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Candesartan protects from cisplatin-induced kidney damage *via* the GDF-15 pathway

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Abstract. – OBJECTIVE: The aim of this study was to explore the protective effect of candesartan against cisplatin-induced kidney damage, with a specific focus on the growth differentiation factor 15 (GDF-15) pathway.

MATERIALS AND METHODS: 24 adult female Wistar rats, with a weight range of 200-210 grams, were enrolled in the study. Eight rats were included as a normal control group and did not receive any medication. 16 rats were administered cisplatin at a dosage of 2.5 mg/kg/day twice a week for 4 weeks (total dose 20 mg/kg). Then, they were randomly divided into two groups and treated with 1 ml/kg/day tap water or 8 mg/kg/day candesartan *via* oral gavage daily for 4 weeks. At the end of the treatment period, animals were sacrificed, and their kidneys were assessed histologically. In addition, plasma malondialdehyde (MDA), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), creatinine, and GDF-15 levels were assessed.

RESULTS: Treatment with candesartan resulted in a significant rise in serum GDF-15 levels and a significant reduction in levels of serum MDA, TNF-α, IL-6, and creatinine compared to the cisplatin and saline group. Candesartan treatment effectively protected the kidney injury, and histopathological examinations of the kidneys confirmed these results.

CONCLUSIONS: This study demonstrates that candesartan alleviates cisplatin-induced renal toxicity by further increasing GDF-15, downregulating inflammatory markers, and reducing oxidative stress.

Key Words:
Angiotensin receptor blocker, Candesartan, Cisplatin toxicity, GDF-15, Renal injury.

Introduction

Cisplatin is an inorganic platinum compound extensively used for chemotherapy of diverse solid tumors. Within cancer cells, cisplatin induces the formation of deoxyribonucleic acid (DNA) crosslinks and adducts, initiating the DNA damage response. This leads to subsequent cell-cycle arrest and ultimately results in cell death[1-3]. Cisplatin administration is associated with several adverse effects on healthy tissues, among which nephrotoxicity stands out as a significant factor adversely affecting clinical outcomes[1,4,5]. The primary elimination route for cisplatin involves renal processes of glomerular filtration and tubular excretion. This pattern leads to a greater drug concentration within the kidneys compared to other organs. The accumulation of cisplatin within the renal system initiates diverse intracellular stresses and activates stress response pathways, culminating in cisplatin-induced nephrotoxicity[6].

Growth differentiation factor-15 (GDF-15), also known as macrophage inhibitory cytokine 1, is a protein that belongs to the GDF subfamily of the transforming growth factor-β (TGF-β) superfamily[7]. Members within this superfamily activate distinct receptors, triggering intracellular signals that regulate immune and various cellular reactions[8]. Within the healthy kidney, GDF-15 is primarily expressed in the proximal tubule, the thin descending limb of Henle's loop, and the medullary collecting duct[9]. Proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), have been identified[10] as inducers of GDF-15 in macrophages. GDF-15 functions as a stress response cytokine, with its expression heightened in reaction to an array of disease processes, such as cancer, cardiovascular disease, and kidney injury. GDF-15 has anti-inflammatory, anti-proliferative, and anti-tumorigenic properties[7].

Recent experimental research[11-14] indicates that the increased endogenous expression of

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GDF-15 after kidney injury assumes a critical function in the kidney protection and repair process. In a particular study by Liu et al[11], it was observed that mice lacking GDF-15 exhibited intensified acute tubular injury and elevated inflammatory responses after experiencing ischemia-reperfusion injury. Comparable results were derived from models of both type 1 and type 2 diabetes[12]. Another study[13] reported that GDF-15 demonstrates an augmented presence in a compensatory manner during instances of acute and chronic kidney diseases. Notably, GDF-15 contributes to kidney protection through various means, such as maintaining the expression of the anti-aging and kidney-protective molecule Klotho. Remarkably, when recombinant GDF-15 was administered, it mitigated kidney injuries provoked by folic acid, cisplatin, or unilateral ureter obstruction[13].

