Egypt. J. Chem. **Vol. 67**, No. 11 pp. 363 - 376 (2024)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

The Importance of Serum Fibroblast Growth Factor-23 in Obesity and Metabolic Syndrome, Potential Effect of Nutritional Therapy Intervention

Salwa M. El Shebini[1], Hend A. Essa[1]*, Maha I. A. Moaty[1], Nihad H. Ahmed[1], Ahmed M. S. Hussein[2], Magda S. Mohamed.[1]

[1]Department of Nutrition and Food Science, National Research Center, 12622, Cairo, Egypt;
[2]Department of Food Technology, National Research Centre, 12622, Cairo, Egypt
(Affiliation ID: 60014618).

Abstract

Background: Fibroblast growth factor-23, a hormone, regulates circulating phosphate and vitamin D levels and also plays a role in some metabolic processes**. Objective**: A food supplement containing Moringa oleifera leaf flour and turmeric powder has been used in conjunction with a low-calorie diet to help people lose weight and improve metabolic and renal problems. **Subjects and methods:** Two-phase interventional study that lasted 8 weeks. Sixty-four volunteer women with varying degrees of obesity and metabolic syndrome criteria took part. Their mean age and BMI were 47.37± 1.31 years and 36.50±0.68 kg/m^2, respectively. All participants followed a low caloric balanced diet for eight weeks. They ate moringa pies during the first phase and the regimen during the second. Patients were clinically, anthropometrically, dietary 24 h recall and biochemically monitored. **Results:** At the end of the first phase, there was a significant reduction in the mean values of the anthropometric and more in the biochemical parameters, which began to fade in the second phase. FGF-23 and various metabolic parameters were found to have negative significant correlations both at baseline and after intervention. Creatinine and IL1β showed a significant positive correlation but a significant negative correlation with eGFR. **Conclusion:** As a bakery product, the health effect of a dietary therapy supplemented with pies fortified with Moringa oleifera leaf and turmeric powder as anti-inflammatory and antidiabeic was demonstrated. The inverse relationship detected in this study between FGF-23 and metabolic syndrome parameters were suggested to maintained serum phosphorus hemostasis. Because of the link between FGF-23, creatinine, and eGFR, it could be used as a valuable factor in kidney function research.

Keywords: Metabolic syndrome, Obesity, Fibroblast growth factor-23, Moringa oleifera leaf, Turmeric

1. Introduction

The combination of obesity-related cardiovascular risk factors, such as hyperinsulinemia, abdominal obesity, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, and/or hypertension, is known as the metabolic syndrome (MetS) [1] The National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) developed a definition for the metabolic syndrome in 2001 (National Cholesterol Education Programme, 2002, which was updated in 2005 by the American Heart Association and the National Heart, Lung, and Blood Institute. Metabolic syndrome is present if three or more of the following five criteria are met: waist circumference over 102 cm (men) or 88 cm (women), blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women), and fasting blood sugar over 100 mg/dl [2].

Fibroblast growth factor-23 (FGF23) is a hormone that regulates the amounts of phosphate and vitamin D that are present in the blood. Recent research has shown that FGF23, in addition to being a key player in the pathogenesis of calcium-phosphorus disorders, may also act as a marker for cardiovascular complications in some patients. It may also function as a "hormone-like" element in some metabolic processes, particularly in the metabolism of fat and glucose. Its potential contribution to the development of the metabolic syndrome (MetS) is still unknown

*Corresponding author e-mail: hendessabio@gmail.com.; (Hend A. Essa).
Receive Date: 31 January 2024, Revise Date: 04 May 2024, Accept Date: 12 May 2024
DOI: 10.21608/ejchem.2024.266936.9269

[3]. However, Mosavat et al. [4] note that two fibroblast growth factors (FGFs), FGF-21 and FGF-23, have been hypothesized to be connected to the metabolic syndrome.

The bone hormone fibroblast growth factor-23 (FGF23) prevents the kidney from producing vitamin D hormone and reabsorbing phosphate. At physiological levels of the hormone, the FGF23's endocrine effects on the kidney are Klotho-dependent because the co-receptor Klotho is necessary for FGF receptors to bind to FGF23 with high affinity on target cells. Phosphate wasting is a well-known symptom in patients with normal kidney function who have high blood levels of intact FGF23 [5]

Serum FGF23 levels are higher in obese people, particularly those who have abdominal obesity. According to the independent associations between the presence of abdominal obesity and the increase in serum FGF23 levels in specific groups, serum FGF23 levels may be a marker of the risk of metabolic and cardiovascular disease in men and postmenopausal women [6]. Ali et al. found an association between obesity and increased blood levels of FGF23, even in the absence of hypertension [7] .

Both FGF23 and Klotho play critical roles in the control of mineral metabolism, and both are changed as a result of renal failure. FGF23 enhances phosphaturia, preventing phosphate buildup in the early stages of chronic kidney disease (CKD). The presence of Klotho in the renal tubules is required for FGF23 to exert this action. However, Klotho expression is reduced as soon as renal function begins to fail, resulting in FGF23 resistance. Changes in these factors have a direct impact on other mineral metabolism parameters; they may impair renal function and cause harm to other organs such as bone, heart, or arteries [8].

The most well-known member of the Moringa oleifera genus and the Moringaceae family is Moringa oleifera. It contains a variety of nutrients and bioactive compounds, including proteins, essential amino acids, carbohydrates, lipids, fibre, vitamins, minerals, phenolic compounds, and phytosterols. These characteristics give it the ability to have hepatoprotective, cardioprotective, anti-inflammatory, anticarcinogenic, antioxidant, and anti-diabetic properties. Although the entire Moringa oleifera plant, including the flowers, is edible, it has been determined that the leaf is the safest due to compounds that are primarily found in the root. Moringa oleifera is known as an excellent source of phytochemicals with potential uses in functional and medicinal food preparations due to its nutritional and therapeutic qualities [9] . Food prepared with Moringa oleifera has many advantages. According to some researchers, foods can be enriched with Moringa oleifera to add nutritional value by adding vitamins, minerals, essential amino acids, and oils [10].

Subjects with chronic kidney disease (CKD) have a significant risk of cardiovascular death, and any strategy that prevents the course of CKD could have a huge influence on public health. Over the last decade, there has been a growing recognition that the gut microbiota (GM) can play a critical role in the pathogenesis of systemic inflammation and CKD progression. Dietary supplements are increasingly being used to improve the quality of life in CKD patients. Curcumin, has shown considerable anti-inflammatory benefits in vitro. [11]. Turmeric (Curcuma longa), a well-known herbal remedy and food additive, contains curcumin, which has potent anti-inflammatory properties. Chronic kidney disease (CKD) is an inflammatory condition that can lead to end-stage kidney disease that necessitates dialysis or transplantation. Diabetes and cardiovascular disease are frequently linked to, as are other inflammatory diseases [12]. Patients with metabolic syndrome and related disorders who consumed curcumin showed significant decreases in body mass index (BMI), weight, waist circumference (WC), and leptin levels as well as significant increases in adiponectin levels; however, there was no difference in hip ratio [13]

Aim: The study's goal was to determine the effects of obesity and its complications on the metabolic profile and renal functions of middle-aged obese Egyptian women who met different metabolic syndrome criteria. To alleviate the complications and aid in weight loss, a food supplement fortified with Moringa oleifera leaf flour and Curcumin powder were used in conjunction with a low-calorie diet. In addition, study the interaction between FGF-23 concentrations and various metabolic and renal parameters

Subjects and Methods

Methods

Supplements composition, preparation and organoleptic characteristics of pie:

Pie making was carried out at the pilot plant at the National Research Centre (NRC) in Dokki, Egypt according to AACC [14**].** The pie ingredients were wheat flour (72%), Moringa oleifera powder extraction), Turmeric, instant active dry yeast, corn oil**,** milk, and water (an amount required to reach 500 Brabender Units of consistency) as presented in table (1). Pie was manufactured as follows: the dry ingredients were manually mixed in a wide bowel and then transferred to mixing bowl. Oil and water were added to all ingredients.

