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# ASSOCIATION STUDY OF cAMP/EPACs SIGNALING PATHWAY MARKERS IN CHRONIC LUMBAR PAIN IN DOLISIE (CONGO)

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**ABSTRACT:** *Chronic low back pain represents a major public health issue, particularly in sub-Saharan Africa where it remains understudied. This cross-sectional case-control study, conducted in Dolisie (Congo), evaluated the involvement of cAMP/EPACs pathway markers (cyclic adenosine monophosphate and EPAC1/EPAC2 proteins) in low back pain. Seventy-five patients with chronic low back pain (pain duration ≥6 months, VAS score ≥30 mm) and 25 healthy controls were included. Intracellular concentrations of cAMP, EPAC1, and EPAC2 were measured in blood mononuclear cells (PBMCs) by ELISA, and pain intensity was measured using a visual analog scale (VAS). Analysis of our data showed a significant increase in cAMP (12.6 ± 2.1 for DL group against 3.2 ± 0.4 pmol/ml for TS group), EPAC1 (7.9 ± 1.2 for DL group against 2.1 ± 0.3 ng/ml for TS group) and EPAC2 (4.8 ± 0.7 for DL group against 1.5 ± 0.2 ng/ml for TS group) levels with a p-value < 0.0001 for the three markers compared. EPAC1 was more expressed than EPAC2, suggesting a predominant role in pain modulation. However, no significant correlation was observed between these biomarkers and VAS scores (p > 0.05), indicating that their activation reflects a pathophysiological mechanism without a direct link to subjective pain intensity. This study reveals dysregulation of the cAMP/EPACs pathway in chronic low back pain, opening up avenues for translational research targeting EPAC1 in a Congolese context. Limitations include the lack of clinical-biological correlation and the need for longitudinal studies to establish a causal link.*

**KEYWORDS:** Low back pain, cyclic AMP, EPACs, Dolisie (Congo).



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## INTRODUCTION

Chronic low back pain is a major public health problem worldwide. It causes significant morbidity and represents a considerable socioeconomic burden due to its impact on quality of life, productivity and healthcare expenditure [Lemmers et al., 2024; Maher et al., 2017; Hoy et al., 2010]. It is estimated that nearly 80% of the world's population will experience an episode of low back pain during their lifetime, making it one of the most common musculoskeletal conditions. Its global point prevalence is estimated at 12–33% [Balagué et al., 2012; Walker et al., 2000]. In sub-Saharan Africa and particularly in Congo, chronic low back pain often remains underdiagnosed, poorly characterized and insufficiently treated. Studies are still rare, despite a significant prevalence reported in several hospital and community surveys [Kunow et al., 2024; Freynhagen et al., 2009]. The socioeconomic context, frequent recourse to self-medication, the arduous nature of manual labor, and limited access to specialized care contribute to the chronicity of lower back pain in Congo. In Dolisie, consultations for lower back pain are frequent, particularly in the outpatient, internal medicine, and physiotherapy departments of the Dolisie General Hospital or Base Hospital, as well as in primary care facilities. However, epidemiological, clinical, and biological data on this pathology remain less documented. Furthermore, the lack of investigation of pathophysiological mechanisms prevents the implementation of targeted and effective therapeutic strategies.

Furthermore, the most common causes of chronic lower back pain include disc degeneration, lumbar disc herniation, lumbar instability syndrome, lumbar spinal stenosis, and lumbar soft tissue injuries [Massengill et al., 2021; Gao et al., 2013]. From a pathophysiological perspective, the study of biological markers associated with this pathology has attracted growing interest, particularly those involved in the mechanisms of pain, inflammation, and spinal degeneration. These biomarkers offer promising prospects as pharmacological targets for the development of more effective therapies [Li et al., 2006; De Rooij et al., 1998].

Among these biomarkers, cyclic adenosine 3', 5’-monophosphate (cAMP) occupies a central place. As the second major intracellular messenger, cAMP is involved in numerous physiological responses to neurotransmitters, hormones, and pharmacological agents [Kawasaki et al., 1998]. Two cAMP-activated signaling pathways have been identified: the protein kinase A (PKA) pathway and the cAMP-activated exchange protein (EPAC) pathway, the latter representing a novel class of intracellular mediators [Hoy et al., 2021; Srivastava et al., 2011].

