








## ARTICLE

# Dexamethasone exposure in normal-weight and obese hospitalized COVID-19 patients: An observational exploratory trial

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## Abstract

During the latest pandemic, the RECOVERY study showed the benefits of dexamethasone (DEX) use in COVID-19 patients. Obesity has been proven to be an independent risk factor for severe forms of infection, but little information is available in the literature regarding DEX dose adjustment according to body weight. We conducted a prospective, observational, exploratory study at Geneva University Hospitals to assess the impact of weight on DEX pharmacokinetics (PK) in normal-weight versus obese COVID-19 hospitalized patients. Two groups of patients were enrolled: normal-weight and obese (body mass index [BMI] 18.5–25 and >30 kg/m<sup>2</sup>, respectively). All patients received the standard of care therapy of 6mg DEX orally. Blood samples were collected, and DEX concentrations were measured. The mean DEX AUC<sub>0–8</sub> and C<sub>max</sub> were lower in the obese compared to the normal-weight group (572.02 ± 258.96 vs. 926.92 ± 552.12 ng/h/ml and 138.67 ± 68.03 vs. 203.44 ± 126.30 ng/ml, respectively). A decrease in DEX AUC<sub>0–8</sub> of 4% per additional BMI unit was observed, defining a significant relationship between weight and DEX AUC<sub>0–8</sub> ( $p = 0.004$ , 95% CI 2–7%). In women, irrespective of the BMI, DEX AUC<sub>0–8</sub> increased by 214% in comparison to men ( $p < 0.001$ , 95% CI 154–298%). Similarly, the mean C<sub>max</sub> increased by 205% in women ( $p < 0.001$ , 95% CI 141–297%). Conversely, no significant difference between the obese and normal-weight groups was observed for exploratory treatment outcomes, such as the length of hospitalization. BMI, weight, and gender significantly affected DEX AUC. We conclude that dose adjustment would be needed if the aim is to achieve the same exposures in normal-weight and obese patients.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

COVID-19 is a disease caused by SARS-CoV-2 virus capable of causing mild to severe infections in humans up to pneumonia and acute respiratory distress

complications. On the sudden emergence of the SARS-Cov-2 virus, analyses of people affected by the disease have suggested that obesity might be associated with worse COVID-19 outcomes compared with the rest of COVID-19 patients. Dexamethasone (DEX) is included in the guidelines by the World Health Organization but the impact of obesity on DEX pharmacokinetics (PK) and pharmacodynamics (PD) remains poorly explored.

#### **WHAT QUESTION DID THIS STUDY ADDRESS?**

Our prospective, observational, exploratory study assessed the impact of BMI on systemic DEX exposure in normal-weight versus obese COVID-19 hospitalized patients to investigate the need for DEX dose adjustment.

#### **WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**

Our study demonstrated that body mass index (BMI) modulated DEX area under the curve (AUC). Obese patients had a lower systemic concentration (160%) than normal-weight patients. We also observed a gender effect. Irrespective of the BMI, women had a statistically significant increase of 214% in DEX AUC compared to men.

#### **HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**

We demonstrated a statistically significant difference in mean DEX AUC<sub>0-8</sub> and C<sub>max</sub> between the normal and obese patient groups. Our results suggest that different dosing would be needed if the aim is to achieve the same exposures in both groups.

## **INTRODUCTION**

After the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19),<sup>1</sup> intensive research was conducted to identify effective therapeutic agents. The RECOVERY multicenter trial, which aimed to assess the effects of potential treatments in COVID-19 hospitalized patients, demonstrated that dexamethasone (DEX) resulted in lower mortality rates than the standard of care.<sup>2</sup> Based on the available evidence, in September 2020, the World Health Organization (WHO) guideline panel recommended the use of systemic corticosteroid therapy (e.g., 6 mg DEX orally or intravenously daily) for 7–10 days in patients with severe and critical COVID-19.<sup>3</sup>