Table (1): Composition of the functional pies (100 g dry weight)

Ingredients	Moringa oleifera Pie
Moringa Powder	7%
wheat flour(72%)	68%
Turmeric	5%
Milk	10%
Corn oil	10%
Yeast	1.5%

The components were thoroughly mixed with electric mixer for 2 min at low speed. The mixing speed was then changed to medium for 2 min and then at high speed for 8 min. The dough was divided into pieces rounded by hand and allowed to relax for 10 min. The dough was molded then panned and left to ferment for 60 min at (30°C) in 86% relative humidity in a fermentation cabinet.

Table (2): Proximate nutrients contents of the supplements.

Constituents (%)	Moringa pie	
	Pie (100 gm)	One pie (50gm)
Energy (kcal)	281.67	140.84
Protein(g)	8.57	4.29
Fat (g)	7.67	3.84
Cholesterol (mg)	0.16	0.08
Fiber (g)	8.16	4.08
Carbohydrate(g)	44.59	22.30
Phosphorus(mg)	213.16	106.58
Potassium(mg)	341.84	170.92
Calcium (mg)	82.51	41.26
Magnesium(mg)	58.61	29.31
Sodium(mg) (mg)	34.02	17.01
Iron(mg)	2.14	1.07
Zinc (mg)	2.13	1.06
Vit.E(mg)	2.50	1.25
Vit. A (µg)	59.43	29.72
Vit. D (µg)	0.29	0.15
VitaminB6 (mg)	0.28	0.14
VitaminB12 (mcg)	0.22	0.11
Riboflavin (mg) B2	0.32	0.16
Niacin (mg)	4.32	2.16
Thiamin (mg) B1	0.34	0.17
Folate (µ g)	58.84	29.42

(Nutrisurvey, 2007) [**15**]

The pieces were baked at 250°C/20 min in an electric oven. Subsequently, the baked pie samples were then cooled for 1hour at room temperature (30°C±2), packed in polyethylene bags and used for further analyses.

The pie formula composition of the raw materials is tabulated in table (1). Proximate nutrients contents of the supplements, macro and micronutrients showed in table (2), using (Nutrisurvey, 2007) **[15].**

Figure (1). Show Fatty acids contents of the pie which were done using the method of AOCS, **[16].**

Table (3): Baking Quality of pie

Sample	Baking quality parameters		
	Weight (g)	Volume (cm^3)	Specific volume (cm3/g)
Moringa oleifera pie	**57.5±1.15**	**205±1.65**	**3.56±2.15**

Physical characteristics of the Pies

Weight, volume, and specific volume of the pie samples were determined as described by AACC [14] Table (3). Organoleptic characteristics of pie samples were evaluated for colour (20), taste (20), Odor (20), texture (20), appearance (20) and overall acceptability (100) Table (4).

Subjects

2-Study design

The study was a two-phase interventional study that lasted 8 weeks. Sixty-four volunteer women with various degrees of obesity and different metabolic syndrome criteria participated. Their mean age was 47.37± 1.31 and their average BMI was 36.50±0.68 kg/m2. Participants with high blood pressure or type 2 diabetes were under medical supervision. For the eight weeks, all participants adhered to a low caloric balanced diet (1000-1200 calories per day). They ate moringa pies for the first four weeks, one for breakfast and one for dinner (each weighed 50 g). Women followed the regimen in the second period, but the pies were replaced with high extract wheat bread, which provides comparable calorie, aiming to reveal the health effect of moringa to determining if the effect of moringa remains or fades when replaced by traditional local bread (Baladi bread).

Full clinical examination of all the subjects was done over the course of the study with weekly follow-up. Ethical approval from Ethical Committee of NRC, (registration number is 19-180) and written informed consent from each of the participated women was taken.

a-Anthropometric Parameters and Blood Pressure Measurements

Relevant anthropometric parameters were reported according to Tanner et al. [17] namely weight, height and mid waist circumference (MWC). Using the Geratherm Body Fitness (B-5010), the BMI (weight in kg//heigh^2 in meters) and bone mass were

calculated. Each patient's blood pressure was checked three times, with the mean reading being recorded. To ensure accuracy, all measurements were made by the same researcher.

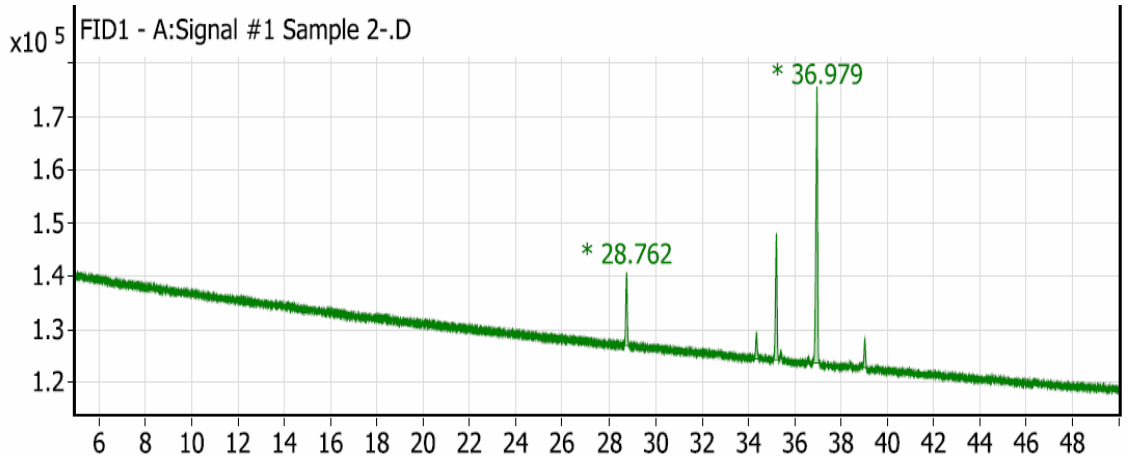

Fig (1): fatty acids in Ground Moringa Leaves, palmitic acid (28.76 min, 12.71%), stearic acid (34.36 min, 4.62%), Oleic acid (35.22 min, 23%), Linoleic acid (36.97 min, 54.89 %) and Linolenic acid (39 min, 4.78%).

