Increasing daily step counts improves physical fitness, and reduces pain and arterial stiffness in sickle cell patients

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Abstract

Patients with sickle cell anemia (SCA) have long been discouraged from physical activity (PA). The aim of the present study was to assess the impact of increasing daily step counts on physical fitness, pain and vascular function in patients with SCA. Thirty-eight patients with SCA were recruited and equipped with a Fitbit wrist-worn accelerometer-based PA tracker for five weeks to objectively quantify their baseline daily step counts. Patients were then randomly assigned to one of three groups: 1) control group - no specific information regarding PA was given for eight weeks (N=12); 2) PA1 group - daily step counts increased by 25% of baseline for eight weeks (N=12); 3) PA2 group - daily step counts increased by 25% for four weeks, then by 50% for an additional four weeks (N=14). Pain intensity and frequency decreased after the intervention in the PA1 and PA2 groups. In addition, patients from these two groups increased the distance walked in six minutes. Arterial stiffness decreased in both PA1 and PA2 groups, without any change in the autonomic nervous system activity. Several inflammatory markers slightly decreased in the PA2 group. Incubation of cultured endothelial cells with patient plasma showed a decrease in the percentage of ICAM-1 positive cells in the PA2 group. This study is the first to show that adopting a simple approach to increase daily PA (i.e., increasing daily step count by 25-50%) for eight weeks is sufficient to decrease pain, and improve physical condition and vascular function of patients with SCA.

Introduction

Sickle cell anemia (SCA) is genetic disorder caused by a single mutation in the β-globin gene, resulting in the production of an abnormal hemoglobin (Hb), called HbS.[1] When deoxygenated, HbS may polymerize causing a mechanical distortion of red blood cells (RBC) or sickling phenomenon. RBC from patients with SCA are very fragile causing chronic hemolytic anemia. In addition, the abnormal rheology of RBC from patients with SCA plays a key role in the occurrence of various clinical complications, such as painful vaso-occlusive crisis (VOC).[2] Chronic hemolysis also promotes inflammation, oxidative stress and alterations in nitric oxide bioavailability, leading to chronic vasculopathy and chronic pain.[3-6]

Patients with SCA have a low exercise capacity, and it has long been suspected that the biological changes occurring during acute physical exercise could increase the risk of HbS polymerization, RBC sickling, and acute complications. However, several studies have shown that acute exercise of mild-to-moderate intensity does not result in consistent RBC alterations or frequent clinical complications.[7]

Because regular physical activity (PA) improves health in the general population and in patients with chronic cardiovascular, respiratory or metabolic diseases,[8-12] recent studies have investigated the biological and physiological impact of different kinds of training programs in patients with SCA.[7] Most of these studies have been conducted in laboratory conditions with exercise training sessions being accurately calibrated (exercise duration, intensity, frequency, recovery period) and supervised by highly qualified medical staff.[7] These research protocols also required substantial organizational efforts to ensure the participation and availability of patients with SCA. Although these studies have reported benefits on exercise tolerance, muscle function and some biological markers,[7,13-16] clinical benefits of such training programs have not been widely tested in SCA. Moreover, such training programs are not easily transferable to settings where medical resources are limited, particularly in sub-Saharan Africa, where SCA is highly prevalent and health systems often face resource constraints. Simple, easy-to-perform PA that is not burdensome for patients with SCA and does not require medical supervision could represent a promising solution, providing a compromise between low-intensity structured exercises and experimental conditions that are difficult to implement in these regions. The aim of the present study was to assess the impact of increasing regular PA by increasing daily step counts on physical fitness, pain and vascular function in patients with SCA from Dakar, Senegal.

Methods

Study subjects and protocol

Thirty-eight men with SCA, at steady-state, from Dakar, Senegal, participated in this longitudinal study (drePAnon clinical trial, UMIN000042826, UMIN-CTR Clinical Trial). Characteristics of the study participants were: age 31.8±8.5 years; weight 57.0±7.2 kg; height 177±6 cm; HbS 87.2±3.0%; fetal Hb (HbF) 10.0±3.1%. The protocol was approved by the Ethics Committee of Cheikh Anta Diop University (Approval N. 0388/2019/CER/UCAD) and was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent. Patients with leg ulcers, osteonecrosis or who had experienced a stroke were not included, because these may negatively impact walking abilities.

At the first visit to the Laboratory (Cheikh Anta Diop University, Dakar, Senegal), patients were equipped with a Fitbit wrist accelerometer-based PA tracker (Alta, Alta HR, or Inspire 2; San Francisco, CA, USA) for at least five weeks of follow-up under real-life conditions. At the end of this 5-week period, a follow-up visit (V1) was scheduled to measure blood biological and physiological parameters. Participant groups were randomly assigned to one of 3 groups. 1) Control group: no specific information regarding PA was given for eight weeks (N=12). 2) Patients had to increase their daily step counts by 25% above the previous 5-week daily step counts, for eight weeks (PA group 1 [PA1]; N=12). 3) Patients had to increase their daily step counts by 25% above the previous 5-week daily step counts, for four weeks, and then by 50% of baseline for four more weeks (PA group 2 [PA2]; N=14). After the 8-week intervention period (i.e., last visit; V3), the same biological and physiological parameters were measured.

Daily pain diary, interference with daily living activities, and daily medication

Pain intensity and frequency were determined using the standardized questionnaire developed by Smith *et al.*[17] The pain interference subscale was used to quantify the impact of pain on daily functioning. SCA-specific treatment information was collected.

