THE THERAPEUTIC EFFECT OF MESENCHYMAL STEM CELLS AND ALFACALCIDOL ON CISPLATIN INDUCED ACUTE NEPHROTOXICITY IN MALE ALBINO RATS.

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Introduction

Acute kidney injury (AKI) refers to the rapid decline of renal function, typically resulting from toxic or ischemic insults due to chemotherapy, antibiotics, or infection-related shock. Notably, approximately one-third of patients undergoing cisplatin therapy develop AKI, predominantly due to the nephrotoxicity of cisplatin. Cisplatin, an anti-neoplastic agent used for various solid-organ cancers, has its use limited by nephrotoxicity, a significant adverse effect. Oxidative stress is a crucial mechanism underlying cisplatin-induced AKI, suggesting that antioxidants like vitamin D may mitigate these adverse effects. Stem cells, particularly bone marrow-derived mesenchymal stem cells (BM-MSCs), offer a promising therapeutic approach for renal repair. These undifferentiated cells possess considerable self-renewal and tissue generation capabilities. BM-MSCs can ameliorate renal functional deficits, tubular necrosis, and apoptosis while promoting tubular regeneration, likely through paracrine or endocrine mechanisms rather than direct engraftment.

Aim of the Work

The aim of the present work was to:

- Study the histological and immunohistochemical changes in a rat model of cisplatin – induced acute nephrotoxicity.
- Study the efficacy of BM - MSCs and alfacalcidol (ALFA) to treat cisplatin-induced acute nephrotoxicity in adult male albino rats.

Materials and Methods

This study was carried out on55 healthy male albino rats from the Animal House Centre, Physiology Department, Faculty of Medicine, Alexandria University, and adhered to ethical guidelines. The experimental group consisted of 50 adult male rats (6 weeks old, 150–200 g) and five young male rats (80 g) for mesenchymal stem cells (MSCs). The 50 experimental rats were divided into three groups:

Group I (Control, n=10): Subgroup Ia (n=5): standard diet and water.

Subgroup Ib (n=5): normal saline (6.5 ml/kg) plus standard diet and water.

Group II (Cisplatin, n=10): Cisplatin (6.5 mg/kg) administered intraperitoneally, sacrificed on day 5.

Group III (n=30): divided into three subgroups: Subgroup IIIa (ALFA-treated, n=10): ALFA (50 ng/kg/day) for 5 days pre- and post-cisplatin.

Subgroup IIIb (MSCs-treated, n=10): Cisplatin, followed by MSCs (2x10^6 cells) tail vein injection.

Subgroup IIIc (ALFA and MSCs-treated, n=10): ALFA pre- and post-cisplatin, followed by MSCs.

On day 5, blood samples and kidney tissues were collected for biochemical, histological, and immunohistochemical analyses.

Results

Table 1: Comparison between the different studied groups according to BUN level (mg/dl)

Biochemical	Group I (n = 10)	Group II (n = 10)	Group IIIa (n = 10)	Group IIIb (n = 10)	Group IIIc (n = 10)	F	P
BUN (mg/dl)							
Min.– Max.	16.40–19.60	78.0–130.0	49.0–70.0	22.40 –35.0	21.0–26.0	165.905*	<0.001*
Mean ± SD.	18.06±1.13	106.0±18.35	58.40 ± 6.88	28.14 ± 4.27	22.60±1.78		
p_1		<0.001*	<0.001*	0.109	0.792		
p_2			<0.001*	<0.001*	<0.001*		
p_3				<0.001*	<0.001*		
p_4					0.647		

Table 2: Comparison between the different studied groups according to area percentage of active caspase-3 immunostaining

	Group I (n = 10)	Group II (n = 10)	Group IIIa (n = 10)	Group IIIb (n = 10)	Group IIIc (n = 10)	F	P
Area % of active caspase 3							
Min. – Max.	2.84–7.10	54.68– 63.76	37.49–44.34	25.84–30.82	15.57–20.07	948.064*	<0.001*
Mean ± SD.	4.76±1.60	59.29±3.19	40.32±2.16	28.36 ± 1.79	17.88 ± 1.58		
p_1		<0.001*	<0.001*	<0.001*	<0.001*		
p_2			<0.001*	<0.001*	<0.001*		
p_3				<0.001*	<0.001*		
p_4					<0.001*		

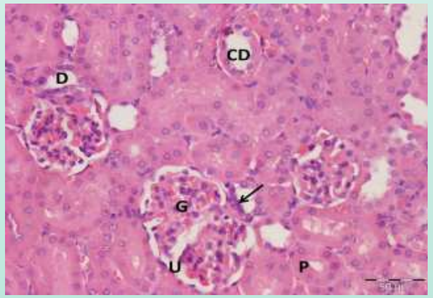

Figure1: A photomicrograph of a section of rat's renal cortex of group I with normal renal architecture. The glomerulus (G) is surrounded by Bowman's capsule having an outer layer of simple squamous epithelium and an inner layer with podocytes and mesangial cells with a urinary space (U). The renal tubules are intact with preserved cytoplasm and nuclei.
↑ maculadensa, P proximal convoluted tubule, D distal convoluted tubule, CD collecting duct.(H&E X400).

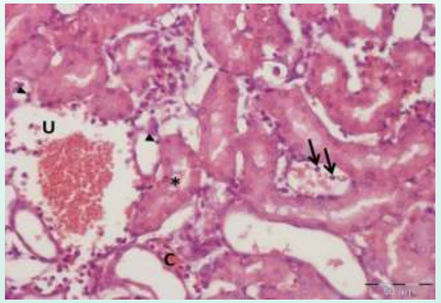

Figure 2: A photomicrograph of a section of rat's renal cortex of group II showing destruction of the renal architecture. The glomeruli (G) are atrophied with wide urinary space (U). Some tubules are dilated with flat epithelial lining and shedding of epithelial cells in the lumen and no PCTs could be identified. Some tubules show cells withpyknotic nuclei(arrowhead). Some cortical congested blood vessels (C) are seen. (H&E X400)

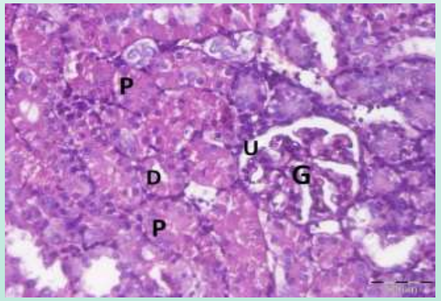

Figure 3: A photomicrograph of a section of rat's renal cortex of group IIIc showing marked restoration of the renal corpuscles with intact glomeruli (G), layers of Bowman's capsule with ordinary urinary space (U). Most cells exhibit normal nuclei, and the tubules restored their normal structure. PCTs show apical brush border. No inflammatory cells are observed. (D) DCT. (H&E X400)

Conclusion

After the accomplishment of the current work, it can be concluded that:

- Both mesenchymal stem cells and ALFA have the ability to ameliorate cisplatin-induced acute nephrotoxicity.
- Based on the histological, biochemical, and immunohistochemical results, the combination of BM-MSCs and ALFA is the most effective approach to curing cisplatin-induced acute nephrotoxicity in rats.