Effect of acute peritonitis on serum fibroblast growth factor 23 (FGF23) level in male albino rats with chronic kidney disease (CKD)

Thesis

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Chronic kidney disease (CKD) comprises a group of pathologies in which the renal excretory function is chronically compromised, mainly resulting from damage to renal structures. CKD results from a variety of causes such as diabetes, hypertension, nephritis, inflammatory and infiltrative diseases, renal and systemic infections, polycystic kidney disease, autoimmune diseases (e.g. systemic lupus erythematosus), renal hypoxia, trauma, nephrolithiasis and obstruction of the lower urinary ways, chemical toxicity and others.

CKD-mineral and bone disorder (CKD- MBD) is one of the major complications associated with CKD, consisting of vascular calcification, renal osteodystrophy and increased fibroblast growth factor 23 (FGF23) secretion. It is at least one of conditions that affect morbidity and mortality of patients with CKD.

FGF23 is a bone-derived hormone secreted by osteoblasts and osteocytes and essential for maintaining normal phosphate and vitamin D homeostasis. Its cleavage into inactive fragments is accomplished by a member of the proprotein convertase enzyme family named furin.

Serum FGF23 level is high and rises progressively up to 100 fold in CKD, suggesting that FGF23 has some role in the development of CKD-MBD. FGF23 rises very early before any abnormality in phosphate metabolism (one of the primary regulators of FGF23 production) in the course of CKD suggesting the existence of phosphorus-independent regulation of FGF23 production in CKD patients.

Inflammation is a novel regulator of FGF23 production. FGF23 has been lately associated directly with inflammatory markers such as c-reactive protein and interleukin (IL)-6 in surveys in patients with CKD. Moreover, systemic inflammation is widely prevalent in CKD patients and considered as one of the non-traditional risk factor for cardiovascular disease (CVD) in this population.

So, the aim of the present study was to clarify the effect of acute inflammation on serum fibroblast growth factor 23(FGF23) in CKD, to investigate whether the expression of furin proprotein convertase enzyme is altered by inflammation in CKD and to clarify the difference in the FGF23 levels to acute inflammation versus CKD.

Forty male albino rats were included in this study and divided into four groups, 10 rats each: **Group (I):** sham-operated control group: the rats were laparotomized in the midline followed by wound closure,

Group (II): Experimentally induced acute peritonitis group: in this group acute peritonitis was experimentally induced by inoculation 1ml/kg of faecal suspension (2:1W/V in saline) into the peritoneal cavity for 4 hours, **Group (III):** Experimentally induced chronic kidney disease (CKD) group: in this group CKD was induced by ligation of the pedicle of one kidney & cautery of the other kidney to destroy 5/6 of its tissue and left for six weeks, **Group (IV):** Experimentally induced chronic kidney disease (CKD) group with induced acute peritonitis: CKD was induced as in group (III), and after six-weeks, acute peritonitis was induced as in group (II).

The serum levels of creatinine, phosphorus, fibroblast growth factor 23 (FGF23), vitamin D, Tumor necrosis factor alpha (TNFa) and C-reactive protein (CRP) were measured. Also, furin mRNA was measured in femur bone tissue.

The results revealed that peritonitis significantly increased serum FGF23, TNFa and CRP levels; meanwhile, it induced significant decrease in serum vitamin D level and bone furin mRNA compared to the control group. CKD whether alone or with peritonitis significantly increased serum creatinine, phosphate, FGF23, TNFa and CRP levels; meanwhile, they induced significant decrease in serum vitamin D level and furin mRNA compared to the control group. CKD significantly increased serum creatinine, phosphate and FGF23 levels; meanwhile, it induced significant decrease in furin mRNA compared to the peritonitis group.

Finally, comparing CKD with peritonitis group with CKD group, there was significant increase in the serum TNFa level only, while there were insignificant changes in the other parameters.

Conclusion:

- Acute peritonitis on top of CKD increased serum FGF23 which may lead to progression of CKD and death.
- The increased serum FGF23 is due to significant decrease of the furin pro-protein convertase enzyme which catalyzes the degradation cleavage of the full-length intact bioactive protein (iFGF23) into inactive C-terminal fragments.
- The acute peritonitis worsens the chronic inflammatory response in CKD by significant increase in TNFa.
- Finally, there were positive correlations between serum FGF23 level and creatinine, phosphate, Tumor necrosis factor alpha (TNFa) and C-reactive protein (CRP) levels, in addition to negative correlation with serum vitamin D and bone tissue furin mRNA levels.