Blood pressure and pulse wave velocity

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the left arm using a manual sphygmomanometer (Omron M3; Intellisense, Kyoto, Japan), and the carotid-femoral pulse wave velocity (PWV; CF-PWV) and carotid-radial PWV (CR-PWV) were measured using an automated system (Pulse Pen; DiaTecne, Milan, Italy). PWV reflects arterial stiffness.[18]

Autonomic nervous system activity

The activity of the autonomic nervous system (ANS) was assessed using heart rate variability (HRV) for at least ten minutes with a heart rate (HR) monitor[19-21] (Memory Belt, Suunto, Vaanta, Finland).

6-minute walking test

Patients performed a 6-minute walking test (6MWT) to measure the maximum walking distance covered in six minutes.[22-24]

Biological parameters

Hematologic, biochemical and plasma inflammatory markers were analyzed.

Endothelial cell incubation with plasma

A subset of 24 plasma samples (8 per group; before and after the 8-week intervention) was randomly selected from the whole population to test the impact of plasma on human umbilical vein endothelial cells (HUVEC) activation.

Statistical analysis

Information on the statistical analysis carried out is available in the *Online Supplementary Appendix*.

See the *Online Supplementary Appendix* for further details on the methods used.

Results

Increasing daily step count increases exercise capacity and decreases pain

Table 1 shows no difference in the clinical characteristics between patients from the three groups at the time of inclusion. The number of days for monitoring the baseline physical activity before the intervention period was the same for all three groups (44.31±8.49, 45.27±11.35, and 39.50±5.0 days for the control, PA1, and PA2 groups, respectively). During the baseline period, there was no significant difference in daily medication frequency between the groups, and no episodes of VOC or acute chest syndrome (ACS) were reported in the study population.

Mean daily step counts were compared between the three groups at baseline and after the 8-week intervention. Control subjects did not significantly increase their daily step count (+14.3 ± 33.3%, *P*=0.22) (Figure 1A) or their 6-minute walking distance (+2.8 ± 7.7%, *P*=0.09) (Figure 1B). In contrast, both the PA1 and PA2 groups significantly increased their daily step count (+25.3 ± 25.2% in the PA1 group, *P*<0.05; +51.8 ± 36.5% in the PA2 group, *P*<0.0001, respectively) (Figure 1A). As a consequence, the PA1 and PA2 groups increased their 6-minute walk distance (+8.9 ± 6.8% in the PA1 group, *P*<0.05; +16.2 ± 12.9% in the PA2 group, *P*<0.0001) (Figure 1B), with the PA2 group having the highest increase (PA1 group *vs*. control group, *P*<0.05; PA2 group *vs*. control group, *P*<0.01; PA2 group *vs*. PA1 group, *P*<0.05).

Figure 1C shows the positive correlation between the changes in daily step count and the changes in the 6-minute walking distance when the three groups are combined (r = 0.30; *P*<0.05). The frequency of daily pain decreased in both the PA1 and PA2 groups (*P*<0.05 and *P*<0.01, respectively) after intervention, while it did not change significantly in the control group (Figure 1D). Mean pain intensity decreased in both the PA1 and PA2 groups after the 8-week intervention (*P*<0.05 for both) while it remained unchanged in the control group (Figure 1E). There was no difference in the number (Figure 1F) and dosage (*data not shown*) of medication per day (mainly iron supplement and acetaminophen) between the three groups before or after the eight weeks of intervention. After the 8-week intervention, daily medication frequency was 0.68 ± 0.20, 0.56 ± 0.29, and 0.58 ± 0.22 for the control, PA1, and PA2 groups, respectively. Interference with daily activities decreased in the PA1 (*P*<0.05) and PA2 (*P*<0.01) groups after the eight weeks of intervention (Figure 1G). No association was found between the percentage of changes in these parameters and HbF levels.

Increasing daily step count decreases arterial stiffness and blood pressure

Both CF-PWV (Figure 2A) and CR-PWV (Figure 2B) decreased in the PA1 and PA2 groups after the eight weeks of increasing daily step count (*P* values ranging from <0.05 to <0.0001) while they remained unchanged in the control group. After the 8-week intervention, the PA1 and PA2 groups had lower CF-PWV (*P*<0.05 and *P*<0.01, respectively) and CR-PWV (*P*<0.01 for the two groups) than the control group. We observed a trend for a negative correlation between the increase in step count and the decrease in CF-PWV when all individuals were combined (r = -0.25; *P*=0.06) (Figure 2C). In the same way, a significant negative correlation was observed between the changes in the 6-minute walking distance and the decrease in CF-PWV (r = -0.34; *P*<0.01) (Figure 2D). Systolic (Figure 2E) and diastolic (Figure 2F) blood pressures was significantly lower after the eight weeks of increasing daily step count compared to before the 8-week intervention in the PA2 group (*P*<0.01 and *P*<0.05 for SBP and DBP, respectively). No significant change was observed in the

Table 1. Clinical characteristics of the study participants at the time of inclusion.