EPACs (Exchange Proteins Directly Activated by cAMP), including EPAC1 and EPAC2, are expressed in most mammalian cells. EPAC2, also known as guanine nucleotide exchange factor RAPGEF4, is highly expressed in neural structures. Its activation, or even overactivation, has been associated with neuronal apoptosis, suggesting its involvement in various neurological disorders [Wang et al., 2017; Hoy et al., 2010]. In this context, it appears essential to conduct specific research in Dolisie (Congo) in order to document, for the first time, the expression of EPAC isoforms in lower back pain. Such a study would not only allow us to better understand the molecular mechanisms underlying this pathology in an African environment, but also lay the foundations for personalized medicine and therapeutic strategies adapted to local realities. It could also contribute to enriching African databases on chronic lower back pain, which are currently very limited, and pave the way for translational research better anchored in the Congolese context.


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## MATERIAL AND METHODS

### Study Design and Participants

This was a cross-sectional, case-control observational study conducted at Dolisie General Hospital (Republic of Congo) between May 2024 and January 2025. Participants were recruited from the physiotherapy and internal medicine departments. The study included two groups: a group of patients with chronic low back pain (LP) and a group of healthy controls (HC). Selection criteria were rigorously defined to ensure homogeneity between the groups and the validity of comparisons. Group 1, with chronic low back pain (LP), included adults aged 18 to 65 years, with persistent low back pain for more than six months. The pain had to be aggravated by physical activity or prolonged posture, without major radiological abnormalities. When available, imaging tests had to be normal or reveal only moderate disc alterations, without signs of significant nerve compression. Inclusion required a pain score ≥ 30 mm on the visual analog scale (VAS), assessed at the time of inclusion.

Non-inclusion criteria included: inability to understand or complete the questionnaires (language barrier, unassisted illiteracy), pregnancy or breastfeeding, and participation in an experimental protocol involving drug treatment.

Exclusion criteria were: known inflammatory pathology (ankylosing spondylitis, rheumatoid arthritis), history of lumbar surgery, radiculopathy or severe disc herniation confirmed by imaging, major psychiatric disorder (schizophrenia, bipolar disorder), substance abuse (alcohol, drugs), or severe comorbid conditions (cancer, progressive neurological disease) likely to influence the perception or expression of pain. Group 2, or the Healthy Control (HC) group, consisted of volunteers aged 18 to 65 years, with no history of chronic pain, no known medical or psychiatric illness, and no treatment likely to influence pain perception or nervous system function. Subjects had to be in good general health, with no significant musculoskeletal history, and provide informed consent to participate in the study.

Non-inclusion criteria included refusal to participate, inability to complete the questionnaires, pregnancy or breastfeeding, and the use of medications likely to alter pain perception (analgesics, psychotropic drugs, neuroactive drugs). Exclusion criteria included the onset of chronic pain during follow-up, the subsequent discovery of an initially undiagnosed neurological, musculoskeletal, or psychiatric condition, or recent use of medications that could interfere with sensory evaluation. All participants received clear and comprehensive information about the study objectives, procedures, and implications. Written informed consent was obtained prior to inclusion, in accordance with the ethical principles of the Declaration of Helsinki.

### Pain Intensity Assessment

Pain intensity was measured using the Visual Analog Scale (VAS), a standard tool in clinical research for the subjective assessment of pain. The VAS consists of a 100-mm horizontal line, the ends of which are anchored by two verbal statements: "no pain" (score of 0 mm) on the left, and "unbearable pain" (score of 100 mm) on the right. Participants were asked to mark the point on the line corresponding to their pain intensity at the time of the assessment, as well as the maximum pain perceived over the past seven days. For patients in the Low Back Pain (LP) group, the VAS was administered in a quiet environment, in a seated position, after a 5-minute rest period, and again after standardized mobilization (trunk flexion-extension). This dual


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assessment aimed to capture the variability of pain related to movement. VAS scores were measured in millimeters from the left extremity and interpreted according to the following classification: mild (0–30 mm), moderate (31–70 mm), and severe (71–100 mm). All measurements were performed by the same trained assessor to ensure consistency across administration conditions. In accordance with the inclusion criteria for the healthy control (HC) group, no pain measurements were performed in these participants, as they had neither pain complaints nor a history of chronic pain.

