

# Possible therapeutic effect of ghrelin and exosomes derived from mesenchymal stem cells on induced chronic pancreatitis of adult albino rats (Histological and Immunohistochemical Study)

## ABSTRACT

**Background:** Chronic pancreatitis (CP) is a disease characterized by permanent damage of the pancreas.

**Objective:** evaluate the possible therapeutic effect of ghrelin and exosomes derived from mesenchymal stem cells in the treatment of chronic pancreatitis.

**Materials and Methods:** Sixty-two adult male albino rats were randomly divided into six groups. Group I (control group). Group II (affected group): Rats were injected intraperitoneally by l-arginine at a dose of 500 mg/100g body weight that is 2.5 ml of l-arginine solution/100g body weight five times at three days intervals, dissolved in citrate buffer. Group III (recovery group). Group IV: CP treated with ghrelin. Group V: CP treated with MSCs derived exosomes. Group VI: CP treated with ghrelin and MSCs derived exosomes. Pancreatic specimens were taken and prepared for histological and immunohistochemical examination.

**Results:** Group II and III showed signs of degeneration. There were distorted acini with cytoplasmic vacuolation, decrease number of cells of islets, empty spaces between islets, dilated congested blood vessels and cellular infiltration. Furthermore, there was intense positive collagen fibers deposition, *iNOS* and [CD8](#) immunostaining. Groups IV and V showed improvement of some histological microscopic changes in group II, significant decrease ( $P < 0.01$ ) of group IV, V, VI compared with group II. While group VI showed histological architecture near to control group.

**Conclusion:** ghrelin and exosomes can treat chronic pancreatitis. However, better results can be obtained when exosomes were given with ghrelin.

**Key Words:** CP, ghrelin, exosomes, Masson trichrome, *iNOS* and [CD8](#).

## INTRODUCTION

Chronic pancreatitis (CP) is characterized by chronic inflammation of the acinar cells leading to progressive fibrosis of the pancreas leading to destruction of the exocrine functions of the pancreas. There are factors responsible for the development of CP involve hereditary factors, alcoholism, autoimmune injury and smoking<sup>1</sup>.

Current therapeutic options, such as lipase, acetaminophen or NSAIDs, octreotide can relief the pain. Surgical methods will use for patients when medical approach failed<sup>2</sup>.

Ghrelin is a 28 amino acid peptide. Oxyntic glands of gastric mucosa responsible for its secretion. It was endogenous ligand of the growth hormone (GH). Ghrelin can regulate food intake and energy expenditure<sup>3</sup>.

Exosomes are small sized (30–120 nm) extracellular vesicles (EVs)<sup>4</sup>. They are differing from microvesicles in size (50– 1500 nm) and shed from the budding of the plasma membrane. Exosomes play an important role in cell-to-cell communication by its contents, including lipids, RNAs, DNAs and proteins<sup>5,6</sup>. Exosomes when reach recipient cells deliver their cargoes, which can induce the intracellular signaling and affect the physiological or pathological status of recipient cells<sup>7</sup>.

The aim of this study was to evaluate the efficacy of ghrelin and exosomes derived from mesenchymal stem cells on L-arginine induced chronic pancreatitis on adult albino rats.

## **MATERIAL AND METHODS**

### **Drugs and Chemicals**

#### **L-arginine:**

Highly purified L-arginine hydrochloride in white powder form was obtained from (*El Ezaby Pharmacies*, Heliopolis, Cairo, *Egypt*). L-arginine solution was prepared by dissolving of L-arginine (2 g) in saline (8 ml) and then adjust volume to 10 ml with saline, so each 1 ml contained 200 mg of l-arginine<sup>8</sup>.

#### **Ghrelin:**

Ghrelin was obtained from (Sigma, St. Louis, MO, USA). Ghrelin solution was prepared by dissolving 1 mg of ghrelin acetate in 1 ml of Phosphate Buffer Solution (PBS) and then adjust volume to 25 ml with PBS. Ghrelin will be administered intraperitoneal with a single dose of ghrelin (20 µg/kg) for successive three days<sup>9</sup>.

#### **Exosomes derived from MSCs:**

Exosomes were prepared in the stem cell and molecular biology unit, central lab, cairo faculty of medicine. Exosomes were isolated from conditioned media of rat bone marrow derived MSC. Rats were injected intravenous with a single dose of 100 µg BMSC-EX diluted in 0.5 ml PBS<sup>10</sup>.