status, older age (5.4 [95%CI 3.4-7.5] per decade older), female sex (5.0 [95%CI 2.5-9.8]) and diabetes (2.9 [95%CI 1.3-6.7]) were all significantly associated with impaired renal function (Table 2). In contrast, we observed no significant association between renal impairment and hypertension in uni- and multivariable analysis.

We found evidence of an interaction between age and HIV status on impaired renal function with accentuated effects of age amongst PLWH. As such amongst PLWH, the increased odds of renal impairment per decade older was as high as 15.8 [95%CI 5.6-44.7] compared to only 4.6 [95%CI 3.2-6.7] for controls ($p = 0.016$ test for interaction).

While there was a marginal non-significant association between diabetes and HIV status ($p = 0.063$) on impaired renal function, we found no evidence of an interaction between HIV status and hypertension ($p = 0.78$).

Impact of HIV-specific variables, PLWH cohort

In a separate model including only PLWH the impact of HIV transmission mode, current and nadir CD4 level, time with a HIV diagnosis and a previous AIDS-defining diagnosis on renal impairment were investigated. However, none of these HIV-specific variables were found to be significantly associated with $eGFR \leq 60 \text{ mL/min/1.73m}^2$ in this virologically suppressed low risk population (Table 3). Due to low numbers we were not able to include use of the potential nephrotoxic antiretrovirals TDF, ATV and LPV in the models. In an explorative analysis, we did, however, not see a difference in the prevalence of impaired renal function when excluding those with prior or current use of TDF (5.0% [95%CI 2.3-10.4], $p=0.4$), ATV (3.6% [95%CI 2.2-5.8],

p=.9) or LPV (3.3% [95%CI 2.2-5.1], p=.6), but numbers were low (Table 3). Furthermore, excluding those with current use of Raltegravir, Dolutegravir, Cobicistat or Ritonavir, which may increase plasma creatinine levels without impairing renal function, did not impact the prevalence of impaired renal function significantly (3.8 [95%CI 2.2-6.5], p=.9).

DISCUSSION

To our knowledge this is the first study of its kind to compare the prevalence and associated risk factors for renal impairment in a group of virologically suppressed PLWH with few confounding renal risks and a matched general population.

We found that amongst PLWH of Caucasian ancestry, on cART, without HCV, IDU or ongoing HIV viral replication, having an eGFR ≤ 60 mL/min/1.73m² was a relatively infrequent event with a 4% prevalence. However, this prevalence was still twice as high as that seen in a matched general cohort with an adjusted odds ratio of renal impairment of more than 3 in PLWH vs. controls.

A prevalence of eGFR ≤ 60 mL/min/1.73m² of only 4% is relatively low compared to the estimates reported in other studies of PLWH (1,2,31–35), but reflective of the overall low risk population investigated in this analysis. In the START study it has equally been shown that renal impairment in PLWH with higher CD4 counts is relatively low (36). The AGEHIV Cohort Study also reported a low prevalence of renal impairment in a relatively well-controlled cohort where the proportions with IDU, HCV and African ancestry were low (37).

With this study it is, however, now evident that even in a virologically suppressed low risk population of PLWH, after adjustment of other common renal risk factors, HIV status itself remains independently associated with impaired renal function which suggests that other pathways than immunosuppression, ongoing viremia and coinfections are driving the pathogenesis of renal impairment. While the pathogenesis, to date, is still not understood, it is highly plausible that the HIV induced increased inflammation and coagulation activation may play a central role for inducing structural changes within the glomerulus and interstitial space of the nephron (38,39). In addition, the kidneys may hold a uremic memory where earlier episode

of acute renal impairment i.e. related to intercurrent disease in relation to acute HIV may also impact on renal health later in life. Examination of long-term renal trajectories on PLWH will therefore be an area to focus on for further studies. The role of potential nephrotoxic antiretrovirals in this pathogenesis should not be overlooked. In this study we were unable to show a statistically significant difference in prevalence of renal impairment amongst those with and without exposure to these drugs, but numbers were very small, and as discussed below inadequately powered to investigate such associations in more detail.

