

ORIGINAL RESEARCH

Effects of Semaglutide in Doxorubicin-Induced Cardiac Toxicity in Wistar Albino Rats

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Background: Doxorubicin (DOX) is used to treat various types of cancers. However, its use is restricted by cardiotoxicity, a leading cause of morbidity and mortality. Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) may be associated with cardioprotective properties.

Purpose: This study aims to determine the protective effects of different semaglutide (SEM) doses on DOX-induced cardiotoxicity in a rat model.

Methodology: Thirty-five female Wistar rats were divided into five groups. The first group received distilled water as a negative control (NC); the positive control (PC) group received distilled water plus DOX; the third group (SL) received a low dose of SEM (0.06 mg/kg) plus DOX; the fourth group (SM) received a moderate dose of SEM (0.12 mg/kg) plus DOX; and the fifth group (SH) received a high dose of SEM (0.24 mg/kg) plus DOX. Blood samples were collected on day 8 to assess serum troponin, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), total lipid profile, and vascular cell adhesion molecule 1 (VCAM-1). Cardiac tissue was sent for histopathological analysis.

Results: DOX increased the total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG), LDH, and CKP levels. Moderate and high doses of semaglutide significantly reduced serum cholesterol levels (*p = 0.0199), (**p = 0.0077), respectively. A significant reduction (***p = 0.0013) in total body weight after treatment with SEM was observed in the SL group and a highly significant reduction (***p < 0.0001) was observed in the SM and SH groups. SEM at all doses reduced CPK levels. The SL group showed a significant reduction in troponin level (*p=0.0344). Serum LDH levels were reduced by all three SEM doses. The histopathological findings support the biochemical results.

Conclusion: Semaglutide may possess cardioprotective properties against DOX-induced cardiotoxicity in a rat model by decreasing serum biochemical markers of cardiotoxicity.

Keywords: cardioprotection, GLP-1 receptor agonists, anthracycline, rodents

Introduction

Doxorubicin (DOX) belongs to the anthracycline group of chemotherapeutic drugs and is one of the most extensively used and effective approaches for treating hematological malignancies, solid tumors, and lymphoma. The essential mechanism of doxorubicin involves the generation of free radicals and inhibition of topoisomerase II in malignant cells; however, it is toxic to several organs, including the heart. Consequently, severe dose-dependent cardiotoxicity limits its therapeutic value.^{1,2}

The basic molecular mechanisms underlying the pathogenesis of doxorubicin cardiotoxicity include oxidative stress, topoisomerase II inhibition, mitochondrial dysfunction, dysregulation of Ca^{2+} homeostasis, and accumulation of intracellular iron, leading to cell death and autophagy. The cardiotoxicity of doxorubicin is the leading cause of noncancerous morbidity and mortality and has limited its clinical application.^{3,4} The emergence of adverse reactions in patients suffering from cancer has severely restricted the use of chemotherapy; therefore, it is essential that researchers develop safe, and efficient treatments that have less toxicity or unwanted effects.

Glucagon-like peptide-1 (GLP-1) is known as the incretin hormone responsible for glucose homeostasis in diabetics; however, it is now clear that it has a broader span of physiological effects in the body. Both in vitro and in vivo studies have revealed that GLP-1 receptor agonists attenuate endoplasmic reticulum stress, regulate autophagy, stimulate metabolic reprogramming, promote anti-inflammatory signaling, alter gene expression, and regulate neuroprotective pathways.⁵

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The beneficial effects of GLP-1 vary among skeletal, smooth, and cardiac muscles, as well as among gastrointestinal, urogenital, and vasculature cells. GLP-1 receptor agonists can affect various pathways that modulate glycemia, weight, lipid metabolism, and blood pressure. They have been indicated and put into practice as potential therapies to mark the increasingly extensive pathologies associated with metabolic syndromes.⁶