Obesity has rapidly emerged as an important determinant of severe COVID-19. In a systematic review and meta-analysis that included 30 studies and 45,650 participants, body mass index (BMI)-defined obesity (BMI > 30 kg/m<sup>2</sup>) was associated with an increased risk of severe disease among patients with COVID-19. In the univariate analysis, the odds ratio of hospitalization was 1.76 (95% confidence interval [95% CI] 1.21, 2.56; *p* = 0.003).<sup>4</sup> In England and France, respectively, 38% and 76% of COVID-19 patients admitted to the intensive care unit (ICU) were overweight

or obese.<sup>5</sup> Patients with obesity also had a higher risk of mortality, although the relationship seems slightly less clear potentially because COVID-19 obese patients often have respiratory deterioration due to non-viral causes.<sup>5,6</sup> Nonetheless, the administered dose of DEX was the same for all patients enrolled in the RECOVERY trial, independent of body weight.<sup>2</sup>

The global prevalence of overweight and obesity has doubled since 1980 and now affects almost one-third of the world's population.<sup>7</sup> Normal weight corresponds to a BMI of 18.5–24.99 kg/m<sup>2</sup>, overweight to a BMI of 25–29.99 kg/m<sup>2</sup>, and obese to a BMI ≥ 30 kg/m<sup>2</sup>.<sup>8</sup> Nevertheless, drug dosing recommendations in the product label are often derived from studies conducted in healthy volunteers or normal-weight patients and rarely contain guidance specific to obese patients.<sup>9</sup> For example, in a study of 100 injectable medications commonly used in an ICU, only 30% of drug labels had a specific weight descriptor in the labeling information.<sup>10</sup> The use of an incorrect weight metric for dosing could lead to treatment failure or drug toxicity.<sup>11</sup> The altered pathophysiology of the obese body may also affect drug distribution in tissues and drug elimination.<sup>12</sup>

Regarding corticosteroids, a recent literature review suggested using the same dose of hydrocortisone in obese and non-obese patients for non-weight-based dosing of

hydrocortisone in patients with community-acquired pneumonia or septic shock unresponsive to fluids and vasopressors. In patients with acute respiratory distress needing methylprednisolone, the authors instead suggested using weight-based dosing based on the ideal or adjusted body weight.<sup>11</sup> Very few pharmacokinetic (PK) studies involving DEX or other corticosteroids have been conducted in obese patients.<sup>13</sup> In a small study performed in six healthy volunteers and eight obese patients, DEX maximum plasma concentrations after 1 mg dosing were similar. However, a positive correlation was observed between the area under the curve (AUC) and the total body weight.<sup>14</sup> In a study enrolling 34 normal-weight and 87 obese individuals, DEX plasma concentrations were measured approximately 8 h after 1 mg dosing. A complex gender and weight interaction affected DEX plasma concentration.<sup>15</sup>

Given the scarcity of data on the impact of obesity on DEX exposure, we performed a prospective study aiming to compare the PK of DEX in normal-weight and obese patients hospitalized for COVID-19 and treated with 6 mg daily DEX.

## PATIENTS AND METHODS

### Study design

This study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04996784) Identifier: NCT04996784) was a prospective, observational, exploratory, monocentric PK study conducted at Geneva University Hospitals (approved by the Ethics Committee of Geneva University Hospitals [ID: 2021-00034]). All patients were informed, agreed to participate, and signed an informed consent form. The study was carried out in accordance with the Swiss national law on clinical trials, following the international guidelines of the International Council for Harmonisation (ICH) and the ethical principles of the Declaration of Helsinki.

### Subjects

Participants were eligible for enrollment if they were hospitalized for COVID-19, required treatment with 6 mg oral DEX, and had a BMI between 18.5 and 24.99 kg/m<sup>2</sup> (normal-weight patients) or  $\geq 30$  kg/m<sup>2</sup> (obese patients). Exclusion criteria included a medical history of cirrhosis, bariatric or other gastric surgery, or the use of drugs that may affect CYP3A activity. We planned to include the same number of individuals in each group and to respect a gender balance within the groups.