The magnitude of the association between renal impairment and HIV itself is also intriguing. As such, in this virologically suppressed low risk cohort, the independent impact of HIV was of a similar magnitude to that of diabetes, a strong risk factor for renal impairment.

We further observed a multiplicative effect of HIV and older age on renal impairment suggesting an almost 16-times higher risk of renal impairment in older PLWH compared to young controls. These observations call for a proactive approach in screening for renal impairment in PLWH, particularly in the growing population of elderly HIV-positive individuals.

The other main risk factors for impaired renal function were diabetes and female gender which is in line with many other renal studies amongst PLWH (11,27,30,40,41). An interaction between diabetes and HIV has previously been reported, we did, however only found a marginal non-significant evidence of such interaction, but the proportion with diabetes was relatively low (30,42).

In this study hypertension was not significantly associated with renal impairment. The hypertension prevalence was however relatively low in this selected population, and it is very likely that by excluding individuals of non-Caucasian ancestry we are also removing most of a hypertension signal, as this is well-described to be stronger in non-Caucasian individuals (43). We also did not observe any association between renal impairment with the length of education beyond high school level after adjusting for other confounders.

None of the investigated HIV-specific risk factors were shown to be significantly associated with $eGFR \leq 60 \text{ mL/min/1.73m}^2$ in the adjusted analysis. In particular, the association between different markers of immunosuppression and chronic kidney disease have been well described in other studies (35,40). The lack of a significant association in this analysis is likely explained by the selection of only virally suppressed individuals on cART in the analysis, and by the very high median CD4 count. In fact, only 2.5% or 15 PLWH had a current CD4 count $< 200 \text{ cells}/\mu\text{L}$. In a descriptive analysis, exclusion of individuals with any exposure to TDF, ATV or LPV did not significantly alter the prevalence of renal impairment as expected based on previous large observational studies (11,35). However, the very low absolute numbers of events rendered it difficult to show any such difference (i.e. only 6 of the 22 cases were not currently on TDF and none of the cases were currently on LPV).

The cross-sectional design of this study prohibits analyses of temporal changes in renal function and on causality. We further based our findings on a single measurement of $eGFR \leq 60 \text{ mL/min/1.73m}^2$ rather than a measured glomerular filtration rate. Consequently, we may have overestimated the prevalence of impaired renal function. On the other hand, we did not have data on proteinuria which would likely have slightly increased the prevalence of renal impairment. These limitations are however equally present for the PLWH and the controls. Another limitation to this study is the relatively limited size. Only 22 PLWH had an $eGFR \leq 60 \text{ mL/min/1.73m}^2$, which significantly limits our power to investigate the impact of possible predictors in more detail due to the lack of sufficient heterogeneity. This was especially problematic when investigating associations between renal impairment and HIV-related variables. Additional investigation of associations between usage of potentially nephrotoxic drugs, was initially envisioned for this study, however the small absolute number of PLWH with $eGFR \leq 60 \text{ mL/min/1.73m}^2$ rendered this impossible to assess reliably. It is, however, of great importance to understand if there are differences in how the kidneys are adversely impacted by these drugs depending on other ongoing risk factors (11).

In contrast, one of the major strengths of this study is the uniform approach to data collection. All eGFR measurements for all study participants regardless of HIV status were done at the same time of day and at the same laboratory. This uniform approach provides a unique opportunity for direct comparison of risks between HIV-positive and negative individuals.

Conclusion

The prevalence of impaired renal function was relatively low among virologically suppressed PLWH with few other ongoing renal risk factors. However, the prevalence, even in this low-risk group, remained significantly higher than in matched controls. HIV status further remained an independent risk factor for renal impairment over and beyond other factors, was of the same magnitude as diabetes, and was accentuated among older individuals.

Impaired renal function, albeit relatively rare in virologically suppressed PLWH, therefore remains a concern requiring ongoing attention and monitoring.

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