The renin-angiotensin system (RAS) functions as a physiological regulator of blood pressure, exerting its influence on cardiovascular, renal, and adrenal functions mainly *via* the actions of angiotensin (Ang) II[14]. Beyond its role in physiological processes, the RAS is also implicated in inflammatory disorders. As a result, there has been a growing focus on the potential of drugs that modulate this system to alleviate inflammation[15]. Within this framework, Ang II receptor blockers (ARBs) have demonstrated[16,17] protective properties against inflammation, apoptosis, and endoplasmic reticulum (ER) stress across various experimental models. Candesartan, a potent and selective blocker of the Ang II receptor, has demonstrated[16,18] favorable outcomes in addressing oxidative damage and inflammation.

While factors contributing to kidney injury have been extensively studied in literature, there remains a limited comprehension of the regulation of nephroprotective factors and the interactions among them[19]. This study aimed to investigate the protective effect of candesartan against cisplatin-induced kidney damage *via* the GDF-15 pathway.

Materials and Methods

Study Animals

The study involved 24 adult female Wistar rats, with a weight range of 200-210 grams. These rats were kept in cages and subjected to standard conditions, including a 12-hour cycle of light and darkness at a room temperature of approximately 22±2°C. Throughout the study, the rats had unrestricted access to a standard pellet diet and tap water. The study's procedural approach received approval from the Institutional Animal Care and Ethical Committee at Demiroğlu Bilim University, identified by the ethical approval number 1723085411. All chemical substances used in the study were sourced from Sigma-Aldrich Inc. (St. Louis, MO, USA), unless explicitly indicated otherwise.

Experimental Procedure

A total of 24 rats were enrolled in the study. Among them, eight rats were included as a normal control group and did not receive any medication. The remaining 16 rats were administered cisplatin at a dosage of 2.5 mg/kg/day twice a week for 4 weeks (total dose: 20 mg/kg) to induce a cisplatin-induced kidney toxicity model. The rats that received cisplatin treatment were divided into two distinct groups. Group 1 rats (n = 8) were administered 1 ml/kg/day tap water *via* oral gavage daily for 4 weeks, and Group 2 rats (n = 8) were administered 8 mg/kg/day candesartan (Cantab 8 mg, Nobel, Istanbul, Turkey) *via* oral gavage daily for 4 weeks. While conducting the study, it was observed that two rats receiving both cisplatin and saline unfortunately did not survive. However, among the rats that were administered both cisplatin and candesartan, there were no recorded instances of mortality.

At the end of the study, the rats were sacrificed under high-dose anesthesia by applying a cervical dislocation procedure. Blood samples were obtained through cardiac puncture to conduct biochemical analysis, and organs were subjected to histopathological examination.

Measurement of Plasma Lipid Peroxidation

Plasma samples were used to assess lipid peroxidation by quantifying levels of malondialdehyde (MDA) as thiobarbituric acid reactive substances (TBARS). In a concise procedure, trichloroacetic acid and TBARS reagent were introduced to the plasma samples. The mixture was then combined, followed by an incubation at 100°C for 60 minutes. Following a cooling period on ice, the samples underwent centrifugation at 3,000 rpm for 20 minutes. The absorbance of the resulting supernatant was measured at 535 nm. The quantification of MDA levels was expressed in nM units, with calibration performed using tetraethoxypropane.

Measurement of Plasma TNF-α, IL-6, GDF-15 Levels

Plasma levels of TNF-α, IL-6, and GDF-15 were assessed using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Houston, TX, USA) that are commercially available.

Determination of Creatinine Levels

The quantification of creatinine concentrations was carried out spectrophotometrically through Beckman-Coulter AU 640 auto-analyzer system (Beckman-Coulter Inc., CA, US). These creatinine concentrations were then presented in units of mg/dl.

Histopathological Examination of the Kidney

For histological and immunohistochemical investigations, anesthesia was induced in all animals using intraperitoneal injections of ketamine 100 mg/kg (Alfamine®, Alfasan International B.V., Woerden, Utrecht Netherlands) and xylazine 10 mg/kg (Alfazyne®, Alfasan International B.V., Woerden, Utrecht Netherlands). Following that, the animals were perfused with 200 ml of a 4% formaldehyde solution in 0.1 M phosphate buffer saline. Kidney sections fixed in formalin (4 µm in thickness) were subjected to hematoxylin and eosin staining. All of these sections were then captured using an Olympus C-5050 digital camera (Olympus Corp., Tokyo, Japan) mounted on an Olympus BX51 microscope (Olympus Corp., Tokyo, Japan).