	Control N=12	PA1 N=12	PA2 N=14
VOC rate, mean ± SD/year	0.46±0.46	0.37±0.44	0.25±0.33
ACS rate, mean ± SD/year	0.36±0.74	0.47±0.92	0.36±0.84
Priapism, N (%)	2 (16.7)	2 (16.7)	3 (21.4)
Stroke, N (%)	0	0	0
Moderately elevated albuminuria, N (%)	7 (58.3)	10 (83.3)	11 (78.6)
Proteinuria, N (%)	1 (8.3)	2 (16.7)	0
HU treatment, N (%)	1 (8.3)	0	0

ACS: acute chest syndrome; HU: hydroxyurea; N: number; PA1: daily step counts increased by 25% of baseline for eight weeks; PA2: daily step counts increased by 25% for four weeks, then by 50% for an additional four weeks; VOC: vaso-occlusive crises; SD: standard deviation.

other two groups (i.e., control and PA1 groups) but both the PA1 and PA2 groups had lower systolic and diastolic blood pressures after the eight weeks of increasing daily step count compared to the control group ($P<0.001$ for SBP and $P<0.01$ for DPB). The percentages of change in SBP and DBP correlated with the percentages of change in CF-PWV ($r = 0.36$; $P<0.05$ and $r = 0.41$; $P<0.01$, respectively) (Figure 2G, H). No association was found between the percentage of changes in these parameters and HbF levels.

It has been previously demonstrated that SBP ≥120 mmHg or DBP ≥70 mmHg (i.e., relative systemic hypertension) may increase the risk for pulmonary hypertension and renal dysfunction.[25] The percentage of patients with SBP ≥120 mmHg or DBP ≥70 mmHg was 75% in the control group, 58% in the PA1 group, and 57% in the PA2 group ($\chi^2 = 0.93$; $P=0.63$). After the 8-week intervention, the percentage of patients with relative systemic hypertension was almost the same in the control group (83%) while it decreased in both the PA1 and PA2 groups (25% and 29%, respectively; $\chi^2 = 12.96$; $P<0.01$). There was no change in resting HR (Figure 3A) or markers of ANS activity (Figure 3B-E) with the 8-week intervention in any group, and there was no difference between the three groups.

Increasing daily step count has no impact on hemolysis

No difference between the three groups and no change in leucocytes and platelets count were observed (*data not shown*). In addition, no difference between the groups and no change between the first and second visit was observed for Hct (Figure 4A) or hemolytic markers (i.e., free Hb, LDH and total bilirubin levels) (Figure 4B-D)

