Letter to the Editor

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"Stay home stay safe?" Systemic inflammation in subjects undergoing routine hematology tests during the lockdown period of COVID-19

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To the Editor,

The outbreak of coronavirus disease 2019 (COVID-19) has spread rapidly all around the world. Human mobility and relevant production and consumption activities have since decreased significantly. The lockdown imposed by many worldwide governments to contain the spread of COVID-19 may be associated with various stress-induced psychological problems and physical inactivity [1]. However, the impact of these stay in place orders on people health and fitness is largely unknown. In this study we aimed to assess inflammatory biomarkers in subjects undergoing routine hematologic tests before and during the lockdown period.

We initially considered 15,294 blood samples collected between the 1st of January 2020 and the 31st of March 2020, corresponding to 12,831 subjects who underwent routine blood sample collection. To evaluate the effect of the lockdown on the hematologic and biochemical parameters, a matched-pair case-crossover design was employed, including in the study only those subjects who underwent blood sample collection both before and during the lockdown (241 subjects; 1.9% of total). Descriptive statistics were reported as median (1st–3rd quartile) for continuous variables and as percentages (absolute numbers) for categorical variables. The effect of lockdown was evaluated using Generalized Linear Mixed Models (GLMM) adjusted by gender, including a random effect to consider the correlation among the matched pairs of observations. Results were reported as fixed effect coefficient β, standard error (SE), 95% confidence interval (CI), and p-Value. A logistic regression model adjusted by gender was used to assess the effect of lockdown on C-reactive protein (CRP) categorized as normal/abnormal (≥8 mg/L) using robust covariance matrix estimates to account for correlation between repeated measurements. Results were reported as odds ratio (OR), 95% CI, and p-Value. Analyses were performed using R software with the packages rms and lme4. The study protocol was reviewed and approved by the Institutional Ethical Committee. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Of the 241 subjects enrolled, 63% (153) were female and 37% (88) were male. The median age was 54 years (range 37–70 years). Platelet counts increased during the lockdown period, even within the normal range. CRP significantly increased during the lockdown period (Table 1). Before the lockdown, CRP was abnormal in 13% and became abnormal in 25% of subjects during the lockdown. Logistic regression analysis adjusted by gender showed that lockdown was a determinant of abnormal CRP values (OR 2.73, 95% CI 1.30–5.73, p=0.03), thus suggesting an association between lockdown and development of systemic inflammatory state.

A key finding from our study is the evidence of increased mild systemic inflammation during the prolonged lockdown. From our preliminary data we can

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Table 1: Distribution of hematological and biochemical parameters before and during lockdown and the lockdown effect adjusted by gender (n=241).

	Before lockdown (n=241)	During lockdown (n=241)	Estimate (β)	95% CI	SE	p-Value
WBC, $\times 10^9$/L	6.58 (5.09–9.18)	6.74 (5.30–9.42)	0.1414	−0.151;0.433	0.1490	0.342
Lymphs, $\times 10^9$/L	1.82 (1.40–2.28)	1.94 (1.45–2.53)	0.03078	−0.165;0.227	0.09999	0.757
Segs, $\times 10^9$/L	3.72 (2.58–5.41)	3.68 (2.68–5.98)	0.03454	−0.167;0.236	0.10272	0.739
PLT, $\times 10^9$/L	220 (177–266)	224 (177–277)	9.542	0.756;18.328	4.483	*0.034*
ESR, mm/h	14 (7–23)	12 (10–25)	−3.677	−10.048;2.695	3.251	0.237
CRP, mg/L	2.28 (1.34–5.90)	2.28 (1.31–7.35)	5.692	1.204;10.181	2.290	*0.015*

CRP, C-reactive protein; ESR, erythrocytes sedimentation rate; Lymphs, lymphocytes; PLT, platelets; Segs, segmental neutrophils; WBC, white blood cells. Descriptive statistics are reported as median (1st quartile-3rd quartile).

hypothesize a link between isolation, chronic stress, and likely physical inactivity caused by the lockdown, and the onset of inflammation.

Psychological stressors like the lockdown can cause physiologic changes [2] disrupting the ability for glucocorticoids to effectively down-regulate inflammatory activity due to decreased sensitivity caused by chronic elevation in cortisol [3], leading in turn to systemic chronic inflammation and multiple inflammation-related diseases, in particular cardiovascular diseases [4]. Amygdala is a key structure in cross-talk between threat-related neural circuitries and peripheral inflammation, particularly in cardiovascular diseases. Therefore, we can speculate that the stress related to the lockdown period of COVID-19 may produce a systemic inflammatory state through the activation of the amygdala. Such a mechanism has already been demonstrated in systemic inflammatory diseases [5]. In particular, systemic inflammatory status may increase cardiovascular risk due to the negative effect on microvascular coronary function [6]. Moreover, it is already known that physical activity may lower cardiovascular risk by reducing inflammation [7]. Since elevated levels of CRP have been shown to be independent predictors of increased cardiovascular risk, the current study implies, although it does not prove, that lockdown related physical inactivity may increase cardiovascular risk by enhancing inflammation. Confirmation of results of this hypothesis-generating study will require a longitudinal trial, including larger numbers of patients.

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