Journal of Pioneering Medical Sciences
Received: October 14, 2025 | Accepted: January 27, 2026 | Published: March 05, 2026
Volume 15, Issue 02, Pages 170-175

DOI https://doi.org/10.47310/jpms2026150223

The Teratogenic Effect of Semaglutide Drug on the Histological Structure of the Lungs in the Albino Mouse (*Mus musculus*)

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Abstract **Objectives: Background:** The current study aimed to determine the teratogenic effect of the drug Semaglutide on the histological structure of the lungs in the albino mouse. **Methods:** The experimental mice were injected with the drug Semaglutide for a period of thirty days at a concentration of 14 mg/kg/day. Twenty male albino mice of *Mus musculus* type were used. They were randomly divided into two groups. Each group included 10 mice. The animals were randomly divided into two groups. The control group was administered physiological saline for 30 days, whereas the treated group was administered Semaglutide at a dose of 14 mg/kg/day for 30 consecutive days. At the end of the experimental period, the animals were anesthetized and sacrificed. The lungs were removed and fixed, then embedded in paraffin wax. Tissue sections were prepared and stained with Hematoxylin and Eosin (H&E). The sections were examined under a light microscope. **Result:** The results of examination of histological sections of the lungs in the experimental groups dosed with the drug showed the occurrence of pathological histopathological changes represented by the detachment of the epithelial layer of the bronchioles from the layer of the basement membrane on which it rests and its accumulation in the lumen of the bronchioles, with the occurrence of necrosis and degeneration in their walls and congestion of the blood vessels, accompanied by bleeding in some parts. Also, increased the thickness of the alveolar walls and their ducts, in addition to the expansion of the alveoli, degeneration and destruction of the alveolar walls, infiltration of inflammatory cells and thickening of the nuclei, swelling and bronchial degeneration were observed, in addition to the occurrence of fibrosis. The lungs showed blood vessel deformation and congestion, alveolar bleeding, fibrosis around vessels and bronchioles and swollen alveolar cells with thickened nuclei.

Key Words Semaglutide, Teratogenic Effect, Lungs, Histological Structure, Albino Mouse

INTRODUCTION

Semaglutide, with a chemical formula of C187H291N45O59 and a molecular weight of 4114 g/mol, is an antidiabetic polypeptide pharmaceutical. It consists of a 31-residue linear chain of amino acids linked by peptide bonds, representing a complex biopharmaceutical structure designed to provide therapeutic benefits in glycemic control [1]. Semaglutide is a GLP-1 analog derived from recombinant human GLP-1, modified through biotechnological techniques to allow the addition of a side chain. This molecular fine-tuning produces a pharmaceutical agent that mimics the physiological effects of endogenous GLP-1 while providing therapeutic properties [2]. Semaglutide was first imagined and produced by the Danish pharmaceutical firm Novo Nordisk in 2012. Then, the injectableive formulation of this drug was approved by prestigious regulatory agencies including the European Commission, Health Canada and their Japanese counterpart, all in 2018 [3]. Semaglutide was ranked 129th on the list of most commonly prescribed drugs in the US in 2020. More than 4 million prescriptions were issued in total, reflecting the widespread use of this drug since it was approved by the US Food and Drug Administration (FDA) in 2017 [4,5]. This drug may be used alone or in combination with other antidiabetic drugs and it is commonly used as an adjunct to diet and exercise programs in the treatment of type 2 diabetes mellitus. [6]. Beyond glycemic control, Semaglutide has been investigated for potential neuroprotective effects, appetite suppression and long-term weight management for obesity [7,8]. It is available in both subcutaneous injectable form (Ozempic) and oral form (Rybelsus), with additional approval for weight management under the brand name Wegovy [9]. Semaglutide acts as a GLP-1 receptor agonist and is designed to mimic the (up to 2-fold) natural incretin hormone, i.e. Glucagon-Like Peptide-1 (GLP-1).