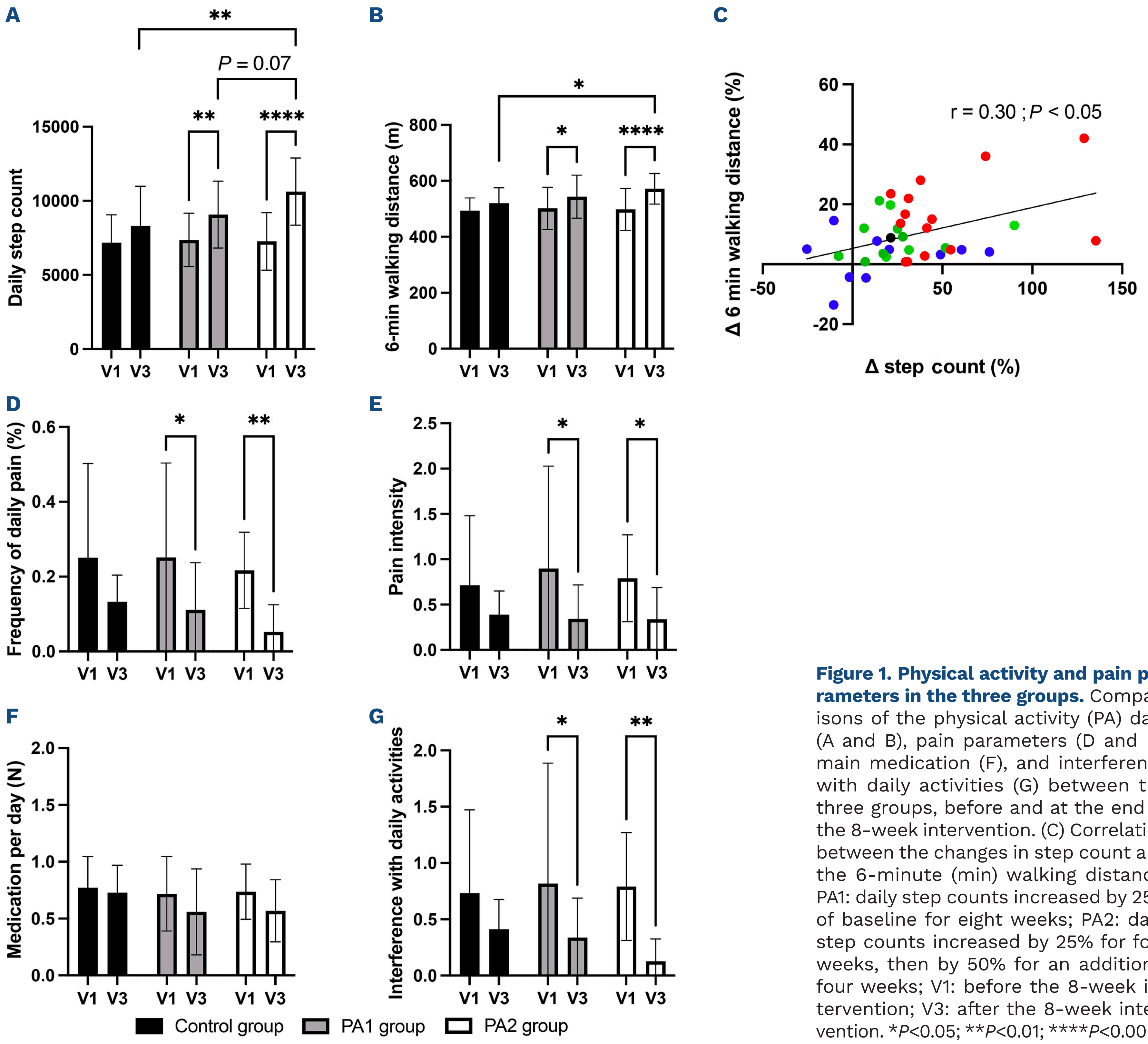

Figure 1. Physical activity and pain parameters in the three groups. Comparisons of the physical activity (PA) data (A and B), pain parameters (D and E), main medication (F), and interference with daily activities (G) between the three groups, before and at the end of the 8-week intervention. (C) Correlation between the changes in step count and the 6-minute (min) walking distance. PA1: daily step counts increased by 25% of baseline for eight weeks; PA2: daily step counts increased by 25% for four weeks, then by 50% for an additional four weeks; V1: before the 8-week intervention; V3: after the 8-week intervention. **P*<0.05; ***P*<0.01; *****P*<0.0001.

Increasing daily step counts reduces inflammation

C-reactive protein did not change over time and there was no difference between the three groups (Figure 5A). IL-6 concentration did not change over time in the three groups, but we observed a lower level after the 8-week intervention in the PA1 group compared to the control group, and a trend for a lower value also in the PA2 group (Figure 5B). TNF-α did not significantly change in the three