## Procedures

The study was carried out during a 1-day session. The morning after an overnight fast, patients received orally with a glass of water 6 mg DEX (Dexamethasone Galepharm). Capillary blood samples from a small finger prick (BD Microtainer, contact-activated lancet, Plymouth, UK) were collected before (time 0) and 0.5, 1, 2, 4, 6, and 8 h after drug administration (Figure S1, [Supplementary Material](#)). Capillary whole blood (10  $\mu$ l) was collected with a device (HemaXis DB 10 kit, DBS System, SA, Gland, Switzerland) integrating a patented microfluidic plate that allowed accurate volume control (10  $\mu$ l) and a conventional filter paper card for blood storage.

## Analytical methods

Succinctly, 6 mm diameter dried blood spot (DBS) discs were punched out and folded into the bottom of individual LC vials containing a 300  $\mu$ l insert. For the extraction, methanol (100  $\mu$ l) containing dexamethasone-d3 as an internal standard (Toronto Research Chemicals, Toronto, Canada) at a concentration of 100 ng/ml was added to each vial. The vials were then sealed, vortexed, mixed, and the extraction solution was then diluted with water by a factor of two. DEX quantification was assessed via an Agilent 1290 Infinity series LC system (Agilent, Palo Alto, CA, USA) coupled to a 6500 QTtrap triple quadrupole linear ion trap mass spectrometer equipped with electrospray ionization (AB Sciex, Darmstadt, Germany). Separation was carried out with a Kinetex C18 column (50  $\times$  2.1 mm, 2.6  $\mu$ m; Phenomenex, Brechbühler, Switzerland). Liquid chromatography–mass spectrometry (LC–MS)/MS analyses for system control, data acquisition, and quantification were performed using Analyst software (version 1.6.2). A linear gradient was applied with a mobile phase composed of (A) water containing 0.1% acetic acid and (B) acetonitrile containing 0.1% acetic acid. Gradient elution was performed at a 600  $\mu$ l/min flow rate as follows: 0–1.5 min 2% B, 1.5–4.5 from 2% to 70% B, 4.5–5.5 70% B, 5.5–6 min from 70% to 2% B, 6–9 min 2% B. The injection volume was set at 10  $\mu$ l. Analytes detection was obtained in positive mode detection using multiple reaction monitoring (MRM).

The method was fully validated according to the guidelines of the European Medicines Agency (EMA).<sup>17</sup> The lower limit of quantification (LLOQ) for DEX was 10 ng/ml, and concentrations below this value (24 values over 240 mainly residual concentrations) were all fixed to 5 ng/ml (half of the LLOQ value). The accuracy of quality control

samples was within 88% and 97% and both intraday and interday variabilities did not exceed 12%.

## Outcomes

The primary end point was to evaluate the impact of BMI on DEX AUC by comparing it in normal-weight versus obese COVID-19-treated patients. Secondary end points included assessment and comparison of DEX PK and PD parameters, including the number of days spent at the hospital in the intermediate and intensive care units in the two study groups.

## Statistical analysis

Based on a previous study using 1 mg DEX, the difference in plasma concentrations in normal-weight versus obese participants is expected to be 30–50%.<sup>15</sup> Using DEX AUC as an outcome of systematic concentrations, a change of 30% in the AUC was considered clinically significant. To demonstrate this difference, a sample size of 30 patients is required to allow a power of 80% with an  $\alpha$  value of 5%. PK parameters were estimated by standard non-compartmental methods using WinNonlin version 6.2.1 (Pharsight, Mountain View, CA, USA). The relationship between the variables of interest (i.e., AUC and peak plasma concentration [ $C_{\max}$ ]) and the patients' characteristics were modeled by means of linear models with BMI and gender as predictors. The natural log scale was preferred for both response variables as this transformation appears to reduce the heteroscedasticity of the residuals and to provide a linear relationship between the response variables and the BMI. Model checks based on standard linear regression estimates suggested that outliers might be present in the data (see, e.g., Stasinopoulos et al.<sup>17</sup> for details) and, therefore, a robust approach was preferred. More precisely, we used the robust regression proposed in Yohai and Zamar<sup>18</sup> which is an M estimator based on Tukey's biweight function where the residual variance was obtained using the re-scaled median absolute deviation of the residuals (see, e.g., Venables and Ripley<sup>19</sup> for details). Robust  $F$ -tests were used to test the significance of the parameters. Descriptive statistics are presented as mean  $\pm$  standard deviation (SD).

