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Kidney function in sugarcane cutters in Nicaragua – A longitudinal study of workers at risk of Mesoamerican nephropathy

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ABSTRACT

Background: Chronic kidney disease is common among sugarcane workers in Central America. The main risk factor seems to be repeated high-intensity work in hot environments. Several cross-sectional studies have been performed but few longitudinal studies.
Objectives: The aim of the study was to examine whether kidney function changes over a few months of work during the harvest period.
Methods: A group of male sugarcane cutters in Nicaragua (N=29, aged 17–38 years) was examined with renal biomarkers before and after shift on the first day at the start of harvest, on the sixth day during acclimatization, and then in mid-harvest 9 weeks later. A reference group (N=25, mainly office workers) was examined with the same biomarkers at start of harvest, and then at end of harvest 5 months later.
Results: The pre-shift renal function decreased significantly during 9 weeks of work in the cane cutters. Mean serum creatinine increased (20%), mean estimated glomerular filtration rate decreased (9%, 10 mL/min), serum urea N (BUN) increased (41%), and mean urinary neutrophil gelatinase-associated lipocalin (NGAL) increased (four times). The cane cutters also developed cross-shift increases in these biomarkers, in particular serum creatinine and BUN, and in urinary uric acid. The longitudinal decrease in eGFR tended to be associated with the cross-shift increase in serum creatinine.
Conclusions: There was a remarkable decrease of glomerular kidney function, after only 9 weeks of harvest. The cross-shift increase in serum creatinine may be caused by dehydration (pre-renal dysfunction), and when repeated on a daily basis this may cause permanently reduced GFR.

1. Introduction

The recognition of Mesoamerican Nephropathy (MeN)-also labelled Chronic Kidney Disease of non-traditional origin (CKDnt) – as an epidemic in Central America, has led to the publication of a number of reports examining risk factors and causal hypotheses (Wesseling et al., 2014; Correa-Rotter et al., 2014). Experimental studies have also been performed (Roncal Jimenez et al., 2014).

To date the findings have shown that the epidemic primarily affects males working in heavy manual labor in hot environments, mainly living in the coastal lowlands. There is generally no history of diabetes or hypertension and no substantial proteinuria. Kidney

Abbreviations: BMI, Body mass index; CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate; KIM-1, Kidney injury molecule 1; MeN, Mesoamerican nephropathy; NGAL, neutrophil gelatinase-associated lipocalin; Hsp72, Heat shock protein 72 kD; NSAIDS, Non-steroid anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system

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biopsies have shown a tubulointerstitial pattern with tubular atrophy and interstitial fibrosis, but also global glomerulosclerosis, often with an ischemic component (Wijkstrom et al., 2013; López-Marín et al., 2014).

The main hypothesis to account for the disease is heat stress with repetitive episodes of dehydration (Peraza et al., 2012; Brooks et al., 2012; Wesseling et al., 2014; Correa-Rotter et al., 2014; García-Trabanino et al., 2015). Suggested pathophysiologic mechanisms driven by strenuous work and heat stress include subclinical rhabdomyolysis (Paula Santos et al., 2015), effects of hyperuricemia and hyperuricosuria (Knochel et al., 1974; Johnson, 2015; Roncal-Jimenez et al., 2015, 2016), hyperosmolality-induced activation of the aldose reductase-fructokinase pathway in the kidney, and vasopressin effects (Roncal Jimenez et al., 2014; Roncal-Jimenez et al., 2015, 2016). It has also been proposed that the disease is multifactorial, and could include additional factors such as self-medication with nonsteroidal anti-inflammatory drugs, exposure to heavy metals or pesticides/agrochemicals, infections, or genetic factors (Correa-Rotter et al., 2014; Herrera et al., 2014; Laws et al., 2015a, 2015b; Ramírez-Rubio et al., 2015; Wesseling et al., 2014).

Most of the epidemiological studies are cross-sectional population based surveys. Two studies have examined cross-shift changes in biomarkers of hydration and kidney function, over a workday, in Brazil, (Paula Santos et al., 2015), and El Salvador (García-Trabanino et al., 2015), and two studies have performed a follow-up of kidney function among sugarcane cutters over the course of a harvest season, in Brazil (Paula Santos et al., 2015) and in Nicaragua (Laws et al., 2015a, 2015b). While the two studies on cross-shift changes both show a decrease in renal function over a cane cutting shift, the two longitudinal studies were not in agreement, and the question of whether the pre-shift glomerular function changes over a harvest period of several months still remains unclear. The aim of the present study was to assess longitudinal changes of kidney function over a harvest period in sugarcane cutters as well as in a reference group. We examined pre- and post-shift kidney function in sugarcane cutters at the start of harvest, on day 1 and day 6 to assess acclimatization effects, and at mid-harvest two months later. A reference group of non-cane cutters was examined at start and end of the harvest.