Morphological assessment was conducted using a computerized image analysis system (Image-Pro Express 1.4.5, Media Cybernetics Inc. Rockville, Maryland, USA). This analysis covered 10 microscopic fields per examined section, observed at a ×20 magnification. The evaluation was performed by an observer who was blinded to the study groups. Kidney sections obtained from each rat across all groups were subjected to a semi-quantitative assessment based on factors like the degree of tubular epithelial necrosis, luminal necrotic debris, tubular dilatation, and interstitial inflammation. These factors were graded using the following scale: 0-5% = score 0; 6-20% = score 1; 21-40% = score 2; 41-60% = score 3; 61-80% = score 4; and 81-100% = score 5.

Statistical Analysis

Statistical analysis was conducted utilizing SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Parametric variables between groups were compared through the Student's *t*-test and analysis of variance, while nonparametric variables were assessed using the Mann-Whitney U test. The differentiation between parametric and non-parametric variables was also verified using the Shapiro-Wilk test. The results were expressed as mean±standard error of the mean (SEM), and a significance level of $p<0.05$ was considered statistically significant.

Results

Plasma MDA, TNF-α, IL-6, Creatinine, and GDF-15 Levels

Lipid peroxidation, assessed as plasma malondialdehyde levels, was determined to assess the effect of candesartan on oxidative stress induced by cisplatin. Plasma MDA levels were significantly increased in cisplatin and saline-administered rats as compared to control ($p<0.001$). Plasma MDA levels were significantly decreased in cisplatin and candesartan-administered rats as compared to the cisplatin and saline group ($p<0.001$) (Table I).

Changes in the expression of cytokines were determined to evaluate cisplatin-induced inflammation and the protective effect of candesartan. The proinflammatory cytokines TNF-α and IL-6 were elevated following cisplatin and saline administration compared to the control group

Table I. Effect of candesartan on biochemical analysis results related to cisplatin-induced kidney.

	Normal control	Cisplatin + saline	Cisplatin + 8 mg/kg candesartan
Plasma MDA (nM) level	54.2 ± 1.5	142.6 ± 3.8**	81.5 ± 2.6$^{\#\#}$
Plasma TNF-α (pg/ml) level	17.4 ± 0.7	71.3 ± 1.4**	30.7 ± 1.8$^{\#}$
Plasma IL-6 (pg/ml) level	12.1 ± 1.9	578.8 ± 10.7**	205.2 ± 9.3$^{\#\#}$
Plasma creatinine (mg/dl) level	0.48 ± 0.05	0.73 ± 0.03**	0.56 ± 0.1$^{\#}$
Plasma GDF-15 (ng/ml) protein level	0.13 ± 0.04	0.18 ± 0.05*	0.29 ± 0.1$^{\#}$

Results were presented as mean ± standard error of the mean (SEM). Statistical analyses were performed by one-way ANOVA test. *$p < 0.05$, **$p < 0.001$ (different from control group), $^{\#}p < 0.01$, $^{\#\#}p < 0.001$ (different from cisplatin and saline group).

(p<0.001). Treatment with candesartan ameliorated the levels of TNF-α (p<0.01) and IL-6 (p<0.001) in cisplatin-administered rats (Table I).

Serum creatinine levels were significantly elevated in cisplatin and saline-administered rats as compared to control (p<0.001). Candesartan-treated rats showed a significant reduction in levels of serum creatinine in comparison to the cisplatin-saline group (p<0.01, Table I).

Serum GDF-15 levels were significantly elevated in cisplatin and saline-treated rats as compared to control (p<0.05). Treatment with candesartan resulted in a significant rise in serum GDF-15 levels when compared to the cisplatin and saline group (p<0.01, Table I).