Table (4): Organoleptic characteristics of pie

Sample	Sensory parameters					
	Crust color (20)	**Texture (20)**	**Taste (20)**	**Odor (20)**	**Appearance (20)**	**Overall acceptability (100)**
Moringa oleifera pie	18.02±2.16	18.25±1.85	17.90±1.78	18.65±1.85	17.19±1.60	90.01±2.50

b-Blood Sampling and Biochemical Analysis

The patients' blood samples were drawn while they had been fasting for 12 hours. Sera were separated after centrifuging samples that had been allowed to clot at room temperature. Fresh samples were used to evaluate fasting blood glucose (FBG) using the glucose oxidase technique. [18]; other biochemical parameters were performed on fasting sera that were stored at -70 C° until used. Serum high density lipoprotein cholesterol (HDL-C) was done using, HDL-C proceed No 0599 Stanio Liquicolor [19] and triglycerides proceed No 2100, [20] (Enzymatic method) respectively. Total antioxidant capacity (TAC) has been measured by colorimetric method according to Ciuti and Liguri, [21]

Serum Creatinine was estimated by kinetic method according to (Bowers and Wong,[22] Urea was determined by colorimetric method [23] Estimated glomerular filtration rate (eGFR) is calculated by the abbreviated MDRD (modification of diet in renal disease) equation:

eGFR=186 x (Creatinine mg/dL)-1.154x (Age)-0.203 x (0.742 if female).

Fibtoblast growth factor- 23 was determined by method-specific differences in plasma using four commercial ELISA [24]. Interleukin1 beta (IL1beta) and insulin were estimated in the serum according to Lopez-Castejon et al .[25] and Temple et al. [26] respectively by EIAab, EIAAB SCIENCE INC, CHINA ELISA kits. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculate by the equation: Fasting glucose (mg/dL) X fasting insulin (µU/mL) / 405, according to Majid et al. [27]

C-Dietary recalls

Data on dietary intake were performed using the 24 hours dietary recall that repeated for 3 successive days and food frequency. The total dietary intake was analyzed using the (Nutrisurvey, 2007) **[15]** computer program. We used the Dietary Approaches to Stop Hypertension (DASH) diet a s a model for a healthy dietary pattern for comparison. We calculated the DASH score to assess participants' adherence to the

DASH diet based on the following eight foods groups: Fruits including fruits juices, vegetables (including potatoes), whole grains, total dairy, nuts, seeds, and legumes, meat and meat equivalent, added sugar ≤3% of total calories, and saturated fat intake ≤5% of total energy). Participants adhered to the RDAs received a score of 1, 0.05 for intermediate intake, 0 for poor intake, while >1 for over intake. Each participant's Dixon DASH score was calculated by adding the scores from all the components as total DASH score [28],

D-Statistical Analysis

Statistical analysis was performed using SPSS software window version 17.0 (SPSS Inc. Chicago, IL, USA, 2008).

All values were expressed as mean value ±SE. Paired-sample *t* -tests were used to compare the data in the same group before and after dietary therapy. Correlation coefficient (r) was calculated to find correlations between different variables. $p < 0.05$ were considered statistically significant.

Results

Tables (2, 3 and 4,) showed the proximal composition, backing quality and .organoleptic characteristics of pies. The chemical composition of the product, showed that it contain good amount of carbohydrate, protein, fat and fiber, while potassium was the highest mineral found in the supplement compared to the other elements, followed by the calcium. (341.84 mg/100g, 82.51mg/100g). The backing properties of the pie as regard its weight, volume (c^3**)** and specific volume were evaluated, 57.50±1.15, 205±1.65 cm ^{3} /g and 3.56 ±2.15 respectively as showed in Table (3), Data showed that all organoleptic characteristics conducted
on the pies were good, and the total acceptance rate of the products was 90.01±2.50%.

Table (5) Distribution of the studied sample according to adherence to Dixon` Dash Diet.

Type of foods	Dixon Dash Index												
	Habitual diet				Regimen With Moringa Pies				Regimen with Bread				P
	0	0.5	1	>1	0	0.5	1	>1	0	0.5	1	>1	
Fruits including fruits juices≥ 4 servings/d	47.5	34.4	13.1	4.9	3.3	23.0	54.1	19.7	4.9	29.5	52.5	13.1	**0.031***
vegetables, which includes potatoes ≥4 servings/d	41.0	37.7	14.8	6.6	4.9	9.8	73.8	11.5	8.2	23.0	55.7	13.1	**0.044***
Whole grains ≥4 servings/d	23.0	44.3	21.3	11.5	4.9	11.5	65.6	18.0	19.7	21.3	37.7	21.3	**0.058**
Total dairy ≥2 servings/d	47.5	32.8	11.5	8.2	4.9	14.8	62.3	18.0	23.0	24.6	41.0	11.5	**0.016***
Nuts, seeds, and legumes ≥3 servings	39.3	21.3	23.0	16.4	6.6	4.9	65.6	24.6	13.1	14.8	54.1	18.0	**0.020***
Meat and meat equivalent intake is <6 oz (170 g)/d,	11.5	29.5	37.7	21.3	24.6	49.2	16.4	9.8	21.3	45.9	24.6	8.2	**0.011** **
Added sugar intake is ≤3% of total energy intake	11.5	9.8	42.8	36.1	23.0	34.4	36.1	6.6	16.4	39.3	32.8	11.5	**0.082**
Saturated fat intake is ≤5% of total energy intake	11.5	36.1	29.5	23.0	27.9	49.2	14.8	8.2	23.0	47.5	19.7	9.8	**0.012***
Total Diet Score	**4.89±0.48**				**7.93±0.21**				**7.51±0.30**				**0.040***

The total score is a summation of the 8 components, with a minimum total score of 0 points and a maximum total score of 8 points. Participants receive 0 point their intake did not reach the RDAs, 0.5 for met intermediate RDAs, 1 point for met the RDAs >1 more the RDAs

p* Significant at p ≤0.05** Highly Significant at p≤0.01

Table (6): Mean ± SE, range and % change of Age, weight, Height, BMI and Bone mass of the studied sample before and after intervention

Parameters	Basal (1)	End of first phase (2)		End of second phase (3)	
	Mean ± SE, Range				
Age (years)	47.37± 1.31 (30-63)				
Height (cm)	157.00±0.71 (145-168)				
	Mean ± SE, Range	Mean ± SE, Range	%Change 1vs 2	Mean ± SE, Range	% Change 2vs3
Weight (Kg)	89.81±1.72 (65.5-126.5)	87.68±1.62 [a**] (65.00-120)	-2.37	87.93±1.78 [b**] (66.5-119)	+0.29
BMI (Kg/m^2)	36.50±0.68 -46.46) (24.96	35.64±0.65 [a**] (25.34-43.71)	-2.36	35.37±0.70 [b**] (25.34-43.71)	-0.76
Bone mass (kg)	2.77±0.019 (3.20-2.50)	2.74±0.023[a*] (3.30-2.40)	-1.08	2.76±0.023[c*] (3.30-2.60	+0.73

Body Mass Index: BMI * Significant at p ≤0.05** Highly Significant at p≤0.01
a: 1 versus 2 b: 1 versus 3 c: 2 versus 3

Table (7): Mean±SE. range and % of change of the different Criteria of Metabolic Syndrome among the studies sample before and after intervention