## RESULTS

### Demographics

A total of 334 patients were assessed for eligibility. Thirty subjects (16 males and 14 females) were included, 15

normal-weight and 15 obese patients (Figure 1). The patients' demographics and medical characteristics were comparable in the different groups (Table 1). Apart from BMI, no significant variation was observed between the two groups as regards demographic features, comorbid diseases, and disease severity on inclusion day. The mean age of the whole population (both groups) was  $63.2 \pm 10.6$  years. Fourteen subjects (47%) were women. The mean BMI in the normal weight and obese groups was  $23.1 \pm 1.4$  and  $33.8 \pm 2.7$  kg/m<sup>2</sup>, respectively.

### Pharmacokinetic outcomes

DEX AUC<sub>0–8</sub> was approximately 1.6-fold higher in normal-weight than obese subjects ( $926.91 \pm 552.11$  vs.  $572.02 \pm 258.97$  ng h/ml, respectively) (Table 1, Figure 2). DEX  $C_{\max}$  was also approximately 1.5-fold higher in normal-weight compared to obese subjects ( $203.44 \pm 126.30$  vs.  $138.67 \pm 68.03$  ng/ml; Figure 3). Each BMI unit increase generated a DEX AUC decrease of approximately 4% of the predicted AUC (Figure 4;  $p = 0.004$ , 95% CI: 2–7%). Each BMI unit increase induced a DEX  $C_{\max}$  decrease of approximately 4% of the predicted  $C_{\max}$  (Figure 5;  $p = 0.02$ , 95% CI 1–7%). Time to maximum plasma concentration ( $T_{\max}$ ) was not significantly different in both groups ( $1.7 \pm 1.1$  vs.  $1.9 \pm 1.5$  h, for normal-weight and obese patients, respectively). Half-life time ( $t_{1/2}$ ) was also comparable ( $4.6 \pm 1.5$  vs.  $3.8 \pm 1.2$  h, for normal-weight and obese patients, respectively). When analyzed from a weight rather than a BMI perspective, the conclusions were the same.

From a gender perspective, irrespective of the BMI, women had a predicted AUC approximately 214% higher than men ( $p < 0.001$ , 95% CI 154–298%) and a predicted  $C_{\max}$  approximately 205% higher than men ( $p < 0.001$ , 95% CI 141–298%).

### Exploratory treatment outcomes

The mean duration of hospital stay was  $12 \pm 5$  days, with no difference between the normal-weight and obese groups (median of 11 days for the normal weight group vs. 9 days for the obese group). The mean number of days spent in intermediate and/or intensive care was comparable between the two groups (for intermediate care  $0 \pm 4$  and  $0 \pm 2$  days, for normal-weight and obese patients, respectively, and intensive care  $1 \pm 2$  and  $0 \pm 1$  day, for normal-weight and obese patients, respectively). There was no difference in hospital stay relative to gender (mean of  $11 \pm 4$  days vs.  $13 \pm 7$  days for women and men, respectively).



**FIGURE 1** Flow diagram of the dexamethasone pharmacokinetic prospective clinical trial in COVID-19 patients. DEX, dexamethasone; NW, normal-weight; Ob, obese.

## DISCUSSION

We demonstrated that BMI and gender had a significant impact on systemic DEX exposure. To the best of our knowledge, this is the first time the DEX PK has been prospectively studied in COVID-19 patients as a function of BMI and gender. The present study highlights a significant difference in mean DEX  $AUC_{0-8}$  and  $C_{max}$  between the normal-weight and obese groups. Mean AUC and  $C_{max}$  ratio (obese/ normal weight) had a value of 0.68 (95% CI 0.46–1.00) and 0.62 (95% CI 0.43–0.89), respectively. This observation raises the possibility that obese patients could be subject to a therapeutic underdosing that may require an increase in DEX dose. We also observed that women had a higher DEX AUC when compared to men. This may result from physiological differences such as body weight, height, surface area, total body water, extracellular and intracellular water, and differences in PK/PD as described by Soldin et al.<sup>20</sup>

