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Effect of Growth Differentiation Factor GDF-15 ,Leucine Amino Peptides LAP and Some Biomarker on Patient with Hypertension

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ABSTRACT

Background: Hypertension is a condition in which the blood vessels have persistently raised pressure, where the heart works harder and blood vessels more pressure. Growth differentiation factor-15 (GDF-15) is a marker of inflammation, oxidative stress and it is associated with adverse prognosis in cardiovascular disease.Leucine amino peptidase (LAP) is an enzyme that analyzes the peptide bonds in the protein chain and its function was to stimulate the hydrolysis of leucine which contains amino peptides. This study evaluated change of level of GDF-15concentrationand increase LAP activity on patients with hypertension as a bio marker to identify it and evaluated the difference of GDF-15level and LAP activity among patients and healthy people, the impact of hypertension on the LAP activity and GDF-15 level and different in the LAP activity and GDF-15 level in gender and ageshow relation between Calcium, Magnesium , Zinc, lipid profile, electrolytes, phosphors and GOT enzyme with LAP activity and GDF-15 level and study relation between GDF-15 level with smoking, BMI and family history with hypertension in addition to that found correlative coefficient (r) between GDF-15level and LAP activity with biomarker above.**Methodology:** hundredsample of patients with hypertension were selected their ages between40 to 70 years old and 75 sample of healthy people as a control group where collected. Demographic data including gender, age, height, weight, history of hypertension and duration of treatment, medical history were recorded. Blood pressure and body mass index were also measured. One blood sample(5ml) was taken from each and patientGDF-15level, LAP activity and biomarkers were measured. **Results:** GDF-15level and LAP activity were significantly higher in patients with hypertension (P<0.001) than in control group,which LAP activity was(225 ±35.7) in female patients and (242±53.5) in male patients and in control group in female was (118± 23.1) and in male was (106±13.3). GDF-15level concentration in patients group was in female(1456.7 ± 77.0) and in male was (1555.0 ± 259) while in control group the concentration of GDF-15 was in female (496±111) and in male was(574 ± 232). GDF-15level and LAP activity were significantly higher male patients with hypertension group than in female (P<0.001). there were significant increase in the probability level (P <0.001) in the rate of efficacy ofGDF-15level and LAP activity in group of (61-70) years old compared with other age group. There was a correlation between LAP activity and diastolic and systolic blood pressure which correlation coefficient between systolic blood pressure and enzyme activity (r =0.243) and with diastolic blood pressure was(r= 0.184). There was a correlation between GDF-15 level and diastolic and systolic blood pressure. There was a linear correlation between the increase of GDF-15 concentration there was a linear correlation between the increase of GDF-15 concentration in patients with diastolic blood pressure which correlation coefficient was(r= 0.53) and with systolic blood pressure was(r= 0.62) and with BMI which correlation coefficient was(r=0.23).**Conclusion:** GDF-15level and LAP activity can be used as molecular marker to diagnosis hypertension in early time, there were a strong positive correlation between systolic and diastolic blood pressure with GDF-15level and LAP activity. Smoking, grow old in age and obesity effect was to increase GDF-15 concentration in plasma in patients with hypertension.

Keywords: Growth differentiation factor-15 (GDF-15),Leucine amino peptidase (LAP), Hypertension, BMI, GOT(Glutamic-Oxaloacetic Transaminase), Smoking

Introduction

Hypertension disease is the increase of blood flow through the blood vessels, where the heart works harder and blood vessels more pressure, making it a major risk factor for heart disease, stroke and other serious problems, and the amount of pressure pumped by the heart and the amount of resistance of the arteries to the force of flow and flow of blood, high blood pressure is generally a disease that develops over the years, and despite what is mentioned above, high blood pressure can be detected early to control it[1]. Systolic hypertension is more dangerous than diastolic, as the effect of its height is directly related to artery functioning, and the height of both is the same risk[2]. Heart pressure is a global, even pandemic, affecting between 4-2 million Americans and more than 15 million people around the world. In 2018, 29.4 million Americans had blood pressure[3]. Tissues and organs need oxygen-laden blood in order to do their job and survive, when the heart beats it created the pressure that drives blood through a network of tube-shaped blood vessels[4], which include arteries, veins and