There is an emerging interest in the potential cardiovascular benefits of GLP-1 receptor stimulation, considering that both type 2 diabetes and obesity are major risk factors for cardiovascular disease. Regardless of the positive effects of GLP-1 analog therapies on metabolic conditions that could theoretically improve cardiovascular disease outcomes, evidence indicates that GLP-1 can also affect the heart tissue through direct receptor-mediated responses. As a matter of fact, it is known that the classical response initiated by GLP-1 receptor activation results in supporting cardiac function by enhancing glucose uptake, improving coronary flow, and in mice, secretion of atrial natriuretic peptide, a regulator of electrolyte and blood pressure. However, studies have found it complicated to define the mechanism through which GLP-1 directly influences cardiac tissue, owing to its broad actions in other tissues, such as blood vessels.⁵

Semaglutide is a glucagon-like peptide-1 (GLP-1) analog treatment for type 2 diabetes. Two cardiovascular outcome trials revealed that semaglutide administration resulted in fewer major adverse cardiovascular events in subjects with type 2 diabetes at a high risk of cardiovascular events.^{7,8}

In an animal model of acute inflammation, semaglutide decreased the levels of plasma markers of systemic inflammation, downregulated multiple inflammatory pathways compared to controls, and was associated with a significant reduction in plaque lesion development,⁹ while other findings revealed only minor changes in some inflammatory markers.¹⁰

The present study was designed to investigate the protective effects of different semaglutide doses on DOX-induced cardiotoxicity in rats.

Materials and Methods

Thirty-five female Wistar albino rats weighing 200–250 g were purchased from the animal house of the University of Sulaimani and maintained in well-ventilated plastic cages at a temperature of $25 \pm 2^{\circ}$ C and humidity of $55 \pm 5\%$ under a 12 h dark/light cycle for 2 weeks before the experiment. The experimental protocols met the Guidelines for Animal Experimentation and were approved by the Ethical Committee of the University of Sulaimani (Registration Number: PH86-23), following the Institutional Animal Ethics Committee. This study was conducted in accordance with the Canadian Council on Animal Care (CCAC) guidelines, 1998. The rats were provided with standard laboratory chow and water ad libitum. All animals were randomly divided into five groups, and the doses and routes of administration of each treatment group were chosen based on previous studies, by thoroughly reviewing the existing literature on the use of SEM in animal studies.^{11–13} The groups comprised seven animals each, as follows.

- Negative control (NC): received distilled water via the s.c. route for 7 days.
- Positive control (PC): received distilled water via the s.c. route for 7 days; on day 7, they received a single dose of DOX I.P (12 mg/kg).
- Semaglutide (low dose) group (SL): received 0.06 mg/kg s.c. for 7 days + single dose of DOX as I.P (12 mg/kg) on day 7.
- Semaglutide (moderate dose) group (SM): received 0.12 mg/kg s.c. for 7 days + single dose of DOX I.P (12 mg/kg) on day 7.
- Semaglutide (high dose) group (SH): received 0.24 mg/kg s.c. for 7 days + single dose of DOX (12 mg/kg) on day 7.

On day 8, all animals were sacrificed, blood samples were collected by cardiac puncture and sent for measurement of biochemical and inflammatory parameters. The blood for the biochemical tests and the extracted heart were labeled and investigated by blind technicians and histopathologist to minimize bias, and the statistics was also conducted by a blind statistician.

Biochemical Tests and Pro-Inflammatory Markers

Blood was collected by cardiac puncture at the end of the study on day 8, centrifuged, and sera were separated and used for assessment of serum troponin T, total lipid profile [TC (total cholesterol), TG (triglyceride), LDL (low-density

lipoprotein), and HDL (high-density lipoprotein)], LDH, and CPK using Elecsys and Cobas e411 analyzers (Germany) according to the manufacturer's instructions. Pro-inflammatory marker (VCAM-1), was determined using (Bioassay Technology Laboratory) according to the manufacturer's instructions. The (VCAM-1) kit is an Enzyme-Linked Immunosorbent Assay (ELISA). The plate has been pre-coated with Rat VCAM-1 antibody. VCAM-1 present in the sample is added and binds to antibodies coated on the wells. Following adding specific antibodies of the test and incubation, the absorbance is measured at 450 nm.