**Data Collection**

All participants signed informed consent prior to inclusion in the study. Sociodemographic and clinical data were collected using a structured form including the following variables: age, sex, and socioeconomic status. Following this step, each participant underwent venous blood sampling and a quantitative sensory assessment.

**Blood Collection and Mononuclear Cell Isolation**

Fasting venous blood samples (0.5 mL) were collected from each participant by antecubital puncture into sterile tubes containing EDTA (Lab-Care Diagnostics, India). The samples were immediately placed at 4°C and processed within two hours. Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation using Ficoll-Paque™ PLUS (GE Healthcare, Sweden), according to the manufacturer's instructions. After isolation, the cells were washed twice in ice-cold PBS buffer and then manually counted using a cytometer. The cell suspensions were adjusted to a standard density for assays.

**Intracellular cAMP Assay**

Intracellular cyclic adenosine monophosphate (cAMP) was assayed from PBMC lysates prepared using the lysis buffer provided in the cAMP Complete ELISA kit (Enzo Life Sciences, USA). The lysates were clarified by centrifugation, and the supernatants were then used for the assay using a competitive enzyme immunoassay protocol. Absorbance was measured at 405 nm using a microplate reader (BioTek ELx800, USA). cAMP concentrations were calculated from a calibration curve established with the kit standards and expressed in pmol/ml.

**EPAC1 and EPAC2 Protein Assays**

Intracellular concentrations of EPAC1 and EPAC2 proteins were quantified in the same cell extracts by sandwich enzyme-linked immunosorbent assay (ELISA), using the EPAC1 Human ELISA Kit (MyBioSource, USA) and EPAC2 Human ELISA Kit (MyBioSource, USA), respectively. Procedures were performed according to the manufacturers' protocols. Optical reading was performed at 450 nm, and concentrations were expressed in ng/ml.

**Statistical Analysis**

Results were generated using Excel software and expressed as mean ± standard deviation. Data were analyzed using GraphPad Prism software, version 05. Between-group comparisons were performed using the Student t-test for quantitative variables and the chi-square test for quantitative variables, followed by the Mt Whitney post hoc test. Correlation analysis was applied to compare pain involvement and cAMP, EPACs biomarkers. A $p\text{-value} < 0.05$ was considered statistically significant.


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## RESULTS

### Sociodemographic Characteristics

Table 1 shows the general characteristics of the participants by group. The overall mean age was 43.8 ± 12.3 years, with no statistically significant difference between the chronic low back pain (LP) group and the healthy control (HC) group (*P = 0.68*). The gender distribution was comparable between the groups (*P = 0.52*), with an overall female predominance (56%), likely reflecting the sociological composition of the recruited population. The proportion of smokers was slightly higher in the LP group (28.0%) than in the HC group (16.0%), but this was not statistically significant (*P = 0.21*). Educational level did not differ significantly between the groups (*P = 0.43*), although the majority of participants had a secondary education. These data suggest relative homogeneity between the groups in terms of sociodemographic and behavioral characteristics, thus reducing the risk of confounding bias.

**Table 1: General Characteristics of Participants**

by Group

| VARIABLES | LP (n = 75) | HC (n = 25) | *P-VALUE* |
|---|---|---|---|
| **Age (year)** | | | 0.68 |
| - Men | 49.5 ± 11.8 | 48.1 ± 10.2 | |
| - Women | 47.3 ± 9.8 | 46.9 ± 8.7 | |
| **Sex** | | | 0.52 |
| - Men | 36 (48.0 %) | 10 (40.0 %) | |
| - Women | 39 (52.0 %) | 15 (60.0 %) | |
| **Smokers** | | | 0.21 |
| - Yes | 21 (28.0 %) | 4 (16.0 %) | |
| - NO | 54 (72.0 %) | 21 (84.0 %) | |
| **Educational level** | | | 0.43 |
| - Uneducated | 9 (12.0 %) | 1 (4.0 %) | |
| - Primary | 21 (28.0 %) | 6 (24.0 %) | |
| - Secondary | 33 (44.0 %) | 12 (48.0 %) | |
| - Higher Education | 12 (16.0 %) | 6 (24.0 %) | |