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capillaries, and this pressure was result of two forcesContraction pressure: 1-Systolic blood Pressure: was the force by which the heart pumps blood all over the body at the time of the contraction of the left ventricle; 2-Diastolic blood pressure: was the pressure produced at the lowest level at the left ventricle, measured when the heart muscle relaxes to receive blood coming from the body called low pressure[5].Growth differentiation factor-15 (GDF-15)was a marker of inflammation, oxidative stress and it is associated with adverse prognosis in cardiovascular diseaseand was known a member of the transforming growth factor (TGF)bone morphogenetic protein super family (BMP) [6]. GDF-15 was known as a macrophage inhibiting cytokine (MIC-1), placental transformation growth factor (PTGF), prostate derived factor (PDF), placental bone morphogenetic protein (PLAB), NSAID activated gene-1 (NAG-1), and PL74 [7, 8]. Initially GDF-15 was reported to inhibit TNF production in lipopolysaccharidestimulated macrophages and concerning illustration named as macrophage inhibitory cytokine-1(MIC-1) [9]. However, Subsequent studied did not confirm the same concept of macrophage suppression [10]. GDF-15 was produced as a propeptide form. The N terminus was cleaved and released as disulphide linked dimeric active protein form [11]. GDF-15 is a growth factor whose expression increases with age, Biologic age was related to the several markers such as oxidative stress, protein glycation, inflammation and hormonal changes[12]. Many of these stresses induce GDF-15 expression by either p53 or early growth response protein-1(EGR-1)transcription factors [13]. Higher level of GDF-15 is associated with increased hypertension; it plays pivotal role in development and progression of hypertension diseases such as heart failure, coronary artery diseases, atrial fibrillation, diabetes and cancer[14].High expression of GDF-15 in tumor is also associated with an increase in serum GDF-15 levels, suggesting the use of serum GDF-15 measurement for the diagnosis and management of cancer [15].

Leucine aminopeptidase (LAP) is α-amino acyl peptide hydrolases cytosol E.C.3.4. 11.1 is an enzyme that analyzes the peptide bonds in the protein chain with water weighting 326,000 Dalton[16]. The function of enzyme was to stimulate the hydrolysis of leucine which contains amino peptides, however, it also stimulates the hydrolysis of other amino acids from the nitrogen end of the existing proteins[17]. Its presence is detected in human tissues, animals, plants and bacteria[18]. The enzyme appears highly effective in the small intestinal mucosa, the heart pancreas, the connective tissue cells in the endometrium, and the hepatic cells[19]. Estimating the activity of microsomal leucine amino peptidase in the serum is of clinical importance, because LAP levels rise in obstructive jaundice, cirrhosis, liver cancer, during the latter part of pregnancy and also high level of LAP may be an indicator of lupus erythematous[20].There is evolving support for LAP in the regulation of arterial blood pressure and the pathogenesis of hypertension, intra cerebra ventricular (i.c.v) infusions of LAP reduces while inhibitors of LAP activity have an effect on blood pressure and Deregulation of LAP has been linked to the pathogenesis of hypertension in the spontaneously hypertensive rat[21]. There is evidence that renal tubule LAP inhibits sodium reflux and mechanistic role in salt-adaptation with the functional polymorphism of the LAP gene has been identified in the Dahl salt-sensitive rat Signaling by LAP impacting on blood pressure was likely mediated by regulation of the metabolism of Ang III to Ang IV[22].

Material and Method

Collection of samples:

hundred blood samples were collected from people with hypertension of both genders. samples of patient's were diagnosed of the disease using by measuring of blood pressure and some biochemistry marker .Blood was drawn from the vein using a 5 ml plastic syringe. The blood was placed in clean, sterile plastic tubes free of anticoagulant. And left to coagulate at room temperature. The blood serum was then separated from the centrifuged at 5000 G for 15 minutes to ensure adequate serum red blood cell extraction. The activity of the enzyme was measured directly *invitro.*

Estimation of enzyme Parameters by ELISA in Blood Serum:

Estimation of GDF-15 Concentration in serum

Principle: The Human GDF15 solid-phase sandwich ELISA (enzyme-linked immune sorbent assay) is designed to measure the amount of the target bound between a matched antibody pair. A target-specific antibody has been pre-coated in the wells of the supplied micro plate. Samples, standards, or controls are then added into these wells and bind to the immobilized (capture) antibody. The sandwich is formed by the addition of the second (detector) antibody, a substrate solution is added that reacts with the enzyme-antibody-target complex to produce measurable signal. The intensity of this signal is directly proportional to the concentration of target present in the original specimen [23].

