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The promising effect of linagliptin and/or indole-3-carbinol on experimentally-induced polycystic ovarian syndrome

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is one of the most common medical conditions that lead to female infertility worldwide. The aim of this study was to assess the effect of linagliptin and/or indole-3-carbinol (I3C) on PCOS in female rats. Fifty female Wistar rats were randomly allocated into five equal groups: Control group; Letrozole-induced PCOS group; Letrozole + Linagliptin group; Letrozole + I3C group and Letrozole + Linagliptin + I3C group. Body weight, body mass index, Lee index and ovarian indices were determined. Plasma levels of luteinizing hormone (LH), free testosterone, estradiol, progesterone, prolactin, fasting blood glucose (FBG) and fasting plasma insulin were measured. Quantitative Insulin Sensitivity Check Index (QUICKI) was calculated. Tissue antioxidant status, transforming growth factor beta 1 (TGF-β1), tumor necrosis factor alpha (TNF-α), interleukin 10 (IL-10) and Nrf2/HO-1 content were assessed. Histopathological and immunohistochemical examination of the ovaries were done. Linagliptin and/or I3C induced significant decrease in tissue TGF-β1, TNF-α, IL-10, plasma free testosterone, luteinizing hormone, progesterone, estradiol, FBG and insulin levels associated with significant improvement of insulin resistance whereas tissue Nrf2/HO-1 content and antioxidant enzymes were significantly increased compared to PCOS group. In addition, final body weight, final body mass and Lee indices were significantly decreased compared to PCOS group. Also, there was significant improvement of the ovarian morphology compared to PCOS group. This improvement was significant with linagliptin/I3C combination compared to the use of each of these drugs alone. In conclusion, linagliptin/I3C combination might represent a beneficial therapeutic modality for amelioration of PCOS.

1. Introduction

Polycystic ovarian syndrome (PCOS) is a medical condition that affects women's menstrual cycles, fertility, hormones, aspects of life and long-term reproductive health [1]. Up till now, the exact cause of PCOS is not fully understood. Hyperandrogenism, menstrual irregularities and insulin resistance are the most prominent features of PCOS. The lines of treatment of PCOS are directed towards these features to improve the clinical picture and decrease morbidity [2]. However, failure of the lines of therapy that are directed towards hyperandrogenism and insulin resistance necessitates the search for other lines of treatment that act on more specific molecular levels [3].

Linagliptin is one of dipeptidyl peptidase-4 (DPP-4) inhibitors that had recently entered the market for treatment of type 2 diabetes mellitus. It acts by increasing the hormones that stimulate the pancreas to produce more insulin and inhibit hepatic gluconeogenesis [4]. Recent studies reported that DPP-4 inhibitors may improve β-cell function and decrease insulin resistance which is the main stay in the pathogenesis of PCOS [5]. Moreover, linagliptin was proven to have an effect on the growth factors, the antioxidant defense mechanisms and the inflammatory cascade which may play a crucial role in the pathogenesis of PCOS. Taken together, these properties may give a promising role to linagliptin for management of PCOS [6].

Indole-3-carbinol (I3C) is produced by breakdown of the glucosinolate glucobrassicin, which may be found at high levels in cruciferous vegetables and is also available as dietary supplements [7]. I3C is considered as the subject of the ongoing research due to its possible anticancer, antioxidant, anti-inflammatory,

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antiapoptotic and anti-atherogenic properties [8]. Recent studies are directed towards assessment of the possible effects of I3C on various endocrine disorders. I3C and its derivatives were proven to have antiandrogenic and growth inhibitory effects which may ameliorate the pathologic events in PCOS [9]. Also, I3C and its metabolite 3, 3′- diindolylmethane were reported to attenuate hyperglycemia-mediated oxidative stress [10]. Moreover, I3C was proven to restore the estrogen levels to the normal values which may contribute to management of PCOS [11].

The aim of this study was to assess the effect of linagliptin and/or I3C on experimentally-induced PCOS in female rats. This was determined by assessment of the anthropometric indices, plasma levels of luteinizing hormone (LH), free testosterone, estradiol, progesterone, prolactin, fasting blood glucose (FBG), fasting plasma insulin and Quantitative Insulin Sensitivity Check Index (QUICKI). Also, tissue antioxidant status, transforming growth factor beta 1 (TGF-β1), tumor necrosis factor alpha (TNF-α), interleukin 10 (IL-10), nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and heme oxygenase-1 (HO-1) content were assessed in addition to pathological examination of the ovaries.