In doing so, it also boosts the release of insulin, a key hormone that reduces blood sugar levels. [10]. Moreover, it has also been demonstrated that the miR may play an important role in pancreatic -- cell proliferation which is critical for insulin synthesis and secretion [11]. Furthermore, it inhibits glucagon which plays a crucial role in increasing glycogenolysis (release of stored carbohydrates from the liver) and gluconeogenesis (fresh glucose production) [12]. This dynamic modulation adds to the plethora of regulation of glucose homeostasis, providing a fine- tuning mechanism in diabetes treatment. Suppression of glucagon, in combination with the stimulation of insulin secretion and possibly also pancreatic β-cell growth underline all intricate ways by which semaglutide could aid metabolic control [13]. As suggested by earlier studies, the reduced food intake induced by semaglutide is achieved via a dual mechanism: (a) appetite suppression and (b) slowing digestion in the stomach. This attenuation does not only lead to a reduction in energy intake but also is crucial for the stimulation of a decrease in total body adipose mass. The delicate balance of these physiological effects situates semaglutide as a multi-factorial mediator in appetite management and body weight regulation [15]. Common side effects of Semaglutide include nausea, vomiting, diarrhea, constipation, headache, fatigue, dyspepsia, abdominal bloating, belching and gastroenteritis [16]. In patients with type 2 diabetes, monitoring for hyperglycemia or hypoglycemia is recommended, as well as for gastroesophageal reflux symptoms. Rare but serious complications, such as pancreatitis, gastroparesis and bowel obstruction, should also be considered in clinical management [17,18]. From this extensive body of clinical trials, the serological profile of elevations in serum enzymes with semaglutide treatment was similar to that with placebo or comparator drugs [19]. Remarkably, no instances of clinically apparent liver damage were observed in the course of these experiments. In fact, other GLP-1 analogs such as semaglutide have been linked to a notable reduction in serum aminotransferase levels and an amelioration of hepatic steatosis with treatment [20]. This suggests that they may have therapeutic potential for nonalcoholic fatty liver disease. A literature review does not reveal any published case reports of hepatotoxicity associated with semaglutide post-approval and liver injury is a noticeably excluded adverse event in the product insert [21]. Therefore, the observed semaglutide-related liver injury is quite rare (if it exists at all), which supports its benign hepatic safety [22].

METHOD

Animals of Experiments

This study used 20 male albino mice of the Mus musculus type; their ages ranged between 3-4 months and their weights ranged between 25-22 grams. They were placed in metal cages for raising mice. The cages were furnished with sawdust and the animals were subjected to similar laboratory conditions, at a temperature of 20-25°C and an illumination period of 12 hours of light and 12 hours of darkness. The animals were given water and food freely and the animals were left for ten days to adapt to the laboratory conditions.

Drug Preparation

Semaglutide was purchased from a local pharmacy in Baghdad with the name Rybelsus) produced by Novo Nordisk® Company, as tablet (14 mg/kg). Tablets were reduced to powder with the aid of a pestle and dissolved in distilled water according to the human dosage.

Experimental Animals

A total of 20 male albino mice (*Mus musculus*) were randomly assigned into two groups of 10 animals each. The control group received physiological saline orally once daily for 30 consecutive days, while the treated group received Semaglutide at a dose of 14 mg/kg/day orally for 30 consecutive days. Randomization was performed using a simple random allocation method to ensure unbiased group assignment. At the end of the treatment period, the animals were anesthetized and sacrificed and the lungs were collected. Tissue samples were fixed, embedded in paraffin, sectioned and stained with Hematoxylin and Eosin (H&E).

Preparation of Histological Sections

The histological section of lung organ sample was processed with technique described by Suvarna *et al.* [23] Histological sections were examined under a light microscope. Representative areas were selected systematically to avoid selection bias. Histopathological changes were evaluated using a semi-quantitative scoring system based on the severity of lesions, including vascular congestion, alveolar hemorrhage, fibrosis and cellular degeneration. Each parameter was scored by two independent observers to ensure reproducibility. Statistical justification for the sample size was based on previous studies assessing similar pulmonary effects in mice, ensuring sufficient power to detect significant differences between groups.

Microscopic Test and Imaging

The prepared glass slides were tested to identify and determine the histological-pathological differences and changes occurring in the studied tissues using an Saba Mustanseriaoptical microscope. Suitable areas of these slides were selected and then photographed using a Phase Contrast optical microscope camera.

RESULTS

Treating mice with the drug Semaglutide at a concentration of 14 mg/kg of body weight for 30 days led to the emergence of pathological effects, as the bronchioles and bronchioles were characterized by the shedding of the epithelial layer from the basement membrane layer on which it rests and its accumulation in the lumen of the bronchioles, with necrosis and degeneration occurring in their walls, as in Figure 1.

In addition to what was mentioned above, it was observed that there was a clear infiltration of inflammatory cells around the bronchioles, especially the blood vessels and a change in the thickness of the bronchioles, as in Figure 2.