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Estimation of GOT Concentration in serum

Principle: glucose level in serum was measured using [kit Aflu Italia]depending on enzyme method that stated onreaction[24,25].

Principle: The reaction system is as follows:

GOT
L-aspartate + 2-oxoglutarate ⟶ oxaloacetate + L-glutamate

MDH
Oxaloacetate + NADH + H^+ ⟶ l- Malate + NAD^+

Determination of LAP activity in serum

LAP activity in serum was measured using Elisa kit according to equation[26,27].

LAP
R-AMC ⟶ R + AMC (Ex/Em 368/460 nm)
R-AMC= Rad21 mitotic cleavage site peptide 7-amido-4-methyl coumaric acid

LAP activity$_{(UI/L)}$**= LAP** activity$_{(nag/ml)}$ **x 40**

Statistical Analysis:

Statistical analysis of data were done using SPSS software version 17, USA. Statistical tests used ANOVA to analysis of variance. Data were expressed as means (±SD); statistical significance was approved at $P<0.05$.

Results and Discussion

There was a strong relationship between GDF-15 level an inflammation, tumor, diabetes mellitus and cardiovascular disease therefore in this study, we will be find effect of GDF-15,LAP and some biomarker on patients with hypertension disease that. We will be explain how GDF-15 And LAP could be used as a prognostic and diagnostic biomarker for cardio metabolic diseases as hypertension. We have also looked into the potential of GDF-15 and LAP as a novel marker for hypertension diseases. Table2. and figure1.show LAP activity,GDF-15 concentration, levels of trace elements (Ca,Mg, Zn) cholesterol , HDL-C,VLDL-C,LDL-C,TG, Total protein ,Albumin Globulin and electrolytes (Na, K,Cl, P) in the group of hypertension patients compared to control group. The results showed There was no significantly difference in age and gender distribution between healthy control and hypertension patients groups (table1, 2). and significant increase in the probability level ($P<0.001$) in the rate of efficacy of LAP and GDF-15 in females of the age groups (40–50) years, (51-60) years and (61-70) years in patients hypertension compared to the control group, and the results showed no significant increase Probability level ($P<0.001$) in the rate of efficacy of LAP and GDF-15 in females in the age group (40-50) in patients with hypertension compared with patients for the same age group and for the age group (51-60)($P<0.001$) at the LAP and GDF-15efficacy rate in females, The results showed no significant increase in the level of probability ($P<0.001$) in the rate of efficacy of LAP and GDF-15 in females aged (61-70) years in patients (247.8 ± 44.1), (1625.5± 200.9) compared to the age group (40-59) years (223.2 ± 42.7),(1493.4 ± 329.5) as well as the significant difference in LAP and GDF-15 efficacy rate at the probability level ($P<0.001$) for male patients and control group when comparing the age group (51-60) years and the age group (61-70) years as in figur2. this results agree with the researchers BarmaMarya, Khan Faisel, et.al.,[28] who was found GDF-15 levels were significantly associated with increasing age groups.the study also agree with[29]S. Inokuma, K. Setoguchi, T. Ohta, Y. Matsuzaki, A. Yoshida who found that activity of LAP was effected with increasing age.Statistical analysis showed an very low significant increase in the rate of enzyme activity for older persons compared to the rest may be due to the genetic deficiency caused by genetic mutations.The results showed a significant decrease in the probability level ($P<0.01$) in the calcium levels of patients of hypertensions compared with the control group, This results agree with a study of Behradmanesh, Saeed, and Hamid Nasri[30], who proved a significant inverse correlation of serum calcium with level of diastolic blood pressure and propose to more attention to serum calcium during the treatment of hypertension in patient with hypertension and diabetes. The study showed that there were significant decrease in the level of magnesium inhypertension patients due to the nature of the food or to an increase in the amount of magnesium produced by the kidney due to dysfunction in hypertension this study agree withGuerrero-Romero F, Rodriguez-Moran M, et.al[31], who conclusion that low serum magnesium is associated with hypertension. . The results showed a significant decrease in the