Histopathological Examination of Kidney Tissue Samples

The histopathological examination of the kidneys of control and cisplatin and saline-treated rats revealed that the kidneys from the cisplatin and saline group show tubular epithelial necrosis (p<0.001), tubular dilatation (p<0.001), luminal necrotic debris (p<0.001), and interstitial inflammation (p<0.01). Candesartan provided significant protection and prevented kidney injury induced by cisplatin. In the cisplatin and candesartan group, there was a decrease in tubular epithelial necrosis (p<0.001), tubular dilatation (p<0.001), luminal necrotic debris (p<0.001), and interstitial inflammation (p<0.05) in the kidneys compared to the cisplatin and saline group (Table II). The histopathological features of the kidneys are shown in Figure 1.

Discussion

Cisplatin is one of the most effective chemotherapeutics and is effective against a wide range of cancer types. Nonetheless, its use is constrained due to nephrotoxicity[20]. Cisplatin-induced nephrotoxicity has been linked[21] to oxidative stress and detrimental inflammatory reactions. Ang II receptor blockers demonstrated[22,23] favorable outcomes in mitigating both inflammation and stress associated with cisplatin-induced nephrotoxicity. GDF-15 stands as a prospective factor with renoprotective potential, primarily eliciting its expression at the proximal tubular location after kidney injury[9]. In this study, we examined the potential protective effect of candesartan against kidney injury induced by cisplatin in rats, with a specific emphasis on the role of GDF-15.

Our study demonstrated that candesartan, an angiotensin receptor blocker, provided substantial protection and effectively mitigated cisplatin-induced kidney injury. This was substantiated through the examination of a nephrotoxicity marker (serum creatinine) and further confirmed by histopathological assessment of kidney tissue. The observed renal injury induced by cisplatin is closely linked to processes involving inflammation, oxidative stress, and apoptosis[24-26]. In the context of inflammation, it was documented[27,28] that TNF-α and IL-6 function as proinflammatory cytokines that act as important mediators of cisplatin-induced inflammatory tissue damage. They can induce direct renal damage and initiate the process of apoptosis and necrotic cell death[28,29]. Our experiment showed a significant elevation of plasma TNF-α and IL-6 levels in the cisplatin and saline group compared to the normal group. A significant decrease in plasma levels of TNF-α and IL-6 was observed in the cisplatin and candesartan group in comparison with cisplatin and saline-treated rats. These findings are in accordance with the literature[22,23].

Considering that oxidative stress has been established[30,31] as a contributing factor in cisplatin-induced nephrotoxicity, we investigated the regulatory effect of candesartan on cisplatin-induced oxidative stress by assessing lipid peroxide levels within the kidney. Concerning lipid peroxidation in the kidney, our study showed that cisplatin and saline-administered rats had signifi-

Table II. Comparison of groups according to kidney histopathological scoring system.

	Normal control	Cisplatin + saline	Cisplatin + 8 mg/kg candesartan
Tubular epithelial necrosis	0.2 ± 0.1	3.1 ± 0.2**	1.2 ± 0.1$^{\#\#}$
Luminal necrotic debris	0.2 ± 0.1	2.9 ± 0.4**	1.1 ± 0.2$^{\#\#}$
Tubular dilatation	0.1 ± 0.2	2.6 ± 0.3**	1.9 ± 0.3$^{\#\#}$
Interstitial inflammation	0.2 ± 0.1	1.5 ± 0.1*	0.8 ± 0.1$^{\#}$

Results were presented as mean ± standard error of the mean (SEM). Statistical analyses were performed by one-way ANOVA test. *p < 0.01, **p < 0.001 (different from control group), $^{\#}p$ < 0.05, $^{\#\#}p$ < 0.001 (different from cisplatin and saline group).