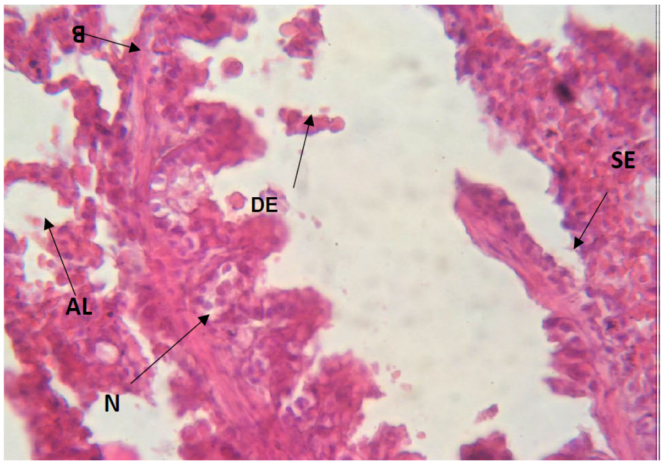

Figure 1: Lung Cross-Section of a Mouse from the Experimental Group Treated with 14 mg/kg/day of Semaglutide for 30 days. Degenerative Changes are observed in the Lung Tissue, Including Hydropic Degeneration of Alveolar Epithelial Cells and Desquamation into the Bronchiolar Lumen (H&E Stain, 40× Magnification)

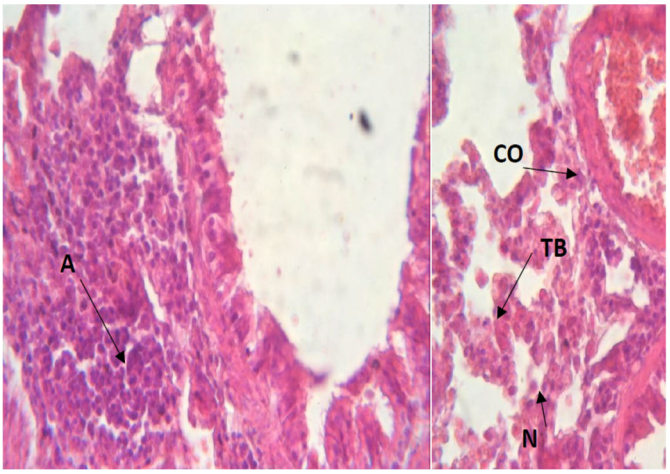

Figure 2: Lung Cross-Section of a Mouse from the Experimental Group Treated with 14 mg/kg/day of Semaglutide for 30 days. The Section Shows Inflammatory Cell Infiltration around the Bronchiole and Blood Vessels (A), Vascular Congestion (VC), Thickening of the Alveolar Septa (AS) and Focal Necrosis (N) (H&E Stain, 40× Magnification)

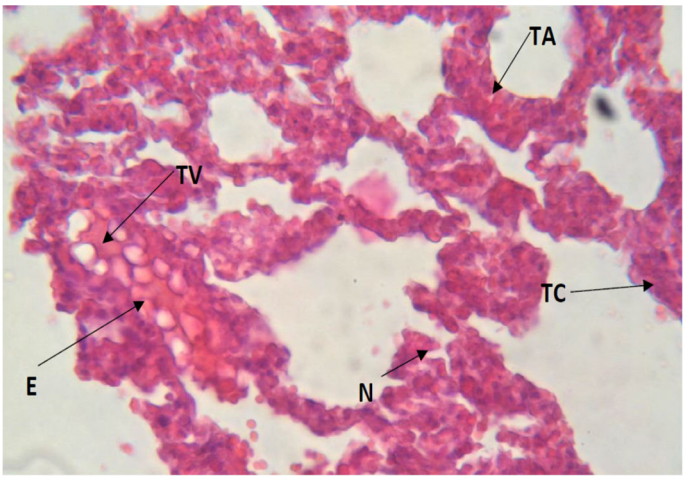

Figure 3: Lung Cross-Section of a Mouse from the Experimental Group Treated with 14 mg/kg/day of Semaglutide for 30 days. The Section Shows Alveolar Necrosis (N), Cytoplasmic Vesicles Indicating Active Transport (TV), Interalveolar Edema (IE), Thickening of the Alveolar Duct Wall (TC) and Thickening of the Alveolar Septa (AS) (H&E Stain, 40× Magnification)