In their paper, Pasquali et al.<sup>15</sup> reported no significant difference between obese and normal-weight men, whereas a significant increase was observed in obese women's DEX levels compared to their normal-weight counterparts. They also described higher plasma DEX levels in both normal-weight and obese men compared to normal-weight and obese women, which differs from what we observed in our study. Indeed, we observed that DEX concentrations were higher in women than in men, independent of the BMI or the weight (on average 2-fold). Despite the study's small size, the significant correlations observed with COVID-19 patients' BMI, weight, gender, and DEX  $AUC_{0-8}$  and  $C_{max}$  are very promising. It indicates that the patient's BMI and gender are a potential metric impacting DEX AUC and  $C_{max}$  and that a BMI increase in both men and women resulted in a decrease in DEX AUC. In Lamielle et al.'s research article, the PK of DEX (1 mg oral administration) in obese patients were evaluated in a small study comparing six normal-weight subjects

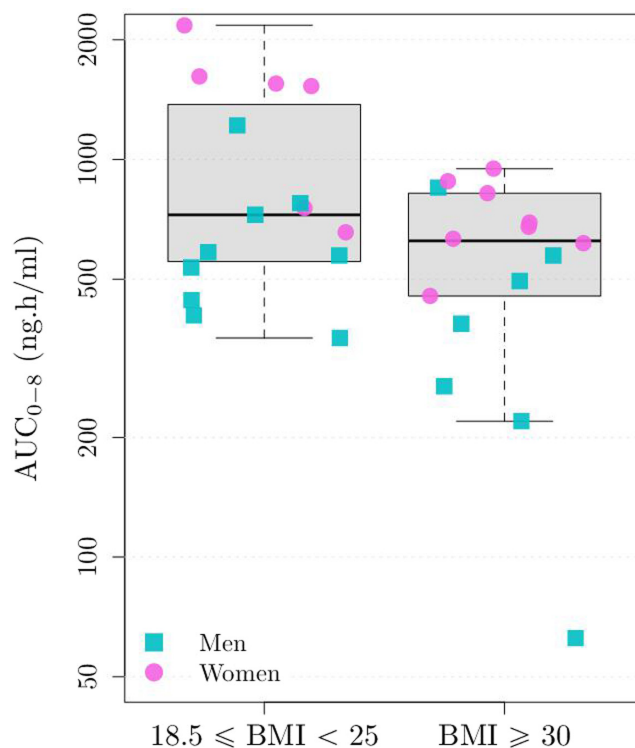


**TABLE 1** Summary of demographic, pharmacokinetic, and pharmacodynamic parameters of study patients in the normal-weight and obese groups

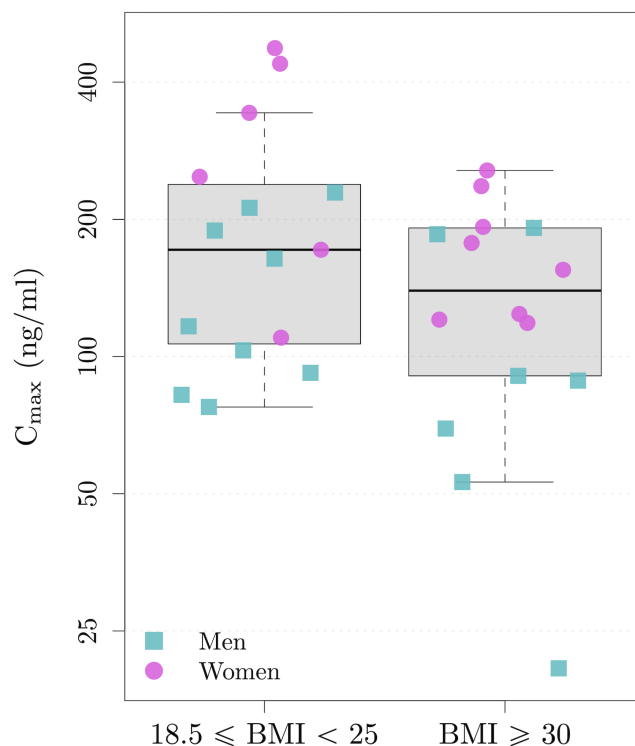
Parameter	Normal-weight (n = 15)	Obese (n = 15)
Demographics		
Female (n)	6 (40%)	8 (53%)
Age (years)	65 (±12)	62 (±9)
BMI (kg/m <sup>2</sup> )	23.1 (±1.4)	33.8 (±2.7)
Weight (kg)	68 (±12)	94 (±13)
Dexamethasone pharmacokinetics		
AUC <sub>0-8</sub> (ng·h/ml)	926.9 (±552.1)	572 (±259)
Mean AUC ratio (obese/normal-weight)	0.62; 95% CI = (0.43–0.89)	
C <sub>max</sub> (ng/ml)	203.4 (±126.3)	138.7 (±68.0)
Mean C <sub>max</sub> ratio (obese/normal-weight)		
T <sub>max</sub> (h)		
T <sub>1/2</sub> (h)	4.6 (±1.5)	3.8 (±1.2)
Exploratory treatment outcomes		
Days spent at the hospital	12 (±5)	12 (±6)

