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Lipodystrophy Increases the Risk of CKD Development in HIV-Positive Patients in Switzerland: The LIPOKID Study

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Introduction: Antiretroviral therapy has improved the life expectancy of patients living with HIV. However, lipodystrophy syndrome (LD) remains prevalent, affecting mostly patients treated with first-generation antiretroviral drugs. This syndrome is characterized by changes in body fat distribution with or without associated metabolic changes. Here, we studied whether clinically evaluated LD is independently associated with chronic kidney disease (CKD) development (sustained estimated glomerular filtration rate [eGFR] $<$ 60 ml/min per 1.73 m^2) in HIV-positive patients.

Methods: We conducted a prospective cohort study (the LIPOKID Study) among all the patients from the Swiss HIV Cohort Study (SHCS) with an eGFR $>$60 ml/min per 1.73 m^2 upon their entry into the cohort with more than 3 months of follow-up from January 2002 to August 2016. Cox regression models were used to estimate the association between LD and CKD development.

Results: Among the 5384 patients included, 1341 (24.9%) developed LD during the follow-up. The mean follow-up time was 72.3 months (SD ±48.4). In total, 252 patients (4.7%) reached the primary endpoint after a median time of 51.3 months (±SD 39.9 months) from inclusion. A diagnosis of LD significantly increased the risk of an eGFR on univariate analysis (hazard ratio [HR] = 2.72; 95% confidence interval [95% CI] = 2.07−3.58; $P < 0.001$) and remained significantly higher after adjustment for known HIV and non-HIV risk factors for CKD (HR = 2.37; 95% CI = 1.67−3.36; $P < 0.001$). The effect of LD on CKD was not mediated through the use of nephrotoxic antiretroviral drugs.

Conclusion: Lipodystrophy syndrome is independently associated with CKD after adjustment for previously reported risk factors.

Kidney Int Rep (2018) ■, ■–■; https://doi.org/10.1016/j.ekir.2018.04.014
KEYWORDS: albuminuria; chronic kidney disease; HIV; lipids
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Chronic kidney disease (CKD) is defined as an alteration in kidney structure and/or function lasting more than 3 months.[1,2] The prevalence of CKD is increasing in the general population and is a major concern for HIV-positive patients,[3] whose life expectancy is reaching that of uninfected patients following the use of combined antiretroviral therapies (ARTs).[4–6] Thus, aging HIV-positive patients are now at risk for metabolic diseases and have a significantly increased risk of developing end-stage renal disease.[7–9] Well-established and HIV-specific risk factors for CKD have been identified in several epidemiological studies. These risk factors include age, diabetes, hypertension, hepatitis B and C co-infections, lower CD4 nadirs, and specific ARTs.[10–14]

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Received 9 January 2018; revised 26 April 2018; accepted 30 April 2018; published online 8 April 2018

First-generation ARTs are associated with multiple side effects. Lipodystrophy syndrome (LD) was reported in 1998 by Carr *et al*. and is characterized by body shape abnormalities caused by changes in body fat distribution.[15] This syndrome comprises the following 3 phenotypes: lipohypertrophy (LH; fat accumulation mainly in abdominal visceral adipose tissue); lipoatrophy (LA; fat loss in the face, limbs and buttocks); or a mixed pattern of both conditions. The diagnosis of LD is typically made by clinical observation; however, anthropometric evaluations or objective quantification of fat deposition may also be performed.[16] These methods are not used routinely in clinical practice given that they are not widely available, are not well normalized, and do not appear to provide a large benefit compared with that of clinical observation or patient reporting.[15,16] Given the variations in the methods used to diagnose LD, the overall prevalence of the disease among HIV-positive patients ranges from 28% to 60%, depending on the approach used for its diagnosis.[15,17–21] The Swiss HIV Cohort Study (SHCS) reported that although the incidence of LD has decreased with the use of newer molecules in patients who initiated combined ART after 2000,[20] LD remains a prevalent syndrome that has affected 33.9% of the patients in the cohort. The mechanisms underlying LD development in HIV-positive patients are only partially understood. Exposure to specific antiretroviral drugs is likely important in the pathogenesis of LD. However, host and/or viral factors also play an important role in disease development.[22] Clinically, LD is associated with an elevated risk of insulin resistance and dyslipidemia.[23,24] Modifications of adipokine secretion by abnormally deposed fat are associated with these metabolic disturbances in HIV-positive patients.[25]

Evidence suggests that long-term overweight is associated with an increased cumulative risk of CKD in the non-HIV population.[26] Specifically, an elevated waist-to-hip ratio (WHR) in adulthood is associated with a lower measured GFR and lower effective renal plasma flow after multiple adjustments.[26] In addition, in a study of 125 obese patients with type 2 diabetes mellitus, WHR was independently associated with CKD.[27] These observations suggest that central fat distribution, which is often observed in LD, is associated with GFR independently of body mass index (BMI).

Therefore, we hypothesize that LD is independently associated with the development of CKD as defined by an eGFR <60 ml/min per 1.73 m^2. In the LIPOKID Study, we assessed this hypothesis using data prospectively collected in a large nationwide prospective community cohort. We also analyzed the association between LD and albuminuria in a subset of the population.

METHODS

Study Design and Setting

The Swiss HIV Cohort Study (www.shcs.ch) is a nationwide prospective longitudinal cohort collecting clinical and biological data twice a year and involves approximately 75% of all the HIV-positive adults living in Switzerland.[28–30] Data are collected by 5 Swiss university hospitals, 2 tertiary care hospitals, 15 secondary care hospitals, and 36 private physicians. The SHCS is registered on the Swiss National Science longitudinal platform (additional information is available at http://www.shcs.ch).

The SHCS was approved by the ethics committee of each center, and the LIPOKID study was accepted by the scientific board of the SHCS in December 2015. The study findings are reported according to the statement on STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE).[31]

Participants and Eligibility Criteria

All HIV-positive adults who underwent creatinine measurement upon entry into the cohort (baseline) from January 2002 (when routine measurement of serum creatinine began in the SHCS) to August 2016 were included in the primary analysis. Beginning in January 2008, a urine dipstick measurement was performed biannually to semiquantitatively determine whether albuminuria was present. Patients enrolled in this subgroup study from January 2008 to August 2016 were included in the secondary analysis. The following patients were excluded from the study: patients with an eGFR <60 ml/min per 1.73 m^2 at baseline (first visit in the SHCS), patients with no follow-up creatinine measurements, and patients who underwent <3 months of follow-up between the first and last eGFR values. First-semester values for each clinical and biological variable were extracted from the SHCS database for every patient.

Outcomes

The primary outcome was CKD, which was defined as an eGFR <60 ml/min per 1.73 m^2 and confirmed on a second measurement within 6 months. We used a 6-month rather than a 3-month interval to confirm the diagnosis, as patients are seen every 6 months in the SHCS. Therefore, CKD was defined according to the second eGFR measurement. The eGFR was estimated at baseline and at each follow-up visit using the equation for GFR from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[32] We defined eGFR categories based on a CKD stage classification (G1, ≥90; G2, 60–89; G3, 30–59; G4, 15–29; and G5, <15 ml/min per 1.73 m^2).[2] Beginning in 2008, dipstick testing was used during the follow-up evaluations of the patients

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