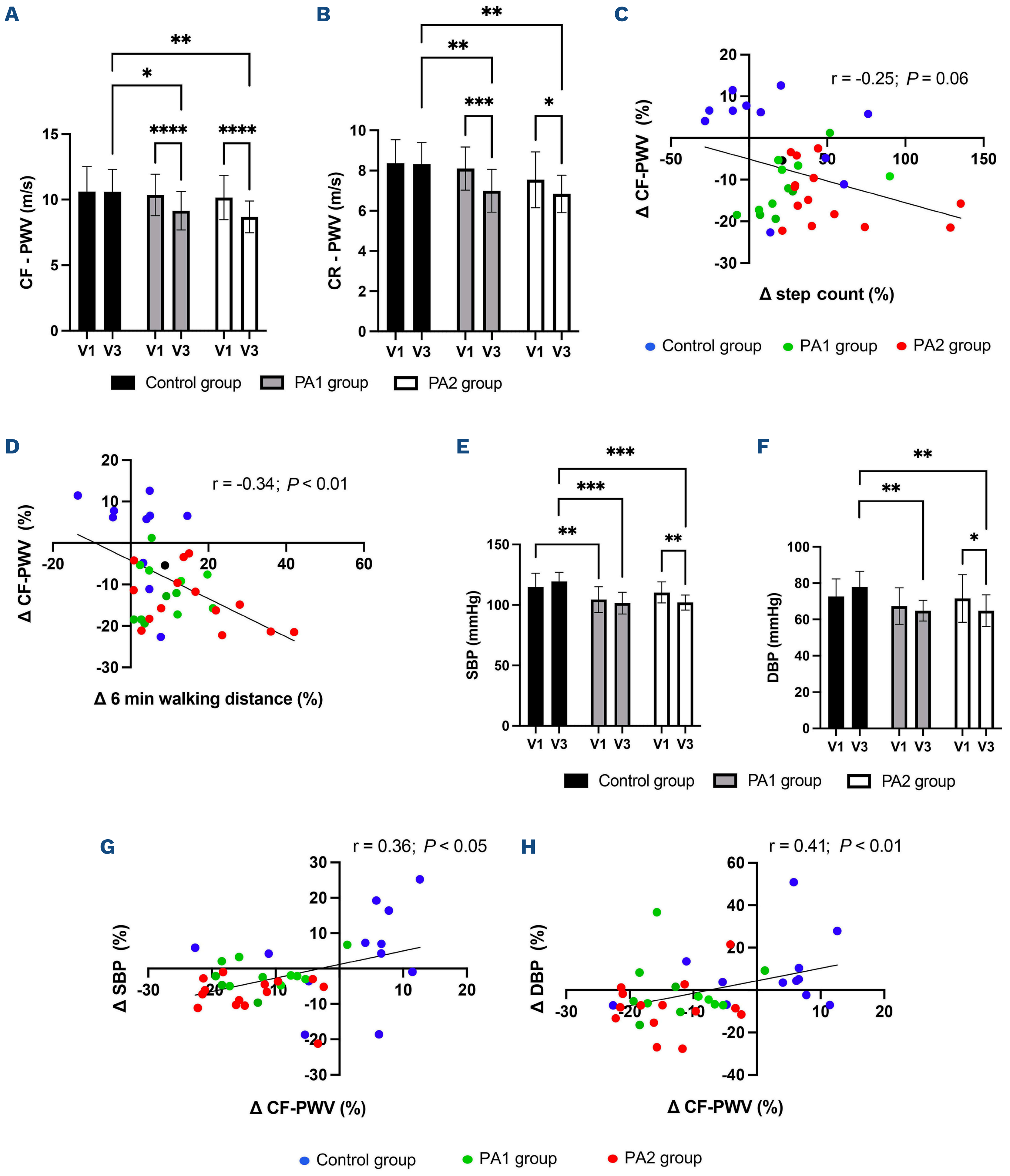

Figure 2. Pulse wave velocities and blood pressures in the three groups. Comparisons of the vascular function parameters (A, B, E, F) between the three groups, before and at the end of the 8-week intervention. Correlation between the changes in vascular function parameters and the changes in step count or in the 6-min walking distance (C, D, G, H). CR-PWV: carotid-radial pulse wave velocity; PA1: daily step counts increased by 25% of baseline for eight weeks; PA2: daily step counts increased by 25% for four weeks, then by 50% for an additional four weeks; V1: before the 8-week intervention; V3: after the 8-week intervention; ΔCF-PWV: changes in the carotid-femoral pulse wave velocity; ΔSBP: changes in systolic blood pressure. **P*<0.05; ***P*<0.01; ****P*<0.001; ****P<0.0001.

groups but the values were significantly lower in the PA2 group compared to control group after the eight weeks of increasing the daily step count (Figure 5C). IFNγ decreased significantly after the eight weeks of intervention in the PA1 and PA2 groups, while increasing in the control group (Figure 5D). Incubation of HUVEC with the plasma of patients showed that the percentage of HUVEC positive for ICAM-1 and ICAM-1 expression decreased in the PA2 group after eight weeks of increasing the daily step count (Figure 5E, F).

Discussion

The present study demonstrates that increasing the daily step count by 25-50% for eight weeks is sufficient to increase physical capacity, decrease pain frequency and intensity, improve vascular function, and decrease inflammation in patients with SCA from Dakar, Senegal.

It is now widely accepted that regular physical activity or exercise training may have beneficial effects on the cardiovascular, muscle, metabolic, respiratory, blood rheolog-