Determination of Atherogenic Indices

The atherogenic indices were calculated as follows:¹⁴

Atherogenic index in plasma = Log([Triglycerides]/[HDL cholesterol])

Cardiac risk ratio = [Total cholesterol]/[HDL cholesterol]

Histological Technique Procedure

After animal sacrifice with a chloroform overdose inside the inhalation chamber, post-mortem inspection was performed by collecting heart tissues for histological procedures. Briefly, tissue samples were placed in tissue cassettes and fixed with 10% formaldehyde solution for 48 h. The dehydration step began by passing the samples through a series of ascending ethanol alcohols, followed by cleaning with xylene. The next step was the process of sample embedding and blocking with melted paraffin using an automated wax embedder at $(60-70^{\circ}C)$. Paraffinized tissue samples were sectioned to 4 μ m thickness using a rotary microtome and fixed on a glass slide. Tissue slides were deparaffinized, cleaned with xylene solution for half an hour and dried. Finally, the fixed sections were stained with Harris' hematoxylin and eosin solution, cleaned with a series of xylene solutions, coverslipped, and examined by an anonymous pathologist.

Semiquantitative Lesion Scoring

Scoring within the myocardial sections, including vascular congestion, some degenerative changes were evaluated and measured in the area of μ m, and statistically assessed as the mean percentage. Inflammatory and myocardial degenerative cells were counted in a total of ten fields randomly chosen under high-power magnification (1000×), and the mean average was calculated as a percentage. The mean percentage of all calculated values was expressed using the following lesion scoring and grading system (score 0–10% no lesions; score 10–25% mild; score 25–50% moderate; score 50–75% severe; score 75–100% critical lesions).

Statistical Analysis

GraphPad Prism7 was used for statistical analysis. The values represent mean \pm standard deviation (SD) of the measured parameters. One-way analysis of variance (ANOVA) was applied for the comparisons between different groups followed by Bonferroni multiple comparison tests. The results were considered statistically significant when the *p*-value was <0.05.

Results

Effect of Semaglutide on Body Weight and Relative Organ Weight (Figure I)

The SL group showed a significant reduction in total body weight (***p = 0.0013) compared with the positive control group (Figure 1A). Furthermore, the SM and SH groups showed a highly significant reduction in total body weight the actual p value (****p < 0.0001) compared with the positive control group. The SM group showed a significant increase (*p=0.0341) relative organ (heart) weight (Figure 1B).

Effect of Semaglutide on Lipid Profile, Plasma Atherogenic Index, Cardiac Risk Ratio, and LDL/HDL Ratio (Figure 2)

The SM group showed a significant reduction in cholesterol levels (*p= 0.0199), while the SH significantly reduced cholesterol levels (**p= 0.0077) the actual value of (p= 0.0077), (Figure 2A). The SH group showed significantly



Figure I Effect of semaglutide on body weight and relative organ weight. Notes: Effect of different doses of semaglutide on (**A**) the change of total body weight and (**B**) relative organ weight. Values were presented as mean \pm S.D (n = 7 animals in each group); values with (*) are significantly different from the positive control using ANOVA and post hoc test (*p < 0.05), (***p < 0.01), and (***p < 0.001).

reduced LDL levels (*p= 0.0245) (Figure 2C). No significant differences were observed in plasma TG, HDL, atherogenic index, cardiac risk ratio, or LDL/HDL ratio (Figure 2B, D, E, F and G respectively).

Effects of Semaglutide on Cardiac Biomarkers and Inflammatory Markers (Figure 3)

Semaglutide at all doses reduced CPK levels but did not reach a significant level (Figure 3A). The SL group showed a significant reduction in troponin level (*p=0.0344). Both the SM and SH groups were able to reduce serum troponin levels, but did not reach a significant level (Figure 3B).

Serum LDH levels were reduced by all three doses of semaglutide when compared with the positive control group, but the difference was not significant (Figure 3C). All semaglutide groups showed increased levels of VCAM-1, but the difference was not statistically significant (Figure 3D).

Histopathology Results: (Table 1), (Figure 4)

Table 1 demonstrates the semiquantitative assessment of heart sections, which showed a significant p < 0.05 reduction in the percentage of degenerative myocardial cells and inflammatory cells, in addition to a significant decrease in the area of fatty infiltration and vascular congestion in SH group (DOX+SEM high dose) in comparison with PC group [PC(DOX) 12 mg/kg], which showed a highly significant increase in lesion severity. Moreover, morphometric evaluation of histopathological lesions in SL group [(DOX+SEM low dose)] and SM group [DOX+SEM (moderate dose)] reveals significant p < 0.05 attenuation in lesion severity when compared with PC group. Furthermore, the scoring and grading of lesion severity were significantly reduced in the high-dose SEM group compared to the low- and moderate-dose groups.