*Values are expressed as mean ± standard deviation (continuous variables) and as absolute numbers (percentages) for qualitative variables. Comparison by Student test or chi² as appropriate.*

### Pain Intensity

Mean pain intensity, measured by the Visual Analogue Scale (VAS), was significantly higher in patients in the low back pain (LP) group than in healthy controls (HC) (*P < 0.0001*). LP patients had a mean VAS score of 72.4 ± 11.6 mm, reflecting moderate to severe pain, while


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controls had negligible scores (3.1 ± 0.4 mm), as expected in a population without a history of pain.

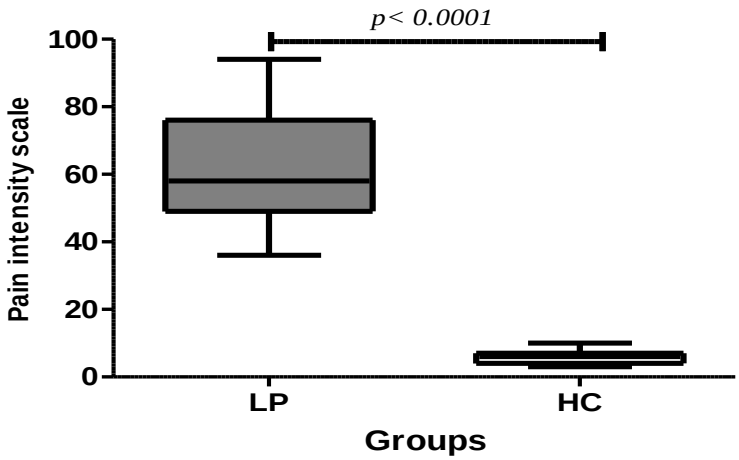


**Fig. 1:** *Comparison of VAS scores (pain intensity) between the two study groups.*

*Patients with chronic low back pain had significantly higher VAS scores than healthy controls (P < 0.0001, Student's t-test).*

**Plasma cAMP and EPAC Levels**

Intracellular cAMP concentrations were significantly higher in PBMCs from patients in the DL group (12.6 ± 2.1 pmol/ml) compared to controls (3.2 ± 0.4 pmol/ml; *P < 0.0001*). Similarly, EPAC1 (7.9 ± 1.2 ng/ml) and EPAC2 (4.8 ± 0.7 ng/ml) levels were significantly increased in patients compared to controls (EPAC1: 2.1 ± 0.3; EPAC2: 1.5 ± 0.2 ng/ml; *P < 0.001* for both comparisons). The elevation of EPAC1 was more pronounced than that of EPAC2, suggesting a more important role of this isoform in the modulation of chronic pain.

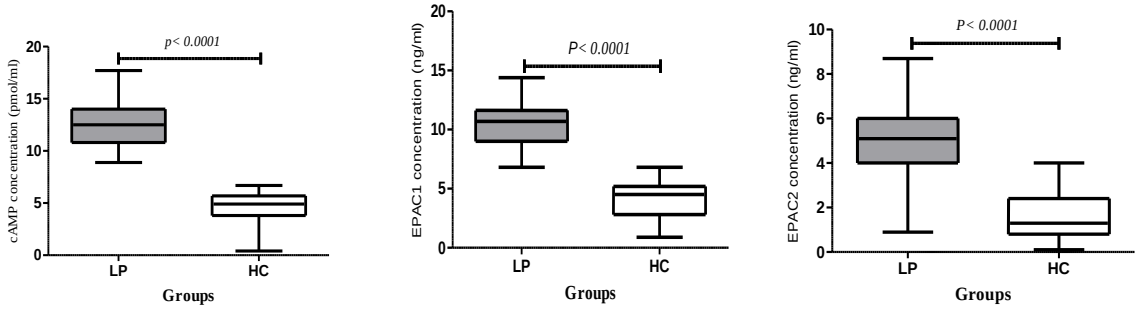


**Fig. 2:** Intracellular concentrations of cAMP, EPAC1, and EPAC2 in PBMCs from both groups.

*Patients in the chronic low back pain group had significantly higher concentrations of these three biomarkers compared to healthy controls. Comparisons were made using Student's t-test (P < 0.0001).*