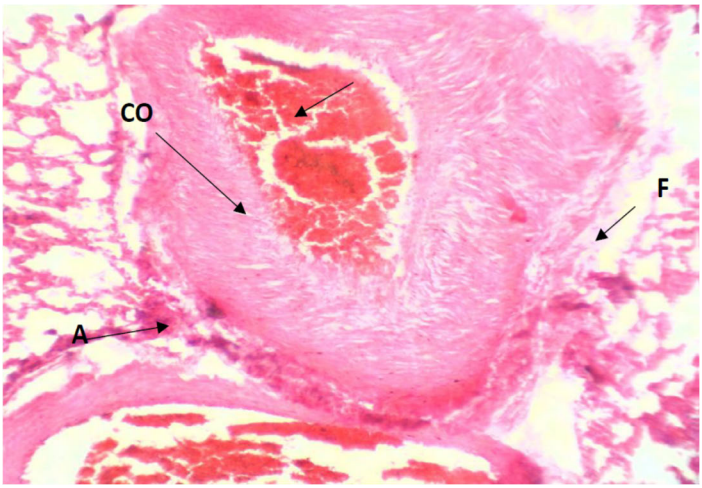

Figure 4: Lung Cross-Section of a Mouse from the Experimental Group Treated with 14 mg/kg/day of Semaglutide for 30 days. The Section Shows Vascular Deformation and Congestion (VC), Fibrosis (F) and Inflammatory Cell Infiltration (A). (H&E Stain, 40× Magnification)

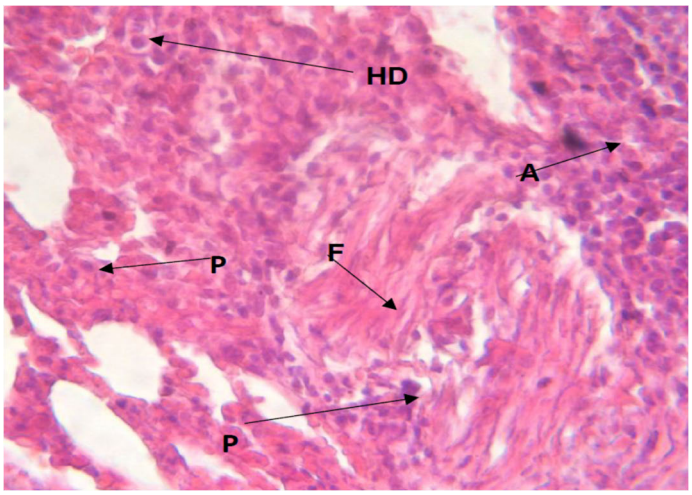

Figure 5: Lung Cross-Section of a Mouse from the Experimental Group Treated with 14 mg/kg/day of Semaglutide for 30 days. The Section Shows Hyaline Degeneration (HD), Fibrosis (F), Inflammatory Cell Infiltration (A) and Nuclear Enlargement (P). (H&E Stain, 40× Magnification)

Histological examination revealed disruption of the alveolar walls and alveolar duct walls, resulting in enlargement of some alveoli. In contrast, increased cellularity of the alveolar septa was observed, causing narrowing of other alveoli. Necrosis and rupture of alveolar cells were also noted, along with interalveolar edema. These findings are illustrated in Figure 3, which also shows the presence of active transport vesicles.

It is also noted that there is deformation and severe congestion in the blood vessel, with bleeding between the alveoli, in addition to severe fibrosis around the blood vessels and some bronchioles. In addition to the changes previously mentioned, the study showed the presence of thickening of cell nuclei and hydropic degeneration in the alveolar cells, where the cell appeared swollen with a centrally located nucleus, in addition to the appearance of fibrosis around one of the blood vessels, as shows in Figures 4 and 5.

DISCUSSION

Lung damage is a frequent cause of morbidity and mortality in patients receiving either cytotoxic or non-cytotoxic medications. Numerous studies have documented that drugs such as immunosuppressants, antibiotics, chemotherapeutic agents and antiarrhythmic medications can induce Interstitial Lung Disease (DILD) [24].

The present study confirmed that administering Semaglutide at a dose of 14 mg/kg/day for 30 days in mice led to multiple histopathological alterations in lung tissue. These changes likely result from the direct toxic effect of the drug or its metabolic derivatives. Pulmonary toxicity induced by drugs has become increasingly recognized, with over 100 medications known to cause lung injury. Because such injuries can be fatal, early detection and understanding of the underlying mechanisms are essential [25].