Figure 4 (Photomicrograph of the heart) shows severe and diffuse infiltration of adipocytes together with inflammatory cells within the heart parenchymal tissue in the PC group (DOX group) compared to that in the negative control group (NC). Histopathological results of heart sections in all treatment groups show a significant alleviation in lesion severity, apparently by the decreased number of inflammatory and degenerative cells, together with the reduction of area of fatty infiltration and blood vessel congestion, the results are still more significant in SH group (DOX+SEM high dose) in comparison to other treatment groups as shown in (Figure 4).



Figure 2 Effect of semaglutide on lipid profile, plasma atherogenic index, cardiac risk ratio, and LDL/HDL ratio.

Notes: Effect of different doses of semaglutide on (A) Cholesterol, (B) TG, (C) LDL, (D) HDL, (E) plasma atherogenic index, (F) cardiac risk ratio, and (G) LDL/HDL. Values were presented as mean \pm S.D (n = 7 animals in each group); values with (*) are significantly different from the positive control using ANOVA and post hoc test (*p < 0.05), (**p < 0.01), and (***p < 0.001).



Figure 3 Effects of semaglutide on cardiac biomarkers and inflammatory markers. Notes: Effect of different doses of semaglutide on (A) CPK, (B) serum troponin, (C) serum LDH, and (D) VCAM-1. Values were presented as mean \pm S.D (n = 7 animals in each group); values with (*) are significantly different from the positive control using ANOVA and post hoc test (*p < 0.05), and (**p < 0.01).

Discussion

The pathogenesis of DOX-induced cardiotoxicity is complex and may involve numerous signaling mechanisms such as free radical stress, calcium overloading, mitochondrial dysfunction, and dysregulation of iron homeostasis.¹⁵ The hypothesis of the current study is to focus on the cardioprotective role of semaglutide in attenuating doxorubicin-induced cardiotoxicity in rats by downregulating the inflammatory response.

The results of the present study demonstrated a significant ***p < 0.001 reduction in total body weight after treatment with SEM in the SL group and a highly significant ***p < 0.0001 reduction in the SM and SH groups when compared with the doxorubicin-treated group. This is in accordance with several clinical trials that reported a decrease in body weight after treatment with semaglutide.^{16–18} Furthermore, an animal study also revealed lowered body weight following administration of semaglutide.¹¹ A recent systematic review and meta-analysis showed that weekly subcutaneous injection of semaglutide resulted in sustainable weight loss and improve cardiometabolic risk factors in overweight or obese non-diabetic individuals.¹⁹ The mechanism behind the resulted weight reduction may be due to the diverse Table I Semiquantitative Assay of Heart Sections

Experimental Groups N=7	Inflammatory Cells (Mean %)**	Cellular Degeneration (Mean %)	Fatty Infiltration* (Mean %)	Vascular Congestion* (Mean %)	Lesion Scoring (0–100%)	Lesion Grading
NC	4.29% ^{A#}	3.12% ^A	7.45% ^A	7.83% ^A	0–10%	No lesion
PC (DOX 12 mg/kg)	79.38% ^E	82.56% ^E	81.33% ^E	91.43% ^E	75–100%	Critical
SL (DOX+SEM 0.06 mg/kg)	72.44% ^D	68.93% ^D	61.24% ^D	73.68% ^D	50–75%	Severe
SM (DOX+SEM 0.12 mg/kg)	53.63% ^D	56.41% ^D	52.13% ^D	67.52% ^D	50–75%	Severe
SH (DOX+SEM 0.24 mg /kg)	37.82% ^C	44.65% ^C	39.22% ^C	48.32% ^C	25–50%	Moderate