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### Correlation between VAS and cAMP, VAS–EPAC1, and VAS–EPAC2

To better understand the relationship between chronic low back pain perception and intracellular signaling, we analyzed the correlation between VAS (Visual Analog Scale) scores and plasma cAMP concentrations, as well as EPAC1 and EPAC2 protein expression in peripheral blood mononuclear cells. The data were analyzed and correlation coefficients were calculated using the Spearman test across all participants. No statistically significant association was revealed between VAS scores and the biomarkers studied. The correlation between VAS and cAMP was weak and non-significant (*R = 0.14; P = 0.21*), that between VAS and EPAC1 was very weak (*R = 0.06; P = 0.60*) and, finally, the correlation between VAS and EPAC2 was weak and non-significant (*R = 0.06; P = 0.6)*. These data indicate that, in this cohort, intracellular concentrations of cAMP, EPAC1 and EPAC2 are not directly correlated with the subjective intensity of chronic low back pain measured by the VAS scale.

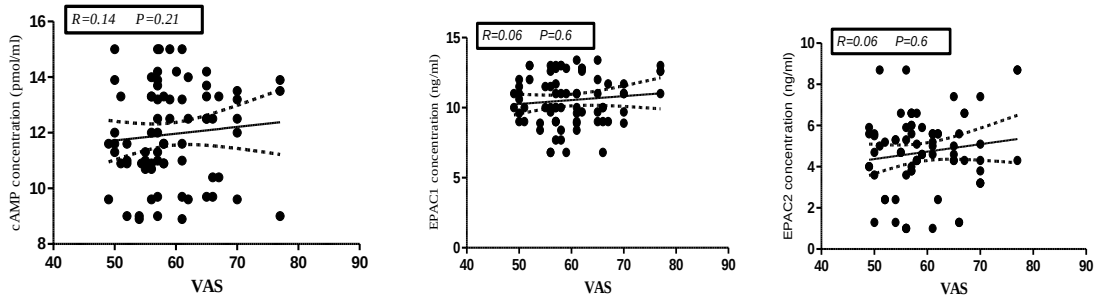


**Fig. 3:** Correlations between VAS scores and intracellular concentrations of cAMP, EPAC1, and EPAC2.

*Spearman correlation coefficients were low and nonsignificant in all cases, suggesting a lack of a linear relationship between these biomarkers and pain intensity in the sample studied.*

## DISCUSSION

This study evaluated, for the first time in Congo, the involvement of the cAMP/EPAC signaling pathway in chronic low back pain by measuring intracellular concentrations of cAMP, EPAC1, and EPAC2 in blood mononuclear cells (PBMCs) and their association with pain intensity measured by the VAS scale. The results obtained open the discussion on several sociodemographic, biological, and pathophysiological aspects. The mean age of participants (43.8 ± 12.3 years) was consistent between the two groups, consistent with previous studies, showing a predominance of lower back pain in working-age adults [George et al., 2023]. This result reinforces the relevance of our sample, given that working age groups are the most exposed to the biomechanical factors of lower back pain.

Regarding gender, the observed female predominance (56%) is consistent with certain African and international studies that describe an increased sensitivity of women to chronic lower back pain, possibly linked to hormonal, psychological, or sociocultural factors, as well as rural activities [Mogil, 2012; Schofield, 2012]. However, the gender difference was not statistically significant between the groups, which rules out recruitment bias. Smoking status, slightly higher in patients (28% in the DL group versus 16% in the TS group), did not reach


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significance, but deserves discussion. Smoking is recognized as an aggravating or triggering factor of chronic low back pain due to its role in disc degeneration and microvascularization [Samantha et al., 2023; Freynhagen et al., 2009]. Our study, although without a direct association, suggests a trend that should be explored in larger studies. Finally, the level of education did not show a significant difference. However, the majority of subjects had a secondary education, which reflects a relatively educated population. The link between education level, health literacy, and pain management is well established: a low level of education is often correlated with poor management and chronic pain [Singhmar et al., 2020; Gao et al., 2013].