Parameters	Basal (1)	End of first phase (2)		End of second phase (3)	
	Mean±SE Range	Mean±SE Range	% change 1vs 2	Mean±SE Range	% change 2vs3
MWC (cm)	92.16±1.01 (80.00-105.00)	90.59±1.02 [a**] (79.00-104.50)	-1.70	90.38±1.13 [b**] (78.00-103.00)	-0.23
FBG (mg/dL)	114.44±3.68 (83-177)	115.75±5.78 (89-259)	+1.45	113.46±4.25 (90-196)	-1.98
TG (mg/dL)	116.69±6.16 (78.14-226.69)	100.00±6.29 [a**] (59.26-211.99)	-14.30	92.10±5.87 [b**] (57.25-205.57)	-7.90
HDL-C (mg/dL)	52.86±1.66 (36.94 – 73.59)	56.44±2.13 [a**] (36.48 – 86.3)	+6.77	50.25±1.48 [c**] (34.2 – 68.97)	-10.97
Blood Pressure					
SBP (mmHg)	133.06±2.85 (98-174)	130.38±2.47 (107-171)	-2.01	128.21±2.29 (92-164)	-1.66
DBP (mmHg)	80.00±0.94 (68-94)	80.06±1.18 (62-101)	+0.08	78.79±1.05 (62-92)	-2.25

Minimal Waist Circumference: MWC, Fasting Blood Glucose: FBG, High Density Lipoprotein-Cholesterol: HDL-C, Systolic Blood Pressure: SBP, Diastolic Blood Pressure: DBP
* Significant at p ≤0.05, ** Highly Significant at p≤0.001 a: 1 versus 2 b: 1 versus 3 c: 2 versus 3

Figure (1) showed the fatty acids in Moringa Leaves pie. The important fatty acids detected were the palmitic acid (28.76 min, 12.71%), stearic acid (34.36 min, 4.62%), Oleic acid (35.22 min, 23 %), Linoleic acid (36.97 min, 54.89 %) and Linolenic acid (39 min, 4.78%). Figure (2) showed the caloric consumption, vitamin D, and the two minerals phosphorous and calcium contents of the habitual diet and the different types of regimens consumed by the volunteers. The result revealed significant decrease in the daily total calories consumed by the volunteers after they followed the different regimens at p≤0.011-0.001. Data showed that the daily intake of the important minerals intake namely phosphorus and

calcium, was greatly improved after the participants followed the regimens, where their daily intake was 71.89% and 52.23% of the RDAs before intervention to reach 91.29% and 94.02% of the RDAs with the moringa regimen, and 90..97% and 92.97% in the second period with bread regimen for the two elements respectively. The daily vitamin D intake reported in the habitual diet of the participants was low when compared to the RDAs (42.8%) After they followed the two regimens obvious improvement was detected where the daily intake of vitamin reached 69.0 and 62.20.0% of the RDAs.

Table (5) showed the distribution of the studied sample according to their adherence to Dixon' Dash Diet
before and after intervention. Data showed that the total dietary scores were 4.89±0.48, 7.93±0.21 and 7.51±0.30 for the habitual diet, the regimen with moringa and the low caloric diet respectively. The analysis of habitual diet indicated that the percentage of the participants was the lowest in the consumption of the food groups, fruits juices, vegetables which includes potatoes, whole grains, total dairy and nuts, seeds, and legumes when compared to their ratio when eating both the moringa regimen and the low-calorie diet. While the percentage was more in terms of eating meat and meat equivalent, added sugar and saturated fat intake.

Table (6) showed the mean ± SE, range and percent change of age, anthropometric parameters and the bone mass of the obese women before and after the two phases of intervention. Data revealed significant decrease in the anthropometric values at p≤0.05-0.01 when comparing the values in the two periods with the basal values at the beginning of the study. The percent changes reported in the first phase in the weight, BMI and bone mass were -2.37, 2.36.and -1.08 respectively, while the changes in the second phase were +0.29, -0.76 and +0,73 when compared to the first phase..

Table (7) showed the mean±SE, range and percent change of the different criteria of metabolic syndrome among the studies sample before and after intervention. The three parameters MWC, TG and HDL-C revealed significant improvement with p≤0.05-0.001 after intervention when compared to the basal values. Yet both FBG and blood pressure values showed only numerically decrease. The percent change between the first phase values of MWC, TG, HDL-C and SBB were higher than the percent changes in their values between the first phase and second phase.

Table (8) showed the mean±SE , range and percent change of inflammatory IL1-beta , TAC ,insulin, HOMA-IR and Urinary function parameters of the studied sample before and after intervention In the first phase, there was a significant reduction in the values of IL1-beta, insulin, and HOMA-IR at p≤0.05-0.001; however, these values increased and returned to their initial levels in the second phase. The FGF-23 concentration and the kidney function parameters serum urea decreased significantly at p≤0.05-0.001, but there were no significant differences in creatinine serum concentrations. In the second phase of the regimen, where the nutritional supplement was omitted, there was a significant increase in the serum concentration FGF-23, creatinine and urea levels compared to the first phase or baseline.. On the contrary serum concentration of TAC and the eGFR significantly increase at the end of the first phase, and decrease significantly at the end of the second phase. Except for TAC and eGFR, all values showed a high percent decrease when comparing the first phase values to the basal values, but an increase in the percent changes when comparing the second phase to the first phase.

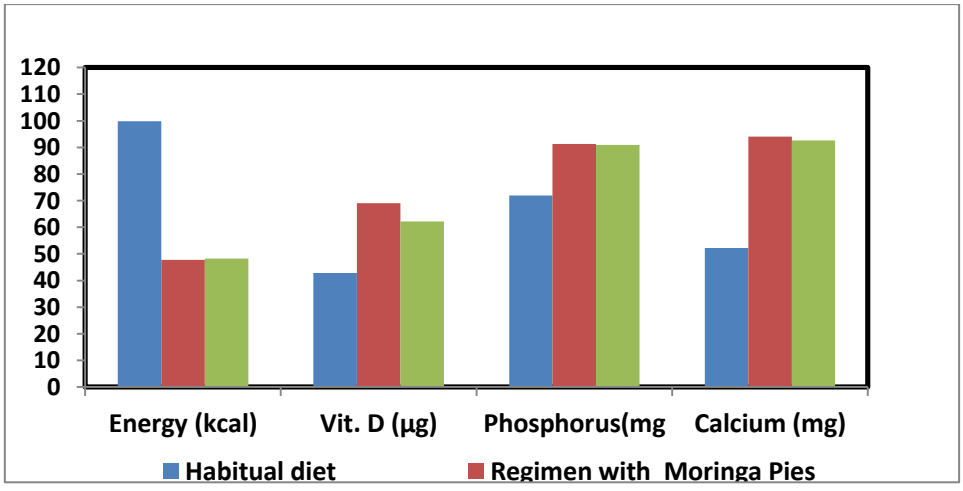

Fig 2: % RDAs of Calories, Vitamin D, Phosphorus and calcium intake Before and after intervention.