2. Materials and methods

2.1. Drugs and reagents

Letrozole was obtained from Natco Pharma Limited, Hyderabad, India. Linagliptin was acquired from Boehringer Ingelheim Pharma GmbH & Co. KG, Bib-erach, Germany. Carboxymethyl cellulose (CMC) was obtained from Sigma Pharmaceutical Company, Quesna, Egypt. I3C and all other reagents were purchased from Sigma-Aldrich Co. (St. Louis, Missouri, USA). Letrozole, linagliptin and I3C were suspended in 0.5% CMC solution.

2.2. Experimental animals

In this study, we used fifty female albino Wistar rats weighing about 100–150 g. They were allowed to acclimatize for two weeks before starting the experiment. The animals were kept in a special room at a constant temperature of 22 ± 3 °C with relative humidity of 55 ± 5% and exposed to 12 h light/dark cycle. They were fed with standard diet and water provided *ad libitum*. All the experiments were conducted according to the National Research Council's guidelines. Animal handling was followed according to Helsinki declaration of animal ethics.

2.3. Study design

All animals except the control group were orally administered with letrozole in a dose of 1 mg/kg by oral gavage once daily for 36 days [12]. Control group received only 0.5% CMC once daily orally for the whole period of the study. Vaginal Smears were collected daily and evaluated microscopically using Giemsa stain to confirm PCOS induction.

Animals were randomly divided into five groups consisting of ten rats in each group as follows: (a) control group (CMC; 2 mg/kg/day, p.o.), (b) PCOS group (letrozole; 1 mg/kg/day, p.o.), (c) linagliptin group (Linagliptin; 3 mg/kg/day, p.o.) [13], (d) I3C group (I3C; 50 mg/kg/day, p.o.) [14], and (e) linagliptin + I3C group (Received linagliptin concomitantly with I3C by the above-mentioned doses). Letrozole and CMC were administered for 36 days while linagliptin and I3C were administered from day 21 to the day 36 of the experiment (Fig. 1). The doses of the drugs used in this study were selected according to previous studies carried out by Koibuchi et al. [13] and El-Naga et al. [14] who reported that these doses are relevant to the human doses and produce the desired effects without significant adverse effects.

On the 37th day of the experiment, animals were fasted overnight and anaesthetized with thiopentone sodium (30 mg/kg body weight, intraperitoneal). Blood was collected from the retro-orbital plexus then prepared and used for assessment of the biochemical parameters. Both ovaries were extracted, freed from blood, cleaned with ice cold saline and weighed. The right ovary was homogenized for determination of the tissue biochemical parameters. The left ovary was used for histopathological examination.

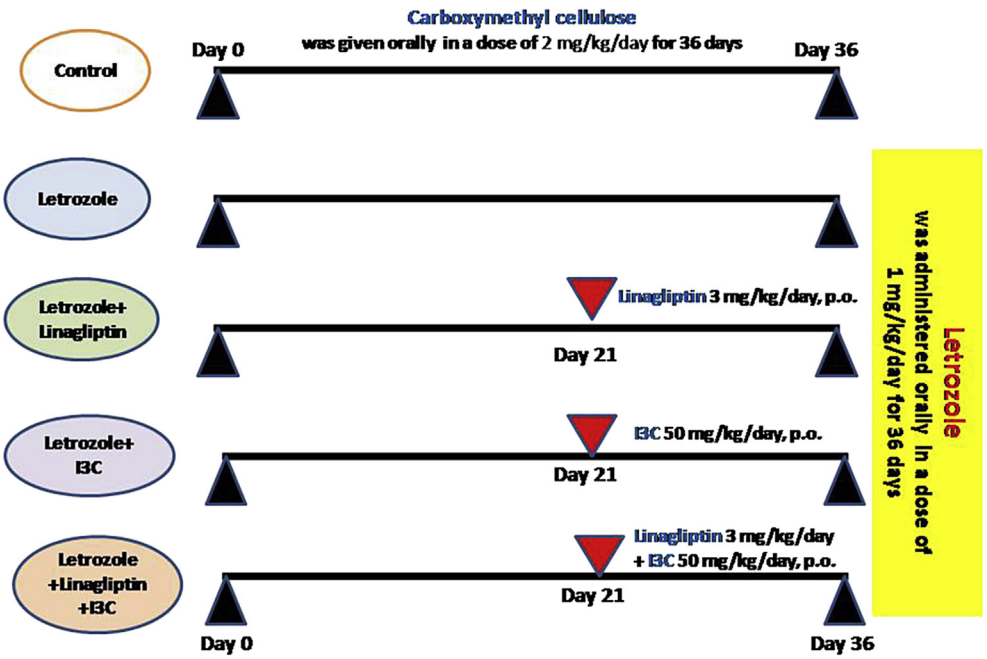

Fig. 1. A timeline schematic diagram for the animal treatment schedule.