Patients in the DL group had a mean VAS score of 72.4 mm, indicating moderate to severe pain intensity. This result is consistent with the literature on chronic low back pain, which frequently shows VAS scores above 60 mm [Sayed et al., 2022; Eijkelkamp et al., 2013]. The absence of pain in the controls (VAS score: 3.1 mm) confirms the quality of the control group and the absence of assessment bias. These data validate the VAS tool in our African context, despite possible linguistic or cultural barriers.

The marked elevation of cAMP, EPAC1, and EPAC2 in patients with low back pain is one of the major findings of this study. These increases indicate an activation of intracellular signaling linked to chronic pain. cAMP is a well-known second messenger involved in nociceptive signal transmission, neuronal sensitization, and synaptic plasticity [Fillingim et al., 2009].

The role of EPAC proteins, particularly EPAC1, is increasingly recognized in pain pathophysiology. EPAC1 activation contributes to Rap1-mediated pain impulse transmission and hyperalgesia [Zhang et al., 2024]. Our study confirms that EPAC1 is more highly expressed than EPAC2, suggesting a dominant role in chronic pain modulation, as observed in mouse models of neuropathic pain [Rang et al., 2021].

EPAC2, although less expressed, also shows a significant elevation. This protein is described as involved in complex neuronal functions, including the modulation of cellular metabolism and synaptic plasticity [Martínez-Rojas et al., 2022; Meadows et al., 2021]. Its precise role in pain remains to be explored, but our results suggest a participation, although less pronounced than that of EPAC1. Despite high biological levels of cAMP and EPACs in patients, no significant correlation was found between these biomarkers and pain intensity measured by VAS. This lack of statistical association (cAMP: $R = 0.14$; EPAC1: $R = 0.06$; EPAC2: $R = 0.06$) can be explained by several factors. On the one hand, pain perception is a complex and multifactorial phenomenon, influenced not only by molecular mechanisms, but also by emotions, beliefs, experience, and comorbidities [Armstrong et al., 2024]. On the other hand, PBMCs represent an indirect biological model because they reflect the systemic inflammatory state but do not necessarily reflect central or peripheral neuronal activity related to pain.

Recent work suggests that activation of the cAMP–EPAC pathway in the nervous system (spinal cord, thalamus) may be more correlated with pain than its peripheral expression [Zhou et al., 2020]. This argues for the future integration of neural markers through functional MRI or cerebrospinal fluid analysis in translational research. Finally, several limitations must be acknowledged, including the modest sample size, which limits the statistical power to detect subtle correlations; the cross-sectional study design, which does not allow for the establishment of a causal link; the assays performed solely in PBMCs, excluding more relevant neurological tissues; and the lack of control for confounding factors such as physical activity level,


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anxiety/depressive disorders, or prior use of analgesics. These limitations call for further research, ideally longitudinal, incorporating central biomarkers, psychological factors, and patient stratification according to clinical subtypes.

## CONCLUSION

This study highlights a significant elevation in intracellular concentrations of cAMP, EPAC1, and EPAC2 in PBMCs from patients with chronic low back pain in Dolisie. Although the perceived pain intensity was significantly higher in patients, no significant correlation was observed between biological markers and VAS scores. These results suggest that activation of the cAMP–EPAC pathway participates in the pathophysiological process of chronic pain without directly reflecting its perceived intensity. However, EPAC1 emerges as a relevant candidate to explore as a therapeutic target. Future studies, on a larger scale and with a multimodal approach, are needed to validate the use of these biomarkers in personalized pain medicine.

## AUTHORS' CONTRIBUTIONS

Mr. LOUBANO-VOUMBI G. designed the study, performed the biological marker assays, and conducted the writing. Mr. BADEMBA C., BIAZO J.M., NDALA B., INANA M., and GOMA-KOUAHI E. participated in drafting and editing the manuscript, and Mr. BOUMBA MAKAYA C.R. and IBINDA J. contributed his expertise in the assessment of chronic lower back pain, in addition to editing. All authors have read and approved the final manuscript.

## CONFLICT OF INTEREST

Authors declare no conflict of interest.

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