P value between groups: for Energy (kcal) 0.001, Vitamin D 0.011, Phosphorus 0.012, and Calcium 0.001
* Significant at p ≤0.05** Highly Significant at p≤0.001

Table (8) Mean ±SE, range and % change of Inflammatory, AOC, HOMA-IR and Urinary function parameters sample before and after intervention

Parameters	Basal (1)	End of first phase (2)		End of second phase (3)	
	Mean±SE & Range	Mean±SE &Range	% change 1vs 2	Mean±SE &Range	% change 2vs3
IL 1β (pg/ml)	95.63±3.23 (69.64-152.78)	74.25±1.94 [a**] (38.89-100.39)	-22.36	94.54±3.43 [c**] (67.30-143.84)	+27.37
TAC (mM/L)	1.22±0.04 (0.67-1.65)	1.45±0.03 [a**] (0.97-1.67)	+18.85	1.31±0.04 [c**] (0.76-1.65)	-9.66
Insulin (µ IU/ml)	24.87±0.74 12.47-32.01	17.12±o.81[a]** 5.21-25.72	-31.16	23.63±1.43[c]** 7.83-43-47	+38.03
HOMA– IR	6.85±0.21 (4.9-9.71)	4.72±0.26 [a**] (1.66-9.56)	-31.o9	6.38±0.38 [c**] (3.04-12.02)	+35.17
Creatinine (mg/dL)	0.88±0.02 (0.63-1.12)	0.84±0.03 (0.61-1.35)	-4.55	0.88±0.03 [c*] (0.63-1.22)	+4.76
Urea (mg/dL)	27.04±0.96 (17.39 – 40.64)	24.53±0.76 [a**] (12.24 – 33.23)	-9.28	25.13±1.13 [b*] (15.84 - 40.12)	+2.45
eGFR (mL/min/1.73 m^2)	76.48±2.20 (53-110.58)	82.22±2.42 [a*] (42.01-115.59)	+7.51	77.30±2.62 [c**] (47.45-111.27)	-5.98
FGF-23 (ng/L)	29.88±0.97 (21.65-42.61)	24.10±0.98 [a**] (15.65-39.9)	-19.34	30.02±1.13 [c**] (20.9-42.03)	+24.56

Interleukin 1β: IL1β, Total Antioxidant Capacity: TAC, Homeostasis Model Assessment-Insulin Resistance: HOMA-IR, Estimated Glomerular Filtration Rate: eGFR,, Fibroblast growth factor 23: FGF23,
* Significant at p ≤0.05 ** Highly Significant at p≤0.001 a: 1 versus 2 b: 1 versus3 c:2vs3

Table (9) showed the correlation Coefficient between FGF-23 and different anthropometric, blood pressure and biochemical parameters of the studied group before and after intervention. Findings revealed negative significant correlation at the basal and after the two periods of interventions between the serum concentration of FGF-23 and the BMI, TG, insulin concentration and the HOMA/values with p values range ≤0.033-0.001. Negative significant correlation at the basal and the first phase only was detected between FGF-23 and MWC and SBP at p≤0.008-0.000 while DBP and FBG concentrations revealed negative significant correlation at the end of the two phases of intervention at p≤0.026-0.001. The correlation between the FGF-23 and creatinine showed positive significant correlation and negative significant correlation with the eGFR (p≤0.001) at the end of the first stage of intervention. Positive significant correlation was reported between FGF-23 and the inflammatory parameter IL1β which was highly significant at the baseline data.

Discussion

In the current study when comparing participants' food consumption with the DASH like diet, the highest score was found in the first phase of the intervention, when the patients consumed the regimen containing the nutritional supplement. In this phase most of the MetS parameters were significantly decrease, in addition to the serum concentration of FBG-23, urea, insulin, HOMA-IR, and IL-1β levels. Significant increase in the level of HDL-C, TAC, and eGFR, was detected. After omitting the dietary supplement, these results were reversed except the adiposity indices and TG which continued to decrease but at a lower rate.

Obesity, metabolic disorders and dietary supplement

In healthy individuals, osteoblasts and osteocytes primarily produce the 32 kDa glycoprotein known as fibroblast growth factor-23 in the bone [**29]** According to Natsuki et al. **[30],** although the underlying mechanism is unknown, FGF23, a crucial regulator of phosphate metabolism, has been connected to obesity, metabolic syndrome, and cardiovascular disease in the general population. Hu et al. **[6]** found that obese individuals, particularly those with abdominal obesity, have elevated serum FGF23 levels. Serum FGF23 levels in men and postmenopausal women may be a marker for the risk of metabolic and cardiovascular disease, according to independent associations between the presence of abdominal obesity and an increase in the serum FGF23 levels of these groups'.

Table (9) Correlation Coefficient between Fibroblast growth factor- 23 (FGF-23) and different anthropometric, blood pressure and biochemical parameters

Parameters	Basal		End of first phase		End of second phase	
	Correlation Coefficient (r & p values)					
Age (yr)	-0.209	0.97				
Height (cm)	-0.591	0.001**				
BMI (kg/m^2)	--0.386	0.002**	-0.266	0.033*	-0.433	0.001**
MWC (cm)	-0417	0.001**	-0.327	0.008**	-0.107	0.449
SBP	-.461	0.001**	-0.414	0.001**	-0.233	0.096
DBP	-0.233	0.064	-0.416	0.001**	-0.309	0.026*
FBG (mg/dl)	0.008	0.95	-0.323	0.009**	-0.437	0.001*
TG (mg/dl)	-0.263	0.036*	-0.459	0.000**	-0.424	0.002**
HDL-C	0.179	0.156	-0.349	0.005**	-0.075	0.536
Urea	-0.127	0.318	-0.125	0.325	-0.023	0.872
Creatinine	0.217	0.085	0.593	0.000**	0.099	0.486
eGFR	-0.140	0.289	-0.460	0.001**	-0.023	0.872
Insulin	-0.588	0.001**	-0.325	0.009**	-0.430	0.001**
HOMA/IR	-0.718	0.001**	-0.558	0.001**	-0.359	0.009**
IL1β	0.766	0.001**	0.076	0.549	0.150	0.288

Body mass index: BMI, Minimal Waist Circumference: MWC ,: Systolic Blood Pressure SBP: ,*:* Diastolic Blood Pressure: *DBP*: , Fasting blood glucose::FBG, Triglyceride: TG. High density lipoprotein -clolesterol :HDL-C , Estimated Glomerular Rate: eGFR, Homeostasis Model Assessment-Insulin Resistance: HOMA-IR , Interleukin 1β: IL1β,
* Significant at p <0.05 ** Highly Significant at p<0.001

This is consistent with the findings of the current study, which showed that in the first-stage when the patients adhered to the recommended diet therapy, data revealed an inequality in the percent decrease in obesity indices compared with the biochemical parameters, where the decrease was significantly greater in the latter, particularly the FBG-23 hormone concentration.

Mitochondria are critical for regulating macrophage polarization, differentiation, and survival. Changes to mitochondrial metabolism and physiology induced by extracellular signals may underlie the corresponding state of macrophage activation. Macrophage mitochondrial dysfunction is a key mediator of obesity-induced macrophage inflammatory response.

Mitochondrial dysfunction drives the activation of the NLRP3 inflammasome, which induces the release of IL-1β. IL-1β leads to decreased insulin sensitivity of insulin target cells via paracrine signalling signalling or infiltration into the systemic circulation [**31].**

Oxidative stress (OS) and intracellular redox imbalance both brought on by the persistence of the chronic inflammatory conditions that characterized MetS, which serve as a link between MetS and the associated diseases. According to Vona et al. **[32]** a major underlying mechanism for mitochondrial dysfunction, accumulation of protein and lipid oxidation products, and impairment of the antioxidant systems is the increase in oxidizing species formation in MetS. In this context, the results of this study

showed a decrease in the level of both the inflammatory marker IL1β and an increase in the serum TAC after following the full nutritional therapy. According to Oyeyinka and Oyeyinka, **[33]** moringa oleifera (MO) plants have the potential to be used in industrial food applications as well as functional food. M. oleifera contains large amounts of proteins, vitamin A, minerals, essential amino acids, antioxidants and flavonoids. The M. oleifera extracts have a wide range of pharmacological or nutraceutical properties, including effects that are anti-inflammatory, antioxidant, anti-cancer, hepatoprotective, neuroprotective, hypoglycemic, and reduce blood lipid levels. M. oleifera's advantageous traits are closely associated with its phytochemicals, particularly with its bioactive flavonoids and isothiocyanates [**34**]. In rats fed a high fat diet (HFD), M. Oleifera leaf extract led to significantly lower fasting glucose and insulin levels **[35].** Additionally in animal models Moringa pterygosperma Gaertn. (MP) and Moringa oleifera (MO) both have shown strong antioxidant, hypolipidemic, anti-atherosclerosis, and hepatoprotective effects. These effects include the suppression of reactive oxygen species (ROS), inhibition of lipid peroxidation, and up regulation of antioxidant gene expression [**36, 37].** In the same time, patients with polycystic ovary syndrome (PCOS) and metabolic abnormalities have been shown to benefit from curcumin's improved glycemic control and lipid metabolism without experiencing any negative side effects **[38].**

According to the aforementioned research, the current study demonstrated the health benefits of using a nutritional therapy supplemented with moringa oleifera and turmeric in management of obesity and the related metabolic abnormalities.