Notes: Myocardial degenerative and inflammatory cells are calculated as the mean percentage of cells. Areas of fatty infiltration and vascular congestion were estimated using the mean percentage (μ m). *Is the different morphological lesions described in mean percentage of (μ m) **Each value represents mean ± SDM (n=7). *Statistical comparison among groups: Mean values with different capital letters are significantly different (p < 0.05). NC: Negative control group (only distilled water); PC: Positive control group [doxorubicin (DOX) 12 mg/kg]; SL: Low dose SEM group [SEM 0.06 mg/kg + DOX 12 mg/kg]; SM: Moderate dose SEM group [SEM 0.12 mg/kg + DOX 12 mg/kg]; SH: High dose SEM group [SEM 0.24 mg/kg + DOX 12 mg/kg].

mechanisms of semaglutide via suppressing glucagon secretion, delaying stomach emptying, decreasing fat absorption, and reducing food intake, leading to weight reduction. Semaglutide appears to be at least as effective as other GLP-1s, if not more so, according to evaluations.²⁰ Regarding the relative organ weight, the significant increase in intermediate dose of SEM remains unknown. In the current study, only female rats were included, as it has been reported that androgens act as a protective measure against the development of DOX-induced cardiotoxicity.²¹



Figure 4 Photomicrograph of the heart.

Notes: Photomicrograph of heart from groups; (G1) NC: received D.W, revealing typically structured myocardial cells (MC); the section reveals the cross-sectional structure of some coronary artery branches [BV (blood vessels)] together with low-grade inflammatory cell (IC) infiltration within the cardiac mesenchymal tissue. (G2) PC: DOX showed significant blood clots within the cardiac chambers (CB) mixed with many sedimented purple inflammatory cells (IC). Presence of edematous fluid (ED) among the myocardial cells (MC) within stromal tissue, together with some vascular congestion. (G3) SL: Group 3 (low dose) received 0.06 mg/kg of SEM+DOX, display clear longitudinal section vascular congestion (VC), together with the presence of perivascular edema (ED) and significant infiltration of inflammatory cells (IC), in addition to a significant congestion of some blood vessels (BV) in the given section. Myocardial cells (MC) reveal a typical arrangement with an acidophilic cytoplasm. (G5) SH: Group 5 (high dose) received 0.24 mg/kg of SEM+DOX, display mild cellular fatty degeneration (yellow arrow) together with low grade vascular congestion (VC). The section also revealed congestion in other blood vessels (BV), with typical eosinophilic myocardial uscle cells (MC) arranged in a way manner. H&E stain. Scale bars: 4 mm.

Regarding the lipid profile, the study showed that animals administered only doxorubicin had a disturbed lipid profile, which involved the elevation of serum cholesterol, TG, and LDL levels. Doxorubicin administration led to dysfunctional lipid and fatty acid storage.²² Semaglutide in moderate and high doses significantly reduced serum cholesterol levels (*p < 0.05, **p < 0.01, respectively). Furthermore, serum TG and LDL levels were reduced. This indicates the positive role of the novel GLP-1 receptor agonist semaglutide in protection against hyperlipidemia and its translation into cardioprotection. This finding is consistent with a review that revealed that GLP-1 receptor agonists are associated with significant improvements in cardiovascular outcomes related to an ameliorated lipid profile.²³ However, the levels of HDL were also reduced after the administration of semaglutide but not significantly, which is contrary to the abovementioned improvement. This finding is in agreement with that of a study conducted in China, which concluded that GLP-1 receptor agonists were associated with moderate reductions in LDL cholesterol, total cholesterol, and triglycerides but no significant improvement in HDL cholesterol.²⁴ Therefore, the atherogenic index of plasma was not reduced by semaglutide treatment, since the atherogenic index of plasma is calculated using the formula log (TG/HDL cholesterol). The atherogenic index is a powerful predictor of atherosclerosis and coronary heart disease.²⁵ Moreover, another study also revealed no change in HDL levels but improved atherogenic index of plasma after treatment with GLP-1 receptor agonist.²⁶ In longer-term trials, one to two years of semaglutide treatment when compared to placebo or sitagliptin was found to slightly improve lipid parameters in T2D individuals.⁸ Despite the short-term use of semaglutide in the current study, the findings revealed no significant improvement in HDL levels.

Cardiac muscles contain enzymes that are essential for metabolic activity. Measurement of these cardiac markers determines heart function. Parameters such as serum CKP, LDH, and troponin levels are diagnostic markers of myocardial injury.^{27,28} Creatine phosphokinase CPK occurs normally in heart tissue, skeletal muscles, and the brain. However, during muscle injury, CPK leaks into the bloodstream. Accordingly, an elevated CPK level indicates muscle damage.