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probability level (P <0.01) in the zinc level of patients with hypertensions compared with control group, This results agree with a study of Clintoria R. Williams, MonishaMistry,et.al [32], who found a significant inverse correlation and low level of serum zinc and cooper with in patient with hypertension. There was a significant increase in the concentration of cholesterol ,TG,VLDL-C and LDL at the probability level (P <0.001) in the serum patients with hypertension a significant difference in the concentration of cholesterol at the probability level (P <0.001) when comparing between control group and hypertension group this result agree withChoudhury, KamrunNahar et al[33] andQin, L., Zhu, X., Liu, X., Zeng, et.al[34], Who had suggested close association with dyslipidemia and need measurement of blood pressure and lipid profile at regular intervals to prevent cardiovascular disease, stroke, and other comorbidities.A decrease was not significant at the level of probability (P <0.01) in total protein concentration of patients of both sexes compared with the control group because of a defect in kidney function leads to crash proteins and decay This leads to a high concentration of urea in the body. This results agree with the study by researcher W.E. Olooto, A.A. Amballi, A.O. Mosuro, A.A. Adeleye and T.A. Banjo [35] and Ahbap E, Sakaci T, Kara E, et.al[36] who didn't find any significant between total protein, albumin and globulins in patients with hypertension. There was significant between control and hypertension group in level of sodium due to this result agree withFeng J. He, Graham A. MacGregor [37] who showed in his studythe time of onset of the rise in arterial pressure appears to be related to the extent of the increase in sodium concentration, so that the delay may take several days with 1 to 3 mmol/L increases in sodium concentration that occur in hypertension.There were no significant in potassium, chloride an phosphorus in group of patents compared with control group this study agree withIqbal S, Klammer N, Ekmekcioglu C [38]their brief exploration showed that lowering chloride and increasing potassium intake would exert convincing blood pressure lowering effects and no significant especially in hypertensive patients. Huang, Cindy Xin et. al [39], they were foundthat serum phosphorus was no significant and independently associated with systolic blood pressure and pulse pressure in the early months and up to 27 months later with hypertension and the role of hyper phsphatemia in vascular calcification and arterial stiffness still needs to be further clarified. In the table 2 there was significant increase in activity of GOT(Glutamic-Oxaloacetic Transaminase) in male and female compared with control group this result agree withRahman, Sadaqur et. al [40], that found the prevalence of elevated liver enzymes was higher in hypertensive individuals, and increased serum GOT and GGT activities were positively associated with hypertension.

Table 1. LAP activity, GDF-15 concentration and some biomarker in the group of hypertension patients compared to control group by gender and age

Variables	**Patients group (Mean ±SD)**		**Control group (Mean ±SD)**	
Gender	**female(30)**	**male(45)**	**female(35)**	**male(65)**
Total LAP activity (IU/ml)	225 ±35.7**	242±53.5 **	118 ± 23.1	106 ± 13.3
Age (40-50) yrs	223.2 ± 42.7	237.4 ± 36.9	105 ± 12.3	109 ± 17.1
Age (51-60) yrs	220.4 ± 27.03	234.1 ± 52.1	103 ± 14.3	106 ± 12.6
Age (61-70) yrs	247.8 ± 44.1	257.4 ± 71.5	114 ± 16.3	113 ± 15.3
P-value – t-test	0.001-17.3		0.001-17.7	
Total GDF-15 (IU/ml)	1456.7 ± 77.0	1555.0 ± 259	232574 ±	496 ± 111
Age (40-50) yrs	1493.4 ± 329.5	1428.9 ± 157.6	482.2 ± 73.3	423.5 ± 74.6
Age (51-60) yrs	1507.4 ± 156.4	1483.4 ± 147.7	524.3 ± 98	473.4 ± 96.7