Correlation coefficient between metabolic syndrome, inflammation renal parameters and FGF-23

As previously mention the results of this study revealed an inequality in the reduction recorded between obesity indices and FGF-23hormone throughout the study. Furthermore intragroup correlation coefficient revealed negative association between FGF23 and the MetS parameters associated with obesity in addition to the eGFR values, yet positive correlation was found with creatinine and IL-1β levels.

Given that both obesity and a high serum FGF-23 concentration are linked to hypophosphatemia [39,5], so the negative correlation between FGF-23 and parameters related to obesity found in this study may help to maintain a healthy serum phosphorus homeostasis among obese patients..

Association between obesity, diabetes mellitus, FGF-23 and phosphate homeostasis

To explain the link between serum phosphate, BMI, and body composition, several hypotheses have been offered [40]. In theory, blood phosphate or its regulators parathyroid hormone (PTH), FGF23, 1,25-dihydroxyvitamin D [1,25(OH)2D], or dietary phosphate can explain the link between phosphate and BMI and obesity. Billington and colleagues [40] reported an inverse connection between phosphate and fat mass in 1676 postmenopausal women and 323 community-dwelling men without current illness. This connection remained significant after adjusting for age, PTH, and estimated glomerular filtration rate (eGFR) [41]. Vitamin D is required for calcium and phosphorus metabolism, as well as the formation of bone tissue. According to recent studies, vitamin D blood levels in obese adults are much lower, most likely due to adipose tissue uptake [41]. To explain the negative relationship between BMI and FGF-23 levels in this study, the decrease in vitamin D associated with obesity, as well as the findings of the study's dietary history of the participants, which revealed an inadequate consumption of vitamin D, calcium, and phosphorous, which was more pronounced at baseline values, may be contributing factors. Alternatively, multiple studies have demonstrated that abnormal phosphate balance may contribute to the development of metabolic syndrome (MetS) [42].

Emerging evidence suggested that patients with diabetes had significantly and independently a higher rate of hypophosphatemia as compared to nondiabetic subjects [43]. Diabetic individuals frequently have dysregulated phosphorus metabolism. Because plasma phosphate levels may be normal or even low early in the evolution of diabetes, these deregulations may be difficult to detect, on the other hand Vaart et al. [44] stated that phosphate deregulation has a deleterious impact on glucose metabolism. Furthermore, several studies have found that enhanced glycemic control in stable diabetic outpatients is associated with increased serum phosphate levels and decreased urine phosphate excretion [45].

Obesity has been linked to metabolic issues such as insulin resistance, dyslipidemia, and changes in bone mineralization [**46**]. In obese subjects with hepatic steatosis, Kutluturk et al. (discovered significant negative correlations between FGF-23 and fasting insulin levels as well as C-peptide levels **[47**]. Several studies have found a link between insulin resistance and elevated FGF-23 levels. **[48,49].** Insulin has been shown in preclinical studies to be a negative regulator of FGF23 by activating the

PI3K/PKB/Akt signalling transcription factor forkhead box protein O1 (FOXO1) [5].
Hyperglycemia, which is associated with high blood insulin levels and HOMA, causes an increase in renal phosphate loss by osmotic diuresis. As a result, the negative association of these parameters with the hormone FGF-23 that found in the current study, and which is consistent with prior findings may be beneficial in preserving serum phosphorus hemostasis. Following nutritional intervention, a substantial negative connection between blood FGF-23 levels and circulating FBG was identified, This association could be explained by the fact that improvement of the glycemic level resulting in less phosphorus loss in the urine.

Inflammation and FGF-23
According to McKnight Q et al. [50] induction of FGF-23 was consistent with renal production of the inflammatory protein IL-1 and its systemic elevation in the circulation. In mice in vivo and in cultured bone chips, IL-1 has been shown to be able to induce FGF-23. Additionally, in both the secondary nephrotoxicity serum-mediated model and the congenital CKD model, neutralising antibodies against IL-1 blocked the expression of FGF-23. Extracts from the leaves and seeds of Moringa oleifera could effectively counteract the negative effects of inflammation and oxidative stress. These extracts, particularly leaf extracts, are notable for reducing prominent pro-inflammatory markers like tumour necrosis factor-, interleukin (1L)-, IL-6, monocyte chemoattractant protein-1, and nitric oxide synthase [51] This effect was clear in this study, as the positive relationship between the inflammatory factor and the hormone did not persist after the use of nutritional therapy.

Kidney functions parameters and FGF-23
The relationship between FGF-23 and the other kidney parameters such as urea, creatinine, and eGFR showed a nonsignificant negative correlation with serum urea and eGFR at the baseline, In the first phase with the dietary supplement creatinine revealed a significant positive correlation, while eGFR showed negatively significant correlated. This link between FGF-23, creatinine, and eGFR suggests that it could be used as an independent factor in kidney function research. Traditional creatinine and indirect glomerular filtration rate (GFR) indicators have significant limitations and are not effective at spotting early glomerular filtration rate declines.

Conclusion
The findings of this study revealed that obese and metabolic patients who consumed a dietary therapy consisting of pies containing Moringa oleifera leaf and turmeric powder as a bakery product, in addition to a low-calorie regimen based on the Dash diet, had potent anti-obesity, antihyperlipidemic, antioxidant, anti-inflammatory, and antdiabetic effects. The effect was transient, as the improvement started to fade after the nutritional supplement was removed. The renal function parameter fibroblast growth factor (FGF-23), which showed a positive correlation with IL-1β, significantly improved. This finding does not rule out the possibility that moringa pie consumption can modulate FGF-23 levels by lowering inflammatory IL-1β concentrations. In contrast to previous research, the current study demonstrated an inverse relationship with a significant difference between serum FGF-23 concentration and metabolic syndrome parameters throughout the study, which may be in favour of maintaining serum phosphorus hemostasis in obese patients. The link between FGF-23, creatinine, and eGFR suggests that it could be a useful factor in kidney function research. However, more research is needed to validate such causal associations.

Consent of publication
All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Conflict of interest:
The authors declare no competing interests.

Funding:
The practical part of the work was financial supported by the National Research Centre, Egypt, as a foundation for the Project Number. No. “1205020” entitled “Metabolic Syndrome and the Development of Chronic Kidney diseases; early diagnosis and better dietary tools for prevention and management”.

Acknowledgements
The authors would like to acknowledge. the National Research Centre, Egypt, for its support and fund the project
We also express our thanks to the volunteers for their participation in this study.