Note: Values are presented as mean ± standard deviation. The confidence intervals for the area under the curve (AUC) and peak plasma concentration (C<sub>max</sub>) ratios are obtained by nonparametric bootstrap (percentile method) based on 10<sup>4</sup> Monte-Carlo replications. BMI, body mass index; t<sub>1/2</sub>, half-life time; T<sub>max</sub>, time to maximum plasma concentration

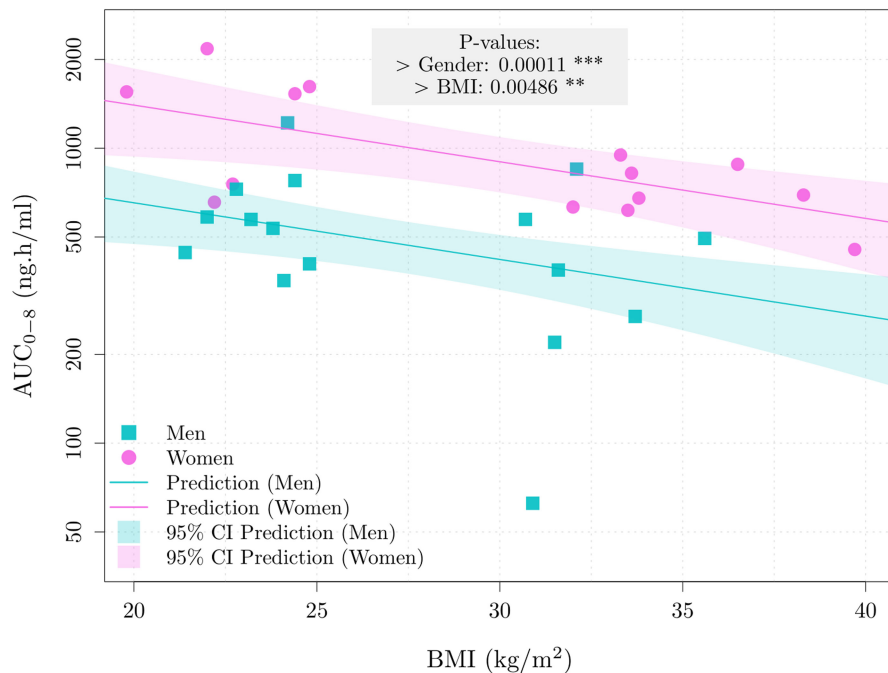
with eight obese patients whose weight was at least 20% above ideal. The absorption, elimination half-lives, and C<sub>max</sub> were not significantly different between obese and normal-weight subjects.<sup>14</sup> Despite the lack of difference in PK between groups, the authors showed a positive correlation between total body weight and DEX AUC and half-life ( $r = 0.7, p < 0.01$ ), suggesting that a higher DEX volume of distribution (V<sub>d</sub>), or lower bioavailability or clearance could explain this result. As summarized in a recent systematic review dedicated to corticosteroids dosing in obese subjects, only a few studies with contradictory results comparing DEX PK in obese and normal-weight subjects have been published to date. In general, correlations between patients' BMI and DEX PK are subject to large discrepancies between studies.<sup>21</sup> These differences can be related to many factors such as the sample size, the subjects involved in these studies, the mode of administration, and the differences in the PK and metabolism of the drug studied. In most DEX PK studies, the subjects were healthy volunteers who do not reflect the population of patients suffering from inflammatory or autoimmune diseases.<sup>13</sup>