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Age (61-70) yrs	1625.5 ± 200.9	1633.3 ± 208.7	525.2 ± 86.4	433.1 ± 88.7
t-test - P-value	0.009-39.38		0.008-23.2	

Table 2. some biomarker in the group of hypertension patients compared to control group by gender and age

Variables	**Patients group (Mean ±SD)**		**Control group (Mean ±SD)**	
Gender	**female(30)**	**male(45)**	**Gender**	**female(30)**
Magnesium (mg\dl)	1.787±0.171	1.739 ±0.194	1.561±0.161	1.643±0.132
Calcium (mg\dl)	7.524±0.67	7.524±0.67	8.92±1.66	9.558±0.30
Zinc	7.65 ± 1.78	7.23 ± 1.12	10.36±1.82	9.76±1.76
Cholesterol(mg/dl)	172.8±26.5	174±31.3	162±49.2	162±56.3
HDL-C (mg/dl)	38±9.14	39.4±9.01	40.2±8.85	40.3±12.5
VLDL(mg/dl)	40.3±15.8	40.7 ± 16.2	22.4 ± 9.64	21.2 ± 8.37
LDL(mg/dl)	122±61.2	150.8 ± 6.57	107±36.4	108.6 ± 4.53
TG(mg/dl)	152±64.9	148±51.2	106±61.8	112±49.1
Total Protein(mg/dl)	7.32±0.94	7.08±1.24	6.32±1.3	7.095±1.18
Albumin (mg/dl)	4.41±1.07	4.68±1.06	4.51±1.04	4.48±1.03
Globulin(g/dl)	2.471±0.97	2.66 ± 23	2.562±0.862	2.65±0.45
Potassium	4.250 ± 0.829	4.586 ± 0.879	4.312±0.756	4.613± 0.747
Sodium	140.88 ± 8.7	143.11 ± 9.86	140.63±5.66	140.42 ± 5.82
Chloride	99.87±5.83	103.15 8.51	98.54±5.43	99.34 ± 7.00
GOT(UI/ml)	±50.1 62.3**	40.4 ±24*	31.3±18.3	30.4±17.2

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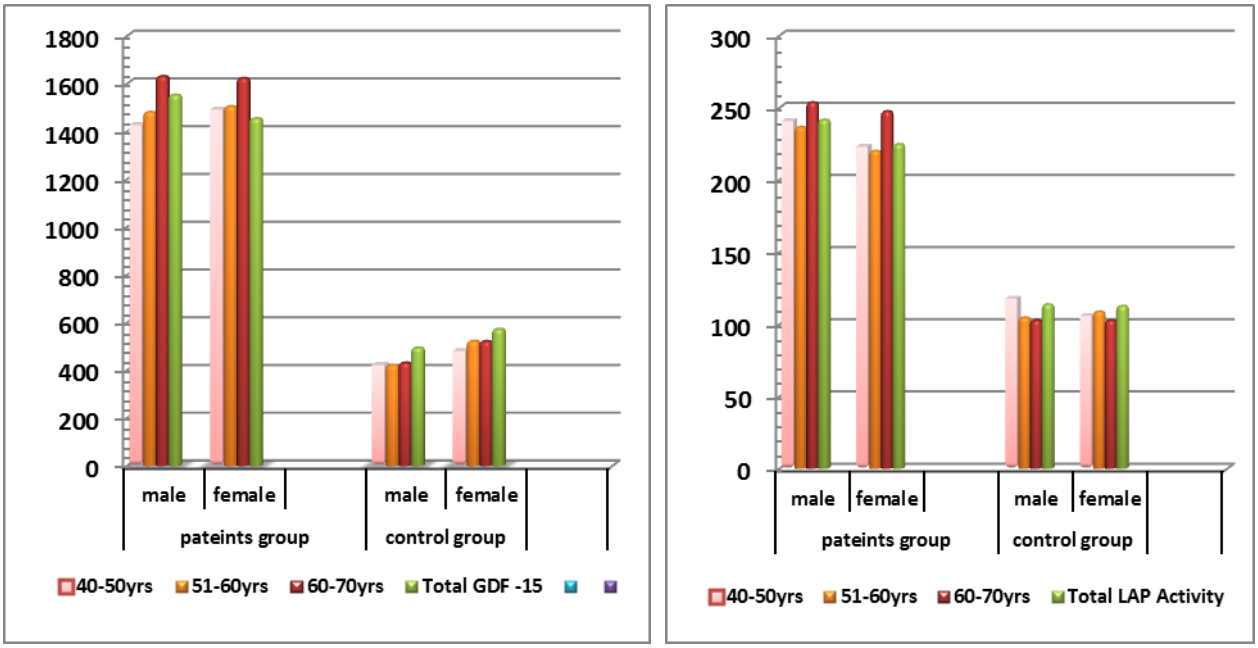

