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Relationship of fibroblast growth factor 23 (FGF23) to antioxidants and lipid level in patients with kidney diseases

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Abstract--The research involved study the relation between FGF23 and some of the biochemical parameters related to the chronic kidney disease (Glutathion GSH and arylesterase ARE enzymes,ceruloplasmin, Malondialdehyde ,glucose ,cholesterol ,triglyceride ,LDL ,VLDL,HDL)in serum blood patients compared with control group,the result demonstration is a significant increase in the mean concentration rate FGF23 was (324.06± 291.1 pg/ml) in patients compared with mean concentration in control group was (273 ± 188.5 pg/ml) , also the result showed a significant increase in the concentration of (ceruloplasmin,malondialdehyde ,cholesterol ,LDL) and a significant decrease had been shown in the concentration of (reduced Glutathion,arylesterase,HDL).while the results had been showed a non significant increase with (glucose,triglyceride,VLDL) in patients compared with control group, Correlation coefficient of FGF23 with these clinical parameters showed a positive significant correlation with(Malondialdehyde) while the result showed a non significant correlation with rest of the biochemical parameters.

Keywords---FGF23, dyslipidemia, antioxidant, BMI, CKD.

Introduction

Chronic kidney disease is defined as either kidney damage or (GFR)less than 60 ml/min/1.73m² more than 3 months,it is associated with increasing ge, hypertension, diabetes, cardiovascular diseases and lack of physical exercis.[1] Oxidative stress (OS) is defined as astate of imbalance between excessive prooxidant relative to antioxidant defens mechanisum ,oxidative stress leads to

oxidation of lipids ,proteins, and nucleic acids and oxidative damage in cells ,tissues and organs caused by Radical oxidative stress(ROS).[2] ,oxidative stress has been linked to the many diseases including chronic kidney disease (CKD)[3]when increased oxidative stress and decreased antioxidant have been found to be associated with the risk of chronic kidney disease[4]

FGF23 was discovered for the first time in the (2000)year,the first known discovery of phosphatonin for its effect on the metabolism of phosphate in body[5] ,it is polypeptide with a molecular weight of (32 kilodaltons),and it contains a polypeptide composed of (24)amino acid in the amino portion of the protein [6]the carboxylic terminus is formed from (72)amino acid [7] The human gene of FGF23 is located on the chromosome 12 and it is a member of the subfamily (FGF19)[6,9]The fibroblast growth factor family (FGF)has divided into seven subcategories based on genetic or genotypic similarity that include FGF1,2 – FGF4,5,6 – FGF3,7,10,22 – FGF8,17,18- FGF9,16,20 –FGF11,12,13,14 and FGF15,19,21,23) [10],FGF23 is secreted from osteoblast and osteocytes in response to increase of phosphate in the blood by binding a receptor FGFR1c with α - klotho to form a complex (FGFR1c - α -klotho) in the kidneys, FGF23 reduces phosphate by inhibiting the reabsorption of phosphate in the kidney and reduces the absorption of phosphate in the intestine,and reductive vitamin D ,FGF23is used to treat diseases that cause an increase in the level of phosphate in the body ,including rickets ,osteomalacia ,osteoporosis and chronic kidney disease[11],FGF23 also increases in the case of inflammation and in the case of left ventricular hypertrophy and congestive heart failure[12] Also higher FGF23 levels are associated with lower body mass index (BMI) and dyslipidemia in dialysis patients [13],FGF23 is inversely correlated with serum diponectin level ,thus that FGF23 is correlated to fat mass and related to dyslipidemia in CKD.[14]

Aim of Researched

Since there were a little previous studies In Iraq about the relation FGF23with metabolism of phosphate in the body ,especially in patients with chronic kidney disease ,so it was proposed to study its mechansium of action in patients and its relationship with oxidative stress, fat mass, BMI.

Experimental

(60) blood samples were collected from chronic kidney patients ,(30)samples for both sexes (females and males) , their ages between (15-55)year and over ,also (30) blood samples were collected from healthy people ,(15)samples for both (females and males) from Ibn-Sina Teaching Hospital .After the blood serum was isolated from the samples ,it was used to estimate the following some biochemical parameters.