The results of the current study revealed that doxorubicin administration in the DOX-treated group increased the levels of cardiac markers, indicating DOX-induced cardiotoxicity. Compared to the group of rats administered only doxorubicin, the levels of cardiac markers, such as CPK, LDH, and troponin, were restored in rats treated with semaglutide. Doxorubicin-treated rats showed elevated creatine phosphokinase (CPK) release from the heart. One study found that doxorubicin toxicity was revealed by elevated serum CPK levels in nontransgenic mice.²⁹ Moreover, lactate dehydrogenase (LDH) release was measured to assess the extent of cardiomyocyte damage. Several studies have demonstrated that treatment with GLP-1 receptor agonists results in reduced serum lactate dehydrogenase (LDH) levels.^{30–32}

A post hoc analysis reported that a 24% reduction in cardiovascular adverse events was achieved by semaglutide compared with placebo.⁷ Semaglutide 2.4 mg subcutaneous once-weekly treatment has been shown to significantly improve cardiovascular risk factors.³³

A study conducted in the United States of America found that females with breast cancer receiving anthracyclines had elevated levels of cardiac troponin, indicating cardiotoxicity.³⁴ The administration of semaglutide in the current study resulted in a significant reduction in the level of troponin in the low-dose group, indicating the cardioprotective property of this drug in the rat model.

The presence of a direct effect on the heart is supported by the expression of the GLP-1R G-protein-coupled receptor in cardiomyocytes. The stimulation of AMP-activated protein kinase (AMPK) signaling and the subsequent translocation of the insulin-regulated glucose transporter GLUT4 could be facilitated by GLP-1 signaling. The elevated levels of phosphorylated AKT seen in mice treated with GLP-1 R agonists probably contribute to enhanced myocardial glucose absorption because insulin-stimulated activation of AKT results in GLUT4 translocation. The increased absorption of glucose may be caused by activation of AMPK α . AMPK is an important molecular contributor in energy homeostasis.^{35,36} Early biomarkers, like creatine kinase, are the gold standard for detecting and monitoring cardiac dysfunction.³⁷ Its levels will be higher in cardiotoxicity brought on by chemotherapy and myocardial infarction.³⁸ Furthermore, lactate dehydrogenase was subsequently discovered, employed in the setting of acute myocardial infarction, and shown to be a sign of myocardial damage. Currently, the evaluation of serum level of troponin is one of the most valuable biomarkers in the early diagnosis of myocardial infarction. Cardiac troponins are essential components of the actin protein in the heart and are involved in controlling intracellular calcium concentrations and cardiac muscle activity throughout the contraction/relaxation cycle.³⁹ Therefore, the correction of the abovementioned biomarkers as well as lipid profile of the current study, can be translated into reduced cardiotoxicity as a result of semaglutide treatment.

The overall results of the current study showed that cardiac biomarkers were reduced by semaglutide; however, not all reached a significant level. A previous study revealed that only minor changes were detected in some inflammatory markers following semaglutide administration.¹⁰ The histopathological findings of the present study support the positive effect of semaglutide on doxorubicin-induced cardiac injury.

This study had several limitations and challenges in interpreting the results. Such as the relative organ weight that did not reflect the results obtained from the other cardiometabolic biomarkers, another limitation was due to the short-term treatment period and exposure to cardiotoxic agent, the cardiac risk ratio changes were not significant. Moreover, in the current study, only female rats were included. It will be important to detect sex specific differences in heart biology and physiology in future studies. Altogether, the present study highlights the cardioprotective impacts of the novel SEM in cardiotoxicity induced by DOX in female Wistar albino rats.

Conclusion

Semaglutide may be associated with cardioprotective properties in doxorubicin-induced cardiotoxicity in a rat model by lowering serum biochemical markers of cardiotoxicity, such as troponin, CPK, and LDH, as well as lipid-lowering properties. However, further in-depth animal studies for longer periods are required to confirm the currently discovered cardioprotective effects of semaglutide.

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Disclosure

The author reports no conflicts of interest in this work.

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