Figure 1. Illustrate value of GDF-15 concentration and LAP activity in serum of normal and patients (men and women) with hypertension according age.

The relation between GDF-15 level with smoking, BMI and family history with hypertension had been studied. The result in table 3. and figure2. shows the mean and standard deviations of serum GDF-15in healthy control group and all hypertension patients groups according to BMI, Smoking and family history with hypertension,there were significantly higher in probability ($p<0.0001$) in the patient groups that (30< BMI) than in patients group with BMI(20-27) and (28-30) and no significant in other BMI of pateints group compared with each other but there was significantin probability in patient compared with control group, this result agree withSarkar, Shreya et. al [41], who suggested that Circulating GDF15 was a salient biomarker likely sourced from heart tissue that appears to predict higher risk obese patients for adverse outcomes, and elevated GDF15 accounted for more sensitive outcome association than BMI at two years post-cardiac surgery. And don't agree withHe, X., Su, J., Ma, X. *et. al*[42], that found High serum GDF-15 levels were significantly correlated with an increased risk of LEAD in Type two of diabetes mellitus patients, and this relationship was independent of BMI.Table3. Show also There was no statistically difference in levels of GDF-15 between control and total patient groups that was smoking and there were significantly higher in probability ($p < 0.0001$) in the patient groups that was suffering from smoking compared with patient was no smoking ,this result agree withWada Hiromichi, AU- Suzuki Masahiro,et.al [43],that suggested was not only current, but also former smoking was independently associated with higher levels of GDF-15and the prognostic value of GDF-15 on mortality was most pronounced in never smokers among patients with suspected or known hypertension disease. There was no statistically difference in levels of GDF-15 between control and total patient groups that was had family history with hypertension and there were no significantly higher in probability ($p < 0.0001$) in the patient groups that was had family history with hypertension compared to patient with no family history of hypertension this result agree withGeorge, Melvin et. al [44], who did not found any significant between family history of hypertension and GDF-15 level in hypertension disease.

Table3.GDF-15 concentration in the group of hypertension patients compared to control group by BMI, smoking and Family history of hypertension

GDF-15 (IU/ml)	**Patients gruop** **Mean ± SD**	**Control group** **Mean ± SD**	**p-value**	**t-test**

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BMI (20-27) yrs	1456.4 ± 237.7	464.6 ± 64.3	0.19	n.s 1.37
BMI (28-30)	1530.9± 176.5	456.1 ± 61.6	0.79	n.s 0.264
BMI ≤30	1534.1 ± 233.8	446.5 ± 62.8	0.0008	*20.93
Smoking	1461.8 ± 88.8	483.3 ± 64.9	0.004	12.3
Non smoking	1453.7 ± 51.68	464.6 ± 97.6	0.56	0.22
Family history of hypertension	1563±48.6	476.4 ± 82.6	0.034	0.98
Nonfamily history of hypertension	1538±20.9	456.2±66.5	0.22	0.76