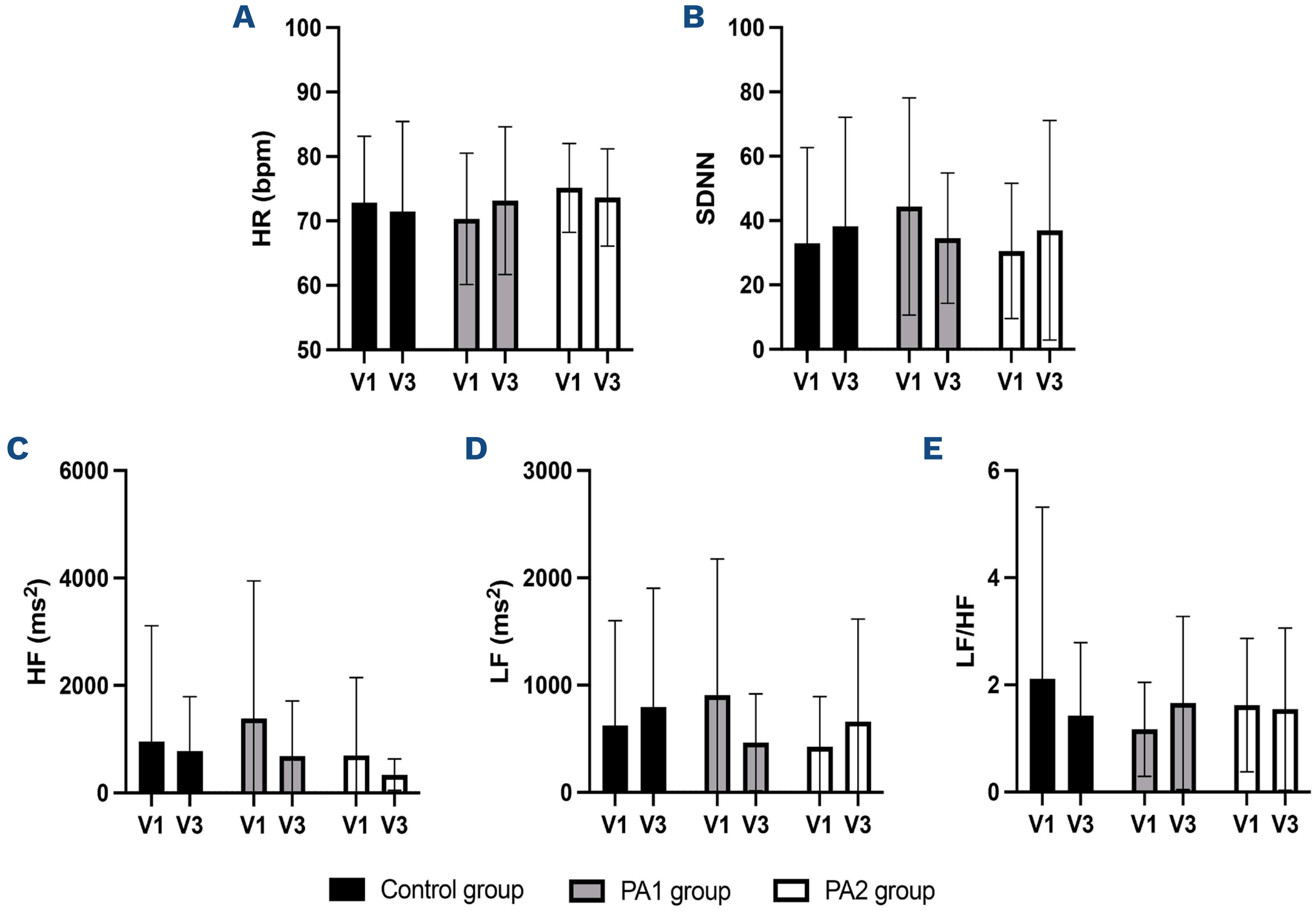

Figure 3. Comparisons of the autonomic nervous system activity parameters between the three groups before the 8-week intervention and at the end of the 8-week intervention. (A) Heart rate (HR). (B) Standard deviation of all normal RR intervals (SDNN). (C) High frequencies (HF) (0.15-0.40 Hz). (D) Low frequencies (LF) (0.04-0.15 Hz). (E) LF/HF. V1: before the 8-week intervention; V3: after the 8-week intervention.

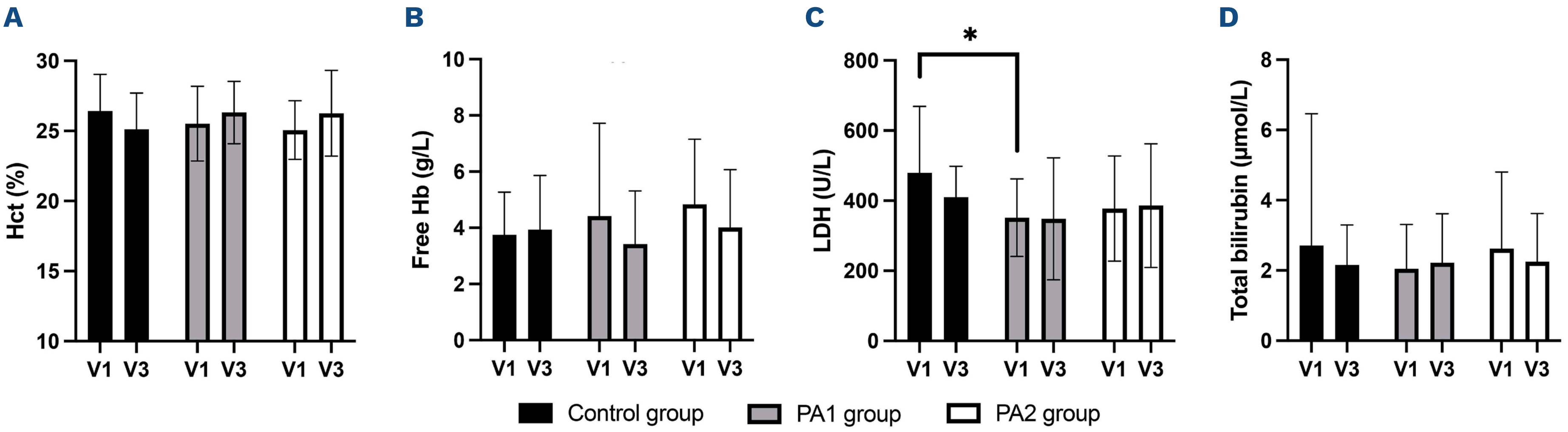

Figure 4. Hematologic and biochemical parameters in the three groups. (A) Comparisons of hematocrit (Hct), (B) free hemoglobin concentration (FreeHb), (C) lactate dehydrogenase levels (LDH), and (D) total bilirubin between the three groups, before and at the end of the 8-week intervention. PA1: daily step counts increased by 25% of baseline for eight weeks; PA2: daily step counts increased by 25% for four weeks, then by 50% for an additional four weeks; V1: before the 8-week intervention; V3: after the 8-week intervention. **P*<0.05.

ical and inflammatory function/profile of various chronic diseases.[26] Previous studies showed that eight weeks of regular training in sickle cell mice decreased inflammation, blood viscosity and oxidative stress.[27-29] In patients with SCA, recent studies showed that training programs of 2-3 training sessions of 20-45 minutes per week for 6-8 weeks improved muscle function, and increased ventilatory efficiency and aerobic physical fitness.[14,16,30,31] The exercise intensity chosen for these training sessions was based on an initial submaximal/symptom-limited cardio-pulmonary exercise test performed by the patients under laboratory conditions.[7,14,30,31] Individualizing and calibrating training programs requires the use of advanced technical tools, such as cardiopulmonary exercise testing with gas exchange analyzers, and the determination of metabolic thresholds during exercise. Consequently, this type of approach is difficult to implement in large populations, particularly in sub-Saharan African countries where medical resources are limited and the prevalence of SCA is particularly high. In contrast, the use of a daily step count as a guide for PA is easily adaptable across diverse contexts from low-income countries with limited healthcare infrastructure to high-income countries such as those in Europe and the United States. It represents a simple, scalable, and cost-effective tool that can complement existing healthcare strategies, and has particular added value in low- and middle-income settings where access to care is often severely constrained. Walking is simple, free, and one of the easiest ways to become more active. A recent meta-analysis conducted in the general population (227,000 participants) showed a significant inverse association between daily step count and all-cause mortality and cardiovascular mortality,[32] which confirms the findings of another meta-analysis.[33]

The present study shows that guiding PA in patients with SCA using an easily wearable activity tracker is both feasible and safe in an African context. Increasing the daily step count improves physical fitness, as evidenced by longer 6-minute walking distances, and reduces pain frequency and intensity. The mechanisms at the origin of the decrease in pain are beyond the scope of this study but could involve a decrease in central nervous system sensitization due to regular PA.[34] Moreover, the lower inflammatory profile found after the eight weeks of increasing the daily step count could have contributed to lower pain frequency and intensity.[35] Consequently, the quality of life of the patients improved, and there was less interference with daily activities.