FGF23-was estimated by using SHANGHAI YEHUA Biological Technology Co.,Ltd kit(China)by enzyme linked immunoassay ELISA technique [15]
 Glutathione redcutase enzyme –was determind by using Elmans reagent by modified method for researchers(Sedlak and Lindsay ;1968) [16]
 Ceruloplasmin –was determind by using (para-phenylendiamine) by modified method for research (Menden et.al.;1977) [17]

Aryl esterase enzyme –was determined by analyzing the substrate phenylacetate to phenol and acetic acid.[18]

Malondialdehyde –was determined by using Thiobarbituric acid (TBA) by modified method for researchers(Guidet and Shah,1989)[19]

Cholesterol was determined by using BIOLABO kit (France).[20]

Triglyceride- was determined by using BIOLABO Kit (France).[21]

LDL-C - was determined by using BIOLABO Kit (France).[22]

VLDL-C-was determined relying on the method of researchers [23]

HDL-C- was determined by using BIOLABO Kit (France).[24]

Data analysis

The obtained data were analysed using T-test used for comparing between two parameters , Standard statistical methods were used to find the mean and standard deviation,also Linear regression analysis pearson correlation coefficient (r)was performed to identify the relation between different clinical parameters.[25]

Results and Discussion

Concentration of FGF23 in chronic kidney disease patients compared with control group

The result in fig.(1) showed that the normal concentration of FGF23 was (273.88 ± 188.5 pg/ml)in healthy group while the result that in chronic kidney patients have a significant increase in FGF23 concentration to (324.06 ± 291.1 pg/ml) compared with healthy group,the reason for the increase FGF23 in chronic kidney disease may be to the conjugate FGF23 with receptors FGFR1c and with α -klotho cofactor ,then in proximal renal tubes FGF23 prevents sodium –phosphate transporters(Npt2a, Npt2c) to crossing the kidney wall for the purpose of reabsorption of phosphate and then excreting phosphate through the urine , FGF23 also inhibits the gene expression of 1- α hydroxylase enzyme ,the enzyme responsible for the formation of vitamin D which reduces the absorption of phosphate in the intestine .[26,27]

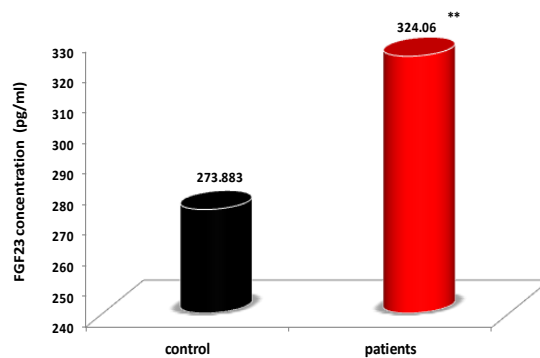


Fig.1: FGF23 concentration in chronic kidney patients and control group

Some clinical parameter concentration in chronic kidney patients compared with control group

The results in table (1) showed a significant increase in concentration ceruloplasmin and malondialdehyde(MDA) the result is in agreement the with finding by both researches [28,29],there were positive correlation between inflammation and(MDA)and between Glomerular filtration rate (GFR)and antioxidant while negative correlation were observed between (GFR)and (MDA), ceruloplasmin also is increase in kidney disease patients response to inflammation, the results also showed a significant increase in (cholesterol,LDL) this result is in agreement with what the researchers said [30,31]that there is a significant increase in cholesterol in CKD due to upregulated activity of HMG-COA (3-hydroxy -3-methyl glutaryl -coenzyme A)reductase ,the rate limiting enzyme in cholesterol biosynthesis and this lead to increase in LDL for patients suffering CKD ,while the result showed a significant decrease in HDL because HDL usually is impaired in renal dysfunction [32],the result also showed a significant decrease in (reduced Glutathione ,arylesterase enzymes),these results were in agreement with those found by [33,34]that there are decreased in reduced Glutathione GSH and arylesterase enzymes in CKD patients ,while the table(1) is showed anon significant increase with the (glucose ,triglyceride, VLDL)in CKD patients .