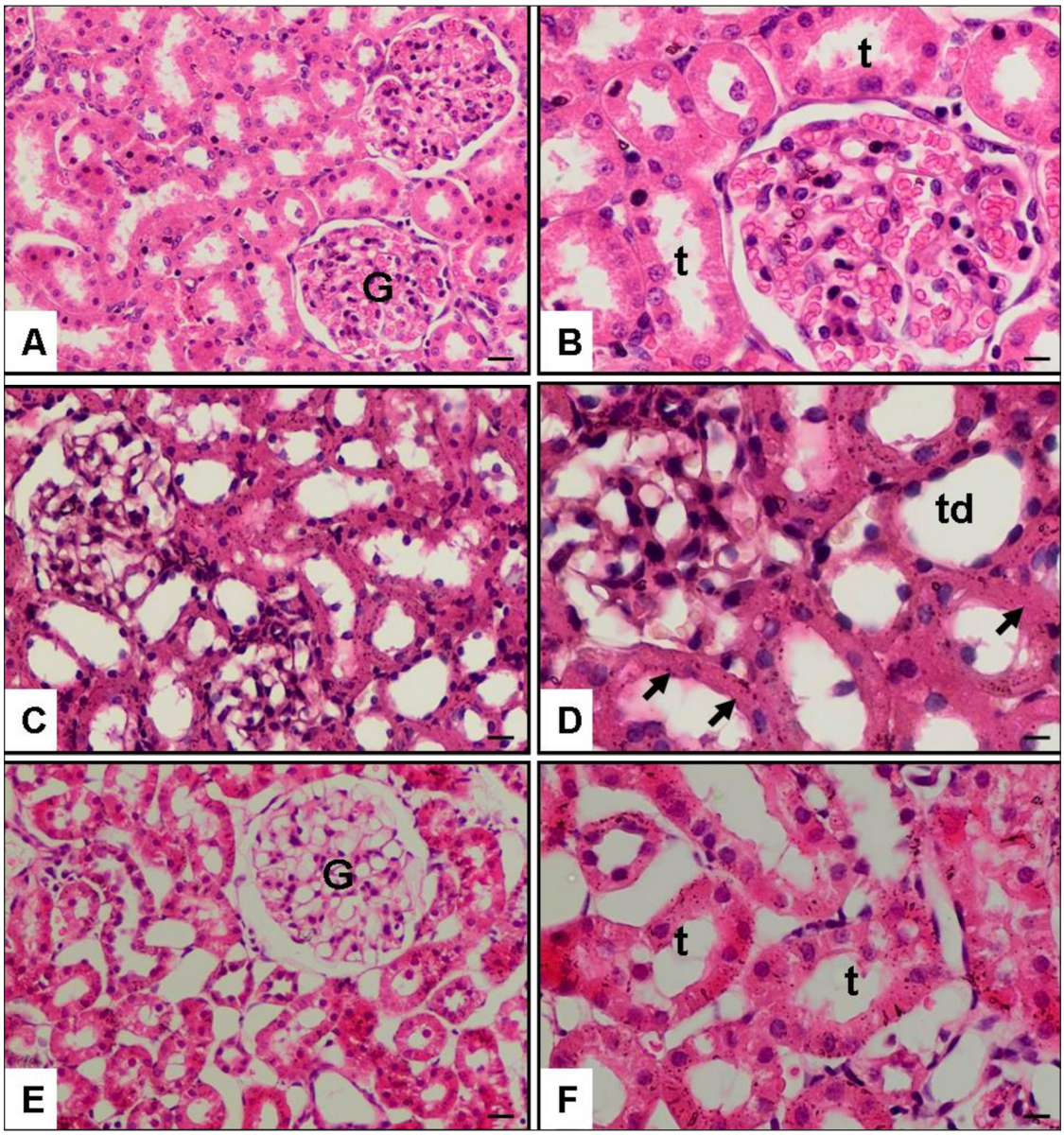

Figure 1. Kidney histopathology. **A-B**, Normal kidney (control group), glomeruli (G) and tubules (t), **C-D**, Cisplatin and saline group kidney have tubular cell necrosis (arrow) and tubular dilatation (td), **E-F**, Cisplatin and candesartan group kidney decreased on tubular dilatation (t) and tubular cell necrosis. H&E (**A**, **C**, **E** ×20 and **B**, **D**, **F** ×40 magnification).

cantly increased plasma MDA levels compared to the normal group. The increased lipid peroxidation might be elucidated by the generation of reactive oxygen species induced by cisplatin, which subsequently leads to a reduction in cellular antioxidant levels[32]. These findings provide additional substantiation for the involvement of oxidative stress in cisplatin-induced nephrotoxicity. Notably, administration of candesartan to rats was observed to significantly mitigate lipid peroxidation induced by cisplatin. Hence, apart from its action in blocking Ang II receptors, the additional mechanism of nephroprotection attributed to candesartan could be attributed to its previously validated antioxidant characteristics[33]. As a result, candesartan has the potential to restore cellular defense mechanisms and hinder lipid peroxidation.