Author contributions
S.M.: conceived and designed the study; she is the PI of the project from which this data was derived and she wrote the draft of the article. H.A: had responsibility for biochemical analysis and laboratory investigations. M.I.A: was responsible for clinical

examination and anthropometric measurements. N.H was responsible for preparation of the supplement and analysis of nutritional intake and dietary habit and also in subject's selections and consent signature by the subjects A.M and M.M had the responsibility for chemical analysis of the supplement. ST revised the final manuscript. H.A, M.I.A and N.H were responsible about statistical analysis.

References

[1] Tune J. D., Goodwill A. G., Sassoon D. J., Mather K. J. (2017). Cardiovascular consequences of metabolic syndrome. Transl. Res. 2017;183: 57–70. doi10.1016/j.trsl.2017.01.001

[2] Wojcik M, Dolezal-Oltarzewska K, Janus D , Drozdz D, FGF23 contributes to insulin sensitivity in obese adolescents - Preliminary results. Clinical Endocrinology 2011; 77(4):537-4 doi:10.1111/j.1365-2265.2011.04299.x, ,

[3] Mosavat M, Omar SZ, Sthanshewar P. Serum FGF-21 and FGF-23 in association with gestational diabetes: a longitudinal case-control study. Horm Mol Biol Clin Investig. 2020 13;41(2). doi: 10.1515/hmbci-2019-0060.

[4] Erben RG. Physiological Actions of Fibroblast Growth Factor-23. Front. Endocrinol.2018; 9:267. doi: 10.3389/fendo.2018.00267

[5] Hu X, Ma X, Luo Y, Xu Y, Xiong Q, Pan X, Xiao Y, Bao Y, Jia W. Associations of serum fibroblast growth factor 23 levels with obesity and visceral fat accumulation. Clin Nutr.2018 ;37(1):223-228.. doi: 10.1016/j.clnu.2016.12.010.

.[6]. Ali FN, Falkner B., . Gidding SS., Price HE., MS . Keith SW., . Langman CB., Fibroblast Growth Factor-23 in Obese, Normotensive Adolescents is Associated with Adverse Cardiac Structure. J Pediatr. 2014 Oct; 165(4): 738–743.e1.

[7] Muñoz-Castañeda JR, Rodelo-Haad C, Pendon-Ruiz de Mier MV , Martin-Malo A. Santamaria R., Rodriguez M. Klotho/FGF23 and Wnt Signaling as Important Players in the Comorbidities Associated with Chronic Kidney Disease . *Toxins* 2020, *12*(3), 185; https://doi.org/10.3390/toxins12030185

[8]. Xu L, Yan X, Zhao Y , Wang J, Liu B , Yu S , Fu J , Liu Y , Su J . Macrophage Polarization Mediated by Mitochondrial Dysfunction Induces Adipose Tissue Inflammation in Obesity Int J Mol Sci. 2022 Aug 17;23(16):9252. doi: 10.3390/ijms23169252.

[9].Milla PG, Peñalver R, Gema Nieto G., Health Benefits of Uses and Applications of Moringa oleifera in Bakery Products. Plants 2021, 10(2), 318; https://doi.org/10.3390/plants10020318

[10]. Oyeyinka, A.T.; Oyeyinka, S.A. Moringa oleifera as a food fortificant: Recent trends and prospects. J. Saudi Soc. Agric. Sci. 2018, 17, 127–136.

[11]. Pivari F, Mingione A, Piazzini G , Ceccarani C, Ottaviano E, Brasacchio C, Dei Cas M, Vischi M, Cozzolino MG, Fogagnolo P, Ri va A , Petrangolini G, Barrea L , Di Renzo L , Borghi E, Signorelli P, Paroni R, Soldati L Curcumin Supplementation (Meriva®) Modulates Inflammation, Lipid Peroxidation and Gut Microbiota Composition in Chronic Kidney Disease Nutrients 2022 Jan 5;14(1):231. doi: 10.3390/nu14010231.

[12].Ghosh, SS, Gehr TWB, Ghosh S. Curcumin and Chronic Kidney Disease (CKD): Major Mode of Action through Stimulating Endogenous Intestinal Alkaline Phosphatase. Molecules. 2014 ; 19(12): 20139–20156. doi: 10.3390/molecules191220139

[13] .Akbari M , Lankarani KB, Tabrizi R, Ghayour-Mobarhan M, Peymani P, Ferns G, Ghaderi A, Asemi Z. The Effects of Curcumin on Weight Loss Among Patients With Metabolic Syndrome and Related Disorders: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front Pharmacol. 2019; 10: 649. doi: 10.3389/fphar.2019.00649

[14]. AACC International (2000) Approved Methods of the American Association of Cereal Chemists, 10th Ed. Methods 10-10B, 26-21A, 44-19, 44-08, and 54-40A. The Association: St. Paul, MN..

[15].Nutri survey (2007). Nutrition Survey and Calculation *Guidelines, Software and additional Information* for Windows – Cop(2007)(Last page modification: April 2nd, 2010.Dr. Juergan Ethardt – SEAMEO-TROPMEP. RCCN-University of Indonesi

[16]. AOCS, (1998). Official Methods and Recommended Practices of the American Oil chemist's Society (5thEdn.). AOCS press, Champaign, Washington

[17]. Tanner JM, Hiernau J& Jerman S. Growth and physical studies. In: Human Biology: A guide to field methods. Eds. Weiner JS, Lourie SA. IBP. London: Blackwell Scientific Publications, 1969.

[18]. Barham D& Trinder P. An improved color reagent for determination of blood glucose by oxidase system.Analyst. 1972; 97:142-45.

[19].Wornick DF, Albers JJ. A comprehensive evaluation of the heparin-manganese precipitation procedure for estimating high density lipoprotein cholesterol. J Lipid Res. 1978;19(1):65-76.

[20].Seidel J, Klos S, Ziegenhorn T. AACC meeting abstract 34. Clin Chem. 1993; 39:1127.

[21].Ciuti, R. and Liguri, GA. Novel Assay for Measuring Total Antioxidant Capacity in Whole Blood and Other Biological Samples. Journal of Biomedical Science and Engineering, 2017; 10, 60-76. doi: 10.4236/jbise.2017.102007.

[22]. Bowers, L.D. and Wong, E.T. Kinetic Serum Creatinine Assays. II. A Critical Evaluation and Review. Clinical Chemistry 1980; 26, 555-561

[23].Tietz NW, ED. Clinical guide to Laboratory tests. 2ND ED. Philadelphia: WB Saunders; 1990:566.

[24]. Smith ER. The Use of Fibroblast Growth Factor 23 Testing in Patients with Kidney Disease, Clin J Am Soc Nephrol. 2014 7; 9(7): 1283–1303.

[25] Lopez-Castejon, Gloria, and David Brough. "Understanding the mechanism of IL-1β secretion." Cytokine & growth factor reviews. 2011; 22. (4): 189-195.

[26]. Temple, R.C., Clark, P.M., Hales, C.N. Measurement of insulin secretion in type 2 diabetes : problems and pitfalls. Diabetic medicine, 1992;. 9:503-512.

[27]. Majid H, Masood Q, Khan AH Homeostatic Model Assessment for Insulin Resistance (HOMA-IR): A Better Marker for Evaluating Insulin Resistance Than Fasting Insulin in Women with Polycystic Ovarian Syndrome. J Coll Physicians Surg Pak. 2017;27(3):123-126..