2. Methods

2.1. Setting and study design

The study was conducted in 2012–2013 in a convenience sample of 29 sugarcane cutters from León and Chinandega municipalities in the northern Nicaraguan Pacific region, and a reference group (N=25, mainly office workers) from the same area. The sugarcane cutters were examined “pre-shift” in the morning between 3 and 5 am and “post-shift” between 4 and 7 pm at their homes on the first day of the harvest in November 2012. The pre-shift examination on the first day (called Cut1) was considered to be the baseline. The examinations (pre- and post-shift) were repeated after 5 days of work (Cut2), and then 9 weeks later in January 2013 (in the mid-harvest period; Cut3). The first (“pre-shift” 7–9 am and “post-shift” 4–6 pm) examination of the reference group was at their work places in November 2012 (Ref1), while the repeated examination was performed at the end of the harvest season in May 2013 (Ref2), again at their workplaces. Originally, a fourth examination of the cane cutters was planned for the end of the harvest in May 2013, together with the reference group, but due to removal of participating workers from their jobs in February 2013, this could not be realized, apart from a small number (n=7) of post-shift urine samples.

2.2. Participants

Community leaders of six villages in the municipalities of León and Chinandega provided lists of men who planned to work as sugarcane cutters. Information meetings were held with these workers in their communities. An invitation to provide blood and urine for a screening test was made to those who were confirmed to be enrolled as sugarcane cutters at plantations of the mill in the study area. The aim was to recruit young healthy men. In total 92 sugarcane cutters <40 years of age participated in the screening test (blood tests for glucose, creatinine, uric acid, lipids, cell count, as well as a urine test with dip-stick and examination of sediment). These analyses were performed in the laboratory of the Medical School of UNAN-Léon. In 45 of them serum creatinine was ≥ 1.1 mg/dL, the strict pre-set exclusion criterion. Another 15 had abnormal results in at least one of the other tests, or a history of diabetes or hypertension. Thus only 32 workers met the inclusion criteria (<40 years of age, serum creatinine ≤ 1.0 mg/dL and all other lab tests within the reference values; in addition no known diabetes, hypertension or kidney disease). Three men decided not to participate, leaving 29 subjects for the study.

A reference group without known diabetes, hypertension or kidney disease was recruited at the town halls near the sugarcane plantations. The group included mostly office workers, but also five persons with a predominantly outdoor job, albeit without major physical effort.

All participants signed a written informed consent to participate in the study, in accordance with the Declaration of Helsinki. The study was approved by the Ethical Review Board of UNAN-León, Nicaragua, and the Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico.

The work conditions were similar to those described previously for sugarcane cutting in this region (Crowe et al., 2015; García-Trabanino et al., 2015).

2.3. Medical examinations

Blood pressure was measured by a technician with a calibrated digital sphygmomanometer (Omron BP710N, Omron Healthcare Inc., Bannockburn, USA) with the participant seated after resting for at least 10 min. Body weight was measured with a calibrated Seca 803 digital flat mobile scale (Seca, Birmingham, UK) with minimal clothing and height with a foldable stadiometer (Seca, Birmingham, UK). Certified technicians collected blood samples in three vacuum tubes (Becton Dickinson & Co., USA), one tube with anticoagulant for blood cell count and two tubes with clot activator and gel for serum separation. All samples were placed on ice and transported immediately to the laboratory at the Research Center on Health, Work and Environment (CISTA) at UNAN-León, where they were centrifuged at 3500 RPM for 10 min at room temperature and the serum was separated into four labeled cryovials and stored at -80 °C.

Each participant delivered a spot urine sample (50 cc) in a sterile polypropylene container (Becton Dickinson & Co., USA), which was aliquoted into vacuum tubes, one with and two without preservative immediately at the participant's home, placed in an icebox (4 °C) and then transported to the laboratory at the Research Center on Health, Work and Environment (CISTA) at UNAN-León, where aliquots were frozen at -80 °C. Serum and urine aliquots were later sent to the Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubiran, Mexico (about seven months after collection), and urine aliquots to the University of Colorado Denver (within a month).

Baseline data were recorded by trained interviewers using a questionnaire recording data on age, education, smoking, alcohol, and some other background factors, as well as health (medically