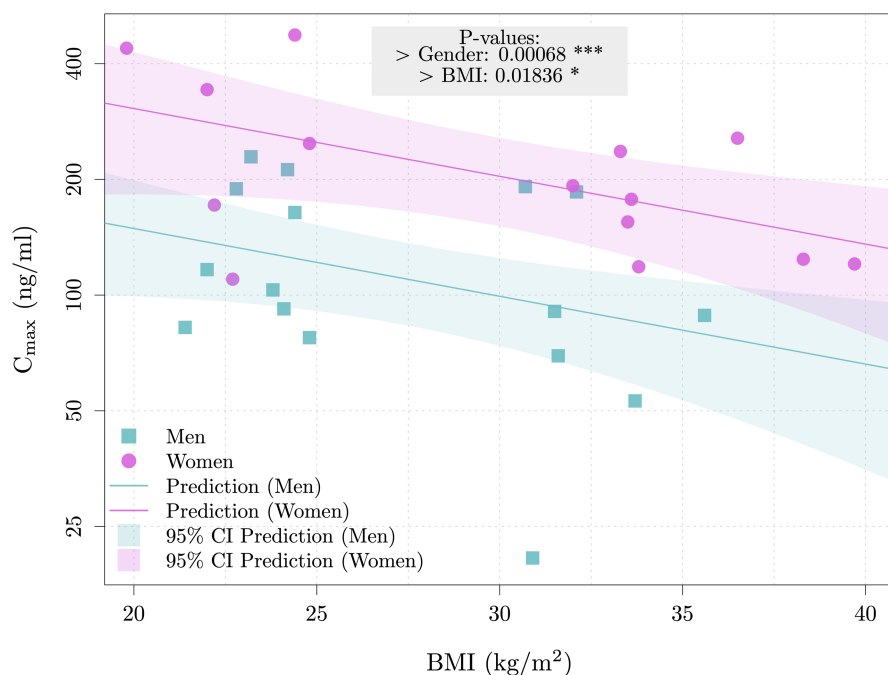
**FIGURE 2** Area under the curve (AUC<sub>0-8</sub>) values dispersion in the normal (n = 15) and obese (n = 15) groups. BMI, body mass index.



**FIGURE 3** Peak plasma concentration (C<sub>max</sub>) values dispersion in the normal (n = 15) and obese (n = 15) groups. BMI, body mass index.



**FIGURE 4** Area under the curve (AUC) values log scale regression according to body mass index (BMI).



**FIGURE 5** Peak plasma concentration (C<sub>max</sub>) values log scale regression according to body mass index (BMI).

With this point in mind, De Backer et al. recently highlighted some limitations of the RECOVERY trial focusing on the fact that several factors such as ethnicity and obesity, known to contribute to mortality in COVID-19 and be important for dosage adaptation, were not measured.<sup>22</sup> Patients included in our study were hospitalized patients suffering from SARS-Cov-2 infection and presenting a similar inflammatory immune response as observed in autoinflammatory or autoimmune conditions.<sup>23</sup> Therefore, a high inter-individual variation was observed in DEX

metrics which will need to be considered and assessed in future studies. Extrinsic factors such as co-medications were considered at the patient inclusion sessions, but the intrinsic ones, other than BMI and hepatic function, potentially influencing DEX PK need to be investigated. DEX is mainly metabolized by the cytochrome P-450 3A4 (CYP3A4). Observed differences in DEX PK between the two genders might be explained by the difference in CYP3A4 metabolic activity.<sup>24</sup> Obesity and inflammation do indeed impact on the activity of drug-metabolizing enzymes. In