[28] Millar P, Cross AJ. Subar AF, Krebs-Smith SM.Comparison of 4 established DASH diet indexes: Examining associations of index scores and colorectal cancer. American Journal of Clinical Nutrition 2013; 98 (3): 794-803. doi:10.3945/ajcn.113.063602

[29] Itoh N, Ohta H, Konishi M. Endocrine FGFs: evolution, physiology, pathophysiology, and pharmacotherapy. *Front Endocrinol* 2015 6:154. doi:10.3389/fendo.2015.00154

[30].Natsuki Y, Morioka T , Fukumoto S, Kakutani Y, Yamazaki Y, Masafumi Kurajoh Q A, Mori K, Shoji T, Imanishi Y, Masaaki Inaba M, Emoto M. Role of adiponectin in the relationship between visceral adiposity and fibroblast growth factor 23 in non-diabetic men with normal kidney function. Endocr J. 2022 ; 69(2):121-129. doi: 10.1507/endocrj.EJ21-0185.

[31].Vona , Gambardella L, Cittadini C, Straface E, Pietraforte D. Biomarkers of Oxidative Stress in Metabolic Syndrome and Associated Diseases Oxid Med Cell Longev 2019 5;2019:8267234. doi: 10.1155/2019/8267234.

[32] Oyeyinka, A.T.; Oyeyinka, S.A. Moringa oleifera as a food fortificant: Recent trends and prospects. J. Saudi Soc. Agric. Sci. 2018, 17, 127–136.

[33].Kou X, Biao Li B , Olayanju JB, Drake JM, Chen N. Nutraceutical or Pharmacological Potential of Moringa oleifera Lam Nutrients . 2018 ;10(3):343. DOI: 10.3390/nu10030343

[34]. Metwally F.M., Rashad H.M., Ahmed H.H., Mahmoud A.A., Abdol Raouf E.R., Abdalla A.M. Molecular mechanisms of the anti-obesity potential effect of *Moringa oleifera* in the experimental model. Asian Pac. J. Trop. Biomed. 2017;7(3):214–221.

[35]. Fard M.T., Arulselvan P., Karthivashan G., Adam S.K., Fakurazi S. Bioactive extract from moringa oleifera inhibits the pro-inflammatory mediators in lipopolysaccharide-stimulated macrophages. Pharmacogn. Mag. 2015;11(4):556–563

[36]. Asgari-Kafrani A., Fazilati M., Nazem H. Hepatoprotective and antioxidant activity of aerialparts of Moringa oleifera in prevention of non-alcoholic fatty liver disease in Wistar rats. S. Afr. J. Bot. 2020;129:82–90.

[37].Chien YJ, Chang CY, Wu MY, Chen CH, Ho rng YS, Wu HC. Effects of Curcumin on Glycemic Control and Lipid Profile in Polycystic Ovary Syndrome: Systematic Review with Meta-Analysis and Trial Sequential Analysis. Nutrient 2021;13(2):684. doi: 10.3390/nu13020684

[38]. Bosman A , Campos-Obando N, Medina-Gomez C, Voortman T, Uitterlinden AG, Zillikens MC. Serum Phosphate, BMI, and Body Composition of Middle-Aged and Older Adults: A Cross-Sectional Association Analysis and Bidirectional Mendelian Randomization Study The Journal of Nutrition, 2022; 152, (1) ;276–285, https://doi.org/10.1093/jn/nxab351

[39] BillingtonEO, GambleGD, Bristow,Reid IR Serum phosphate is related to adiposity in healthy adult. Eur J Clin Invest 2017;47(7):486–93.

[40] Buscemi S, Buscemi C, Corleo D, De Pergola G, Caldarlla R, Meli F, Randazzo C, Milazzo S. Barile AM, Rosafio G, Settipani V, Gurrera S, Borzì AM , Ciaccio M. Obesity and Circulating Levels of Vitamin D before and after Weight Loss Induced by a Very Low-Calorie Ketogenic Diet. Nutrients 2021 ;13(6):1829. doi: 10.3390/nu13061829.

[41].Wong SK. A Review of Current Evidence on the Relationship between Phosphate Metabolism and Metabolic Syndrome Nutrients 2022 ;14(21):4525. doi: 10.3390/nu14214525

[42].Rashed P, Hyassat D, Batieha A, Aldabbas M, Aldarabah F, EL-Khateeb M, Ajlouni K. Prevalence and Correlates of Hypophosphatemia Among Type 2 diabetic patients attending the National Center for Diabetes, Endocrinology and genetics (NCDEG). Annals of Medicine and SurgeryVolume 78, June 2022, 103770, https://doi.org/10.1016/j.amsu.2022.103770

[43].van der Vaart A, Stanley M.H. Yeung, Peter R. van Dijk, Stephan J.L. Bakker, and Martin H. de Borst Phosphate and fibroblast growth factor 23 in diabetes Clin Sci (Lond). 2021 ; 135(14): 1669–1687. doi: 10.1042/CS20201290

[44].Nagasaka S., Murakami T., Uchikawa T., Nagasaka S., Ishikawa S.E. Saito TE. Effect of glycemic control on calcium and phosphorus handling and parathyroid hormone levelin patients with non-insulin-dependent diabetes mellitus. Endocr. J. . 1995; 42: 377–383 10.1507/endocrj.42.377

[45].Kutluturk Y, Akinci A, Ozerol IH, Yologlu S. The relationship between serum FGF-23 concentration and insulin resistance, prediabetes and dyslipidemia in obese children and adolescents. J Pediatr Endocrinol Metab. 2019 ;32(7):707-714. doi: 10.1515/jpem-2018-0507.

[46] Hanks L.J., Casazza K., Judd S.E., Jenny N.S. and Gutiérrez O.MAssociations of fibroblast growth factor-23 with markers of inflammation, insulin resistance and obesity in adults. PLoS ONE. 2015 10, *(3): e0122885*. https://doi.org/10.1371

[47]. Nakashima A., Yokoyama K., Kawanami D., Ohkido I., Urashima M., Utsunomiya K.et al.. Association between resistin and fibroblast growth factor 23 in patients with type 2 diabetes mellitus. Sci. Rep. 2018;8, 13999 10.1038/s41598-018-32432-z

[48]. Bär L., Feger M., Fajol A., Klotz L.-O., Zeng S., Lang F.et al.. (2018) Insulin suppresses the production of fibroblast growth factor 23 (FGF23). Proc. Natl. Acad. Sci. U.S.A. 2018;115 (22) :5804–5809. . doi: 10.1073/pnas.1800160115

[49] McKnight Q , Jenkins S , Li X, Nelson T, Marlier A, Cantley LG , Finberg KE, Fretz JA. IL-1β Drives Production of FGF-23 at the Onset of Chronic Kidney Disease in Mice. J Bone Miner Res, 2020 ;35(7):1352-1362. doi: 10.1002/jbmr.4003

[50]MthiyaneFT , Dludla PV, Ziqubu K, Mthembu SXH, Muvhulawa N, Hlengwa N, Nkambule BB, Mazibuko-Mbeje S E A. Review on the Antidiabetic Properties of *Moringa oleifera* Extracts: Focusing on Oxidative Stress and Inflammation as Main Therapeutic Targets. Front Pharmacol, 2022 11;13:940572. doi: 10.3389/fphar.2022.940572.