Histological analysis revealed vascular congestion in the lungs, which may be attributed to decreased blood flow, impaired cardiac function affecting systemic circulation, or direct vascular injury caused by the drug. This observation aligns with previous findings; Zoccali *et al.* [26] reported that pulmonary congestion can result from elevated pulmonary artery pressure due to asymmetric pulmonary vasoconstriction induced by hypoxia. Congestion may also arise from an increase in blood flow or blood volume, or from reduced flow due to high pulmonary vascular or cardiac filling pressures [27].

Furthermore, vascular congestion can be associated with disruption of the endothelial barrier, which reduces vascular elasticity and increases permeability. This, in turn, may trigger an inflammatory response through the activation of oxidative stress signaling pathways [28]. Such mechanisms could explain the inflammatory cell infiltration, edema and structural changes observed in the lung tissue of Semaglutide-treated mice in the present study.

The results also showed that there was degeneration and necrosis of cells and destruction of alveolar walls. The main reason for the damage occurring to various cells in the lung could be due to the negative effect of the drug on the histological structure of the lung.

Inhaled or systemically given chemicals that bioactivate to more reactive molecules frequently cause toxicity to lung tissue cells. Oxygenation, reduction, or dealkylation, as well as the production of reactive electrophilic species such epoxides, quinones, methylene imines and acyl radicals, cause biotransformation. These species interact with the cell's biomolecules, changing them or creating covalent connections. As a result, many substances that induce toxic lung injury damage target cells following metabolic activation rather than being hazardous to the lung itself. Despite this, the lung has numerous enzyme pathways that may break down harmful and alien compounds. However, it is generally agreed that the Cytochrome P (CYP) family of enzymes is the main system that catalyzes the oxidative metabolism and metabolic activation of most toxins and drugs [29].

Alveolar epithelial cell injury is induced by various stimuli including oxidative stress, endoplasmic reticulum stress and the formation of reactive oxygen species [30]. The resulting inflammation can also contribute to cell damage and tissue destruction [31]. Necrosis and cell death can also occur as a result of ischemia [32].

Cell damage and degeneration may result from a significant decrease in antioxidant levels in lung tissue and an increase in lipid peroxidation through oxidation by Reactive Oxygen Species (ROS) of fatty acids, which leads to irreversible cell damage. It is known that membrane lipids, proteins, nucleic acids and DNA molecules are the most sensitive cellular formations to Reactive Oxygen Species (ROS), which cause cell injury, membrane damage, protease activation and DNA damage [33].

The presence of the drug or one of its metabolic derivatives can lead to its interference with the mitochondrial respiratory chain, which leads to the formation of oxygen free radicals. These free radicals cause lipid oxidation and damage to endothelial cells of alveolar capillaries and pulmonary cells [34].

Also, the destruction of the alveolar wall can be caused by proteolytic enzymes action, which affects the Extracellular Matrix (ECM) components and the integrity of its components, especially the elastic fibers [35].

CONCLUSION

In some sections, the walls of blood vessels appeared thickened due to an increase in the muscular layer. This structural change may result from inflammation, pulmonary hypertension, or partial obstruction/interruption of blood flow. Myocyte hypertrophy can be explained by a decrease in the nuclear-cytoplasmic ratio, accompanied by increased density of mitochondria and sarcoplasmic reticulum [36].

Edema was also observed in certain sections, likely caused by disruption of the cell membrane, leading to altered cellular fluid regulation. Neutrophil-mediated hyperinflammation is thought to compromise the alveolar-capillary barrier, contributing to noncardiogenic pulmonary edema and impaired gas exchange [37]. Assaad *et al.* [38] reported that systemic inflammatory responses are a key factor in the development of lung edema.

The study further demonstrated infiltration of inflammatory cells, with severity varying according to the concentration of the administered drug. This infiltration may result from accumulation of the drug within pulmonary blood vessels. Enhanced transport of inflammatory cells across the endothelial lining, reflected by the presence of cytoplasmic vesicles (active transport vesicles), indicates an active role of the endothelium in cellular defense and tissue repair. These findings align with observations by Ahmed *et al.* [28].

Fibrosis was also detected in the lung tissue, indicating a detrimental effect of Semaglutide on pulmonary histology. This observation is consistent with reports by the British Lung Foundation [39], which state that fibrosis is a recognized side effect of certain medications.

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