Table (1):Some clinical parameters concentration in chronic kidney patient and control

Clinical Parameters	Control Group	Patients
Glutathion $\mu\text{mol/L}$	2.11 + 1.4	** 1.58 + 0.82
Arylesterase U/ml	111.83 + 35.27	** 52.03 + 16.89
Ceruloplasmin $\mu\text{mol/L}$	357.61 + 227.4	* 412.07 + 261.63
Malondialdehyde $\mu\text{mol/L}$	1.71 + 0.96	* 5.02 + 19.14
Glucose mg/dl	92.5 + 38.66	97.06 + 21.17
Cholesterol mg/dl	168.84 + 41.68	* 183.83 + 28.64
Triglyceride mg/dl	138.66 + 62.58	153.96 + 76.47
LDL mg/dl	86.49 + 19.34	** 103.57 + 37.13
VLDL mg/dl	27.193 + 12.6	31.26 + 15.29
HDL mg/dl	46.62 + 11.7	** 41.06 + 9.8

Significant difference at * $p < 0.05$, ** $p < 0.01$

Correlation between FGF23 Concentration and some clinical parameters in Chronic kidney diseases (CKD) patient comparing to control group

The result in table(2) showed that FGF23had a positive significant correlation with Malonodialdehyde, this due to the patients with CKD had significantly higher levels of malondialdehyde while had significantly lower antioxidant enzymes activities compared with healthy group [35] ,while FGF23 had a non significant correlation with the rest of the biochemical parameters these results were agreement with those found by [14]that there are not any significant correlations between FGF23 and lipid profile.

Table (2): Correlation between FGF23 concentration and some clinical parameters in chronic kidney patient comparing to control group

Clinical Parameters	Control Group r-value	Patients r-value
Glutathion $\mu\text{mol/L}$	0.086	- 0.141
Arylesterase U/ml	0.163	- 0.11
Ceruloplasmin $\mu\text{mol/L}$	- 0.199	- 0.226
Malondialdehyde $\mu\text{mol/L}$	0.277	0.273 *
Glucose mg/dl	- 0.146	0.088
Cholesterol mg/dl	0.08	0.186
Triglyceride mg/dl	- 0.134	- 0.153
LDL mg/dl	0.114	0.158
VLDL mg/dl	- 0.118	- 0.179
HDL mg/dl	0.023	0.049

* Correlation is significant at the 0.05 level

Effecte of Body Mass Index (BMI)on FGF23 Concentration in patients and control groups

The result in table (3)showed that there is increase in FGF23 concentration with lower BMI in patients group ,this result is in agreement with the research findings[13]while the result was showed there is increase FGF23 with higher BMI in control group,this due to an inverse relationship between serum phosphate and fat mass in healthy while FGF23 was positively correlated with BMI [36].

Table (3): FGF23 Concentration in chronic kidney patients compared with control group A cording to BMI

BMI kg/m^2	FGF ₂₃ conc. pg/ml mean + SD	
	Control Group	Patients
18.5 - 24.9	264.2 + 172.4	* 385.4 + 341.7
25 - 29.9	271.2 + 186.3	* 219.5 + 155.7
30 - 39.9	398 + 289	* 211.1 + 95
≥ 40	414.2 + 19	-

* Correlation is significant at the 0.05 level

Body mass index (BMI):is defined as the product of dividing bod weight in kilograms by the squar of height in meters,using the world health organization (WHO)body mass index (BMI) is divided into four groups : normal weight (18.5-24.9 K/M2) ,overweight(25-29.9 Kg/m2 ,obese(30-39.9 Kg/m2),and morbidly obese ($\geq 40\text{Kg/m}^2$)[37]

Conclusion

In this study, FGF23 was increased in CKD patients response to hyperphosphatemia, dyslipidemia, oxidative stress while FGF23 was has inverse

correlated with BMI in patients and it was positively correlated with BMI in healthy group.

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