Growth differentiation factor 15 is gaining heightened recognition as a potential target for therapeutic intervention in kidney injury. GDF-15 functions as a stress-induced cytokine, with its

expression being amplified as a response to kidney injury[9]. Experimental models[11,34,35] of kidney injury in animals have demonstrated that deficient GDF-15 levels escalate inflammatory reactions and exacerbate kidney injury, whereas GDF-15 overexpression protects the kidney and exerts immunomodulatory influences. In our study, serum GDF-15 levels were significantly elevated in cisplatin and saline-treated rats as compared to control. Treatment with candesartan resulted in a significant rise in serum GDF-15 levels when compared to the cisplatin and saline group.

The renin-angiotensin system is proinflammatory and involved in inflammatory disorders[15]. During kidney injury, activated RAS may limit the increase of GDF-15. Candesartan, by blocking RAS, may enable further increase of GDF-15. Additionally, treatment with candesartan may increase renal messenger ribonucleic acid (mRNA) expression and plasma protein levels of GDF-15. Finally, candesartan could initiate a cascade of defensive reactions, encompassing the stimulated proliferation of tubular epithelial cells, inhibition of extracellular matrix protein accumulation, and hindrance of the recruitment of inflammatory cells *via* GDF-15 increase[36] and prevent cisplatin-induced kidney injury.

Elevated plasma GDF-15 levels preceding the onset of kidney injury may be a sign of previous subclinical kidney injury that eludes detection through routine clinical measures. GDF-15 secretion occurs at the early stage of renal endothelial dysfunction and anticipates the emergence of microalbuminuria[37,38]. Therefore, treatment with candesartan, by further increasing GDF-15, may be important in preserving the kidney from cisplatin-induced renal failure before it develops.

Valiño-Rivas et al[13] demonstrated that despite a compensatory rise in GDF-15 expression during kidney injury, complete prevention of kidney injury was not achieved; nevertheless, the absence of GDF-15 exacerbated kidney injury. Nevertheless, further increments in GDF-15 (i.v. administration of recombinant GDF-15) protected the kidney from nephrotoxicity.

In our study, we did not administer exogenous GDF-15 to the rats. However, through candesartan treatment, we managed to protect the kidneys from nephrotoxicity by further increasing GDF-15. In this context, we demonstrated the feasibility of kidney injury prevention through the administration of candesartan, a therapeutic strategy that holds potential for evaluation in clinical trials.

Conclusions

The results of this study offer novel insights into the protective effect of candesartan against cisplatin-induced kidney injury, along with potential insights into the underlying mechanisms. GDF-15 is a nephroprotective factor, and its nephroprotective action is associated with the downregulation of inflammation. The inherent upregulation of endogenous GDF-15 expression in the kidney cannot alone entirely prevent kidney injury; however, additional increments in GDF-15 levels offer protective effects for the kidneys. Candesartan is capable of improving kidney injury in cisplatin nephrotoxic rats by further increasing GDF-15. As a result, candesartan has the potential to protect against kidney injury induced by cisplatin, thus enhancing the feasibility of utilizing cisplatin as an efficacious antineoplastic agent while minimizing concerns of renal harm. This knowledge can be used to design clinical trials.

Conflict of Interest
The authors declare that they have no conflict of interests.

Ethics Approval
The study was approved by the Institutional Animal Care and Ethical Committee at Demiroğlu Bilim University, Turkey, identified by the ethical approval number 1723085411.

Informed Consent
Not applicable.

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Authors' Contribution
All the authors contributed substantially to the study's conception and design. Material preparation and data collection were performed by G.G. and O.E. Statistical analysis was performed by O.E. The first draft of the manuscript was written by G.G., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of Data and Materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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