addition to metabolism, several physiological dissimilarities between obese and normal-weight subjects can influence drug PK parameters and explain these observations. As drug distribution in the body is driven by its composition, regional blood flow, and binding to tissue and plasma proteins characteristics, it may differ depending on BMI.<sup>25</sup> In an average subject and after oral administration, DEX is rapidly and completely absorbed in the stomach and upper small intestine. Peak blood levels are reached after 1–2 h. The bioavailability of DEX after oral administration is approximately 80–90%. DEX is dose-dependently bound to plasma proteins, mainly to plasma albumin, up to about 80%. The volume of distribution ( $V_d$ ) of DEX is 0.6–0.8 L/kg, indicating moderate tissue distribution. The lipophilicity, expressed as  $\log(P)$  of DEX, is 1.8. Therefore, intravascular and fat mass distribution is expected, but the proportion should be higher in extracellular fluid than in fat mass. Obese patients have increased total body weight, increasing both fat body weight and lean body weight. Indeed, while the lean mass accounts for 20–40% of the excess weight, fat mass is significantly enhanced in obese subjects, and the lean mass per kilogram of body weight is reduced.<sup>26,27</sup> Some authors assumed that lean body mass decline might be accompanied by a reduction in physical function, which may be the case in the obese population.<sup>26</sup> PK data and recommendations are available for certain drugs, mainly those with narrow therapeutic windows, such as anticancer drugs, antibiotics, and anesthetic drugs. Glucocorticoids (GCs) are among the most widely used and effective treatments to control inflammatory and autoimmune diseases. They have been used to treat COVID-19 patients worldwide in a practical one-dose-fits-all approach that may now require some fine-tuning. A statistical analysis of the exploratory treatment outcomes did not highlight any significant difference in the length of hospitalization or the level of C-reactive proteins measured in patients (data not shown). Exploratory treatment outcomes analysis suggests that despite the PK differences, an underdose of DEX does not appear to pose a great risk to the patient studied. Nevertheless, we observed that in cases where the patients were transferred to the intensive care unit, increased doses of DEX were often required, even after receiving tocilizumab (20% of the patients in the study of which 17% were of normal weight) in intermediary care units. Some authors have reported that the anti-inflammatory and immunosuppressive effects of GCs are dose-dependent, with immunosuppressive effects seen mostly at higher doses. Most effects of GCs are via the genomic mechanisms which takes time, while the immediate effects via the non-genomic mechanisms occur at high doses of GCs.<sup>28,29</sup> Given the diversity in the mechanism of action of GCs, systemic plasma concentrations are subject to high variability that can cause

a wide array of drug-related problems ranging from mild to severe adverse effects on one hand and treatment failure on the other. Of all the factors influencing the efficacy of GCs, the therapeutic dose is one of the most important independent and well-documented risk factors.<sup>29</sup> In their recent paper, the COVID STEROID 2 trial group has addressed the issue of doubling the DEX dose (from 6 to 12 mg daily) in COVID-19 patients with more severe disease.<sup>30</sup> They reported no statistically significant difference in the reduction of the number of days alive without life support at 28 days. However, while the trial did mention the median weight of patients, no information or analysis was available regarding the BMI of the study subjects, which suggests that no adjustment to the BMI was made.

Our study has some limitations. It focused on PK differences between normal-weight and obese patients, and therefore it was not designed to demonstrate differences in clinical outcomes. In addition, limited data regarding the CYP3A4 genotype and phenotype may have reduced any effect observed. Moreover, the subjects included in this trial had little variability in their ethnicity, which may reduce the generalizability of our results. Further trials with larger sample sizes, more ethnic variability, and more baseline variables such as hepatic function or prevalence of diabetes are needed to validate the results of the current trial.

## CONCLUSIONS

We evaluated the impact of obesity on the PK of DEX by comparing it in normal-weight and obese/morbidly obese patients hospitalized with COVID-19. We demonstrated a statistically significant difference in mean DEX  $AUC_{0-8}$  and  $C_{max}$  between the normal-weight and obese groups. In addition, women displayed a higher DEX AUC than men, highlighting a gender effect on DEX PK parameters, irrespective of the BMI. Our results suggest that different dosing would be needed if the aim is to achieve the same exposures in both groups.

## CONFLICT OF INTEREST

The authors declared no competing interests for this work.

## AUTHORS' CONTRIBUTIONS

K.A. and K.R.I.L. wrote the manuscript. All authors designed the research. K.A. and P.G. performed the research. K.A. and S.G. analyzed the data. All authors approved the final version of the manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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