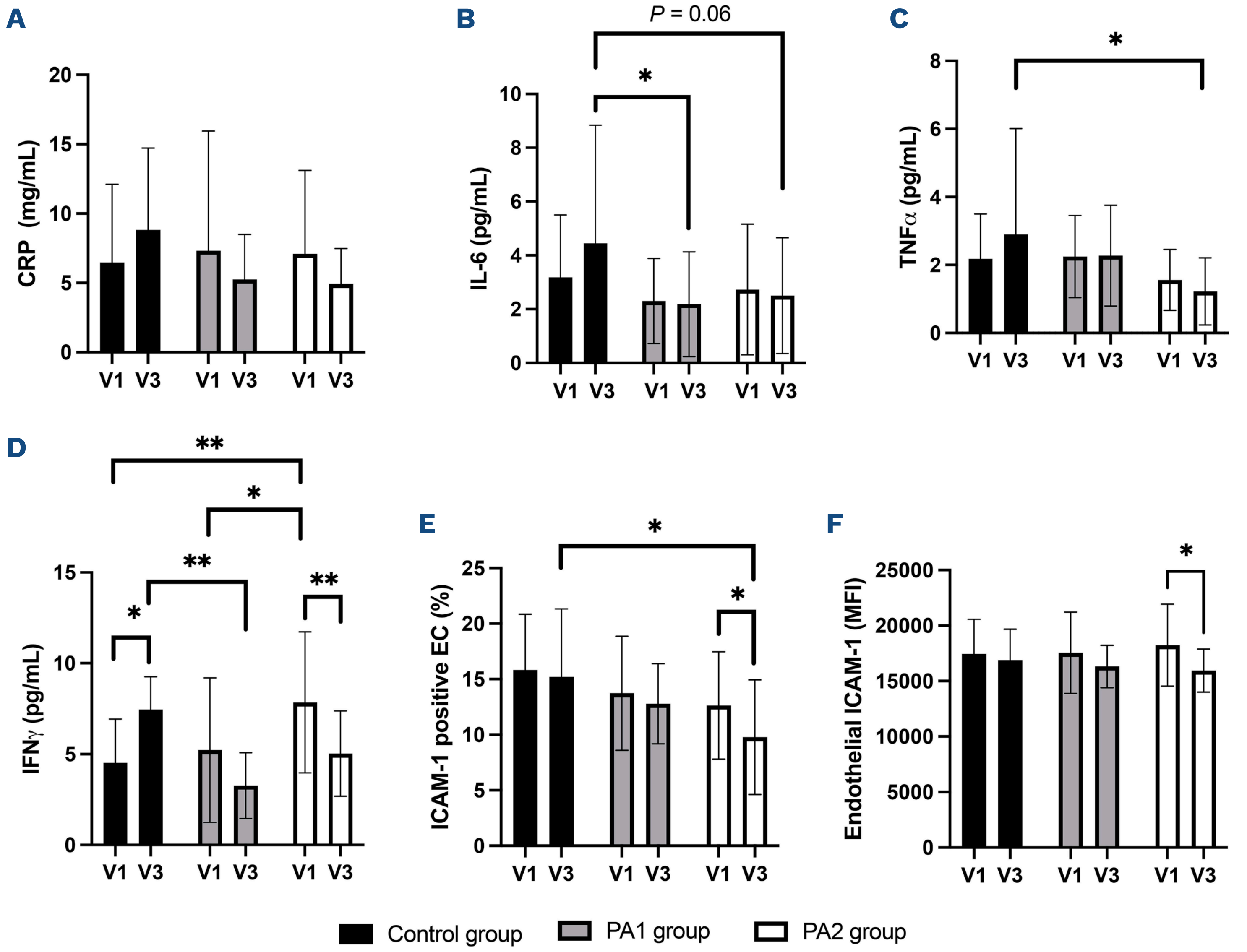

Figure 5. Inflammation and endothelial cell activation. (A-D) Comparisons of plasma inflammatory molecules and (E and F) markers of endothelial activation between the three groups, before and at the end of the 8-week intervention. CRP: C-reactive protein; EC: endothelial cells; ICAM-1: intercellular adhesion molecule; IFNα: interferon g; IL-6: Interleukin 6; MFI: median fluorescence intensity; TNFγ: tumor necrosis factor a; V1: before the 8-week intervention; V3: after the 8-week intervention. *$P<0.05$; **$P<0.01$.

Increasing the daily step count also resulted in a decrease in arterial stiffness, both in the PA1 and PA2 groups, indicating an improvement in vascular function. These findings are in agreement with studies showing an improvement in vascular function in patients with prehypertension after an 8-week program of mixed aerobic-resistance training (three 1-hour sessions per week[36]) or in young individuals with cardiovascular risk factors after six weeks of increasing daily step counts.[37] A systematic review and meta-analysis showed that aerobic exercise performed more than three times per week, for sessions under 60 minutes, and over an intervention period of up to eight weeks is associated with significant improvements in vascular function in patients with heart failure.[38] In our study, improvement in vascular function may have contributed to the improvement in physical fitness, systolic and diastolic blood pressure, and pain. Vascular function has been reported to be impaired in SCA and to contribute to the occurrence of several acute and chronic complications.[39-41] The development of chronic vasculopathy in SCA is multifactorial and may involve alterations in the ANS activity, inflammation and hemolysis.[40,41] We did not observe any difference in ANS activity between the three groups, and increasing the daily step count had no effect.

Moreover, the 8-week intervention was found to have no effect on hemolytic markers (i.e., LDH, bilirubin, and free Hb), and no difference was observed between the three groups. In contrast, we observed some differences in cytokine levels (IL-6 and TNFα) between the three groups at the end of the follow-up, with both PA1 and PA2 groups having less inflammation than the control group. In addition, IFNγ level was lower in the PA2 group after the eight weeks of increasing the daily step count compared to before the intervention. Regular exercise is known to decrease inflammation in the general population and in patients with various chronic disorders,[26,42] but this is the first time that such a result has been observed in the context of SCA.

Both IL-6 and TNFα have been shown to increase ICAM-1 expression on endothelial cells through the modulation of the STAT3 and NFκB pathway, respectively, and of the Rac1 pathway.[43,44] IFNγ has been reported to increase the expression of ICAM-1 on endothelial cells through the activation of protein kinase C. ICAM-1 plays a crucial role in the pathophysiology of SCA by promoting the adhesion of sickle cells to the endothelium, contributing to vaso-occlusion and tissue damage.[45-47] In non-sickle cell patients with chronic pain, a positive correlation has been reported between pain intensity and the plasma concentration of the soluble form of ICAM-1[48] and any change in pain intensity over time was reflected by changes in ICAM-1 levels. Although we did not measure directly the soluble form of adhesion molecules in the plasma of the patients, incubation of HUVEC with plasma showed a decrease in the percentage of HUVEC positive for ICAM-1 and a decrease in ICAM-1 MFI in the PA2 group after the 8-week intervention. The changes in ICAM-1 expression observed in the PA1 group were of lower magnitude than for the PA2 group and did not reach statistical significance.

Our findings suggest that the slightly lower inflammation after eight weeks of increasing the daily step count could result in lower endothelial cell activation, which could have contributed to the improvement in vascular function. Other mechanisms, such as a decrease in oxidative stress or an increase in nitric oxide (NO) production could also be at the origin of the improvement in vascular function found in the present study. A decrease in oxidative stress has been previously reported in sickle cell mice following a multi-week training protocol,[49] while an increase in NO production was suggested by the results reported by Grau *et al.*[16] in a small group of children with SCA after a 6-week training protocol conducted in laboratory conditions.

An important limitation of the present study is the non-inclusion of women. Women were not included because hormonal changes that may occur during the menstrual cycle could affect some key parameters measured in this study, such as arterial stiffness. For instance, it was demonstrated that flow-mediated dilation of the brachial artery and arterial compliance increased from the follicular to the late follicular phase, decreased during the early luteal and then re-increased during the late luteal phase.[50] Moreover, there could be potential confusion between painful symptoms related to SCA and other pain, more specifically, painful menstruation, which may be common in young women. Finally, the level of menstrual flow may affect the severity of anemia, periodically impacting lifestyles and the level of physical activity. Future studies should include women but specific analysis to characterize the luteal and follicular phases of the menstrual cycle will be needed to take into account the impact of both regular physical activity and hormonal changes on clinical, biological, and physiological parameters.

A second limitation is the fact that patients included in the present study were already quite active, with a mean daily step count ranging from 3,000 to more than 9,500-10,000. The limited car ownership and the underdeveloped public transportation network in Dakar are probably at the origin of the active lifestyle of the inhabitants of this city. While this active lifestyle could probably be true of other African regions, it is not the case in other world regions, such as in Europe or USA. Further studies conducted in regions where sedentary behavior is more common are needed to test whether a 25-50% increase in daily step count is sufficient to improve pain, vascular function, and physical capacities of SCA individuals. Finally, the limited sample size of the present study does not allow identification of an optimal step count threshold that could provide the greatest clinical and biological benefits to the patients.

In conclusion, this study is the first to show that adopting a simple approach to increase daily PA (i.e., increasing the daily step count by 25-50%) for eight weeks is sufficient to improve the physical condition and vascular function of patients with SCA, as well as to decrease pain frequency and intensity. Although increasing the daily step count by 25% or 50% resulted in very similar effects, it seems that an increase of 50% had slightly greater effects, notably on inflammation. Most importantly, this change in PA behavior had no negative impact on the participants; nor did it lead to any adverse events. It is recommended that physicians encourage patients with SCA to engage in regular daily PA, with objective monitoring of their daily step count using validated trackers or connected devices (e.g., wearables or smartphones), and to progressively increase their daily step count by at least 25% above their baseline level. The long-term clinical effects of increasing daily PA need to be investigated in the future.

Disclosures

No conflicts of interest to disclose.

Contributions

FDL, MR, RC, MDi/MDu, MSC, MMa, MS and SD performed experiments; MDi/MDu, MSC and SD provided patients; FDL, MDi/MDu, EN, KC, MGG, SD, BR, JT and PC analyzed results and made the figures; MDi/MDu, EN, KC, MGG, MMi, TY, AS, JT and PC designed the research; FDL, MR, EN, KC, MGG, JT and PC wrote the paper. All authors read and approved the final version of the manuscript for publication.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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