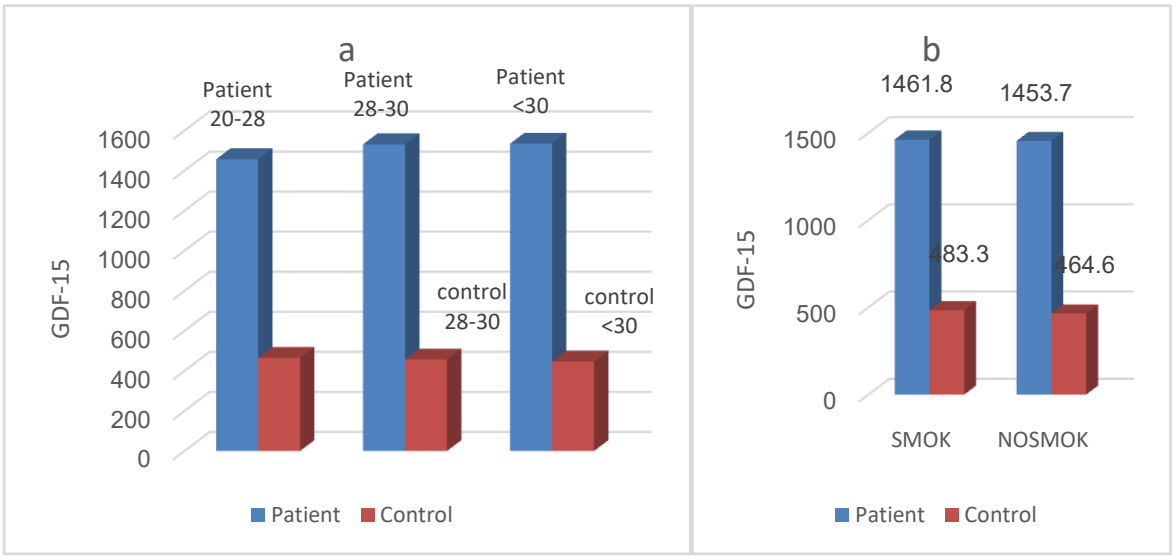

Figure 2. Illustrate value of GDF-15 concentration in serum of normal and patients with hypertension compared with a- BMI, b- smoking

Correlative between LAP and a number of clinical Parameters in patients with hypertension and control groups:

To find the relationship between LAP and a number of clinical Parameters in patients with hypertension and control groups, correlative coefficient (r) was found .The result intable4. and Figure (3) shows There is a linear correlation between the increaseof LAP activity in patients with Hypertension, and its activity in the control group, as the value of the correlation coefficient between systolic blood pressure and enzyme activity (r =0.243) and with diastolic blood pressure was(r= 0.184)and with BMI was(0.23). This results agree with the Danziger, Robert S[45] who found positive correlation enzyme activity in hypertensions compared to control group due to

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low level of antioxidants for hypertension patients because of metabolic disorder caused by disease . The absence of a linear correlation between LAP activity in patients with hypertension and the level of concentration of calcium and magnesium , as the value of their correlation coefficient (0.061)and (0.065) respectively .there were a positive correlation between LAP and Zinc which value of correlation coefficient (0.47) this result agree with Pincus MR, Tierno PM, Gleeson E, Bowne WB, Bluth MH[46]who found positive correlation between LAP activity and zinc concentration in human body.
The absence of a linear correlation between LAP activity in patients with hypertension and cholesterol , HDL ,LDL , VLDL , TG and Globulin levels. The value of their correlation coefficient (0.043), (0.065), (0.034), (-0.189),(0.047) respectively .there was a linear correlation between enzyme activity in patients with hypertension and the level of concentration of total protein and Albumin the correlation coefficient was (0.17) and (0.194) respectively there was appositive correlation as show in table3. and figure8.,figure9. This result agree withS. Inokuma, K. Setoguchi, T. Ohta, Y. Matsuzaki, A. Yoshida [47], who found serum LAP level may be a potential activity had positive correlation with total protein and albumin but hadn't any correlation with globulins.There were absence of a linear correlation between LAP activity in patients with hypertension and electrolyte (potassium, sodium, chloride and phosphorus) which the value of correlation coefficient was (0.038, 0.198, 0.02, 0.078)In addition to that there was a linear correlation between the activity of GOT enzyme in patients with diastolic blood pressure which correlation coefficient was(r= 0.33) and with systolic blood pressure was(r= 0.42) this result agree withRahman S, Islam S, Haque T, Kathak RR, Ali N.[48],who suggested that the prevalence of elevated liver enzymes was higher in hypertensive individuals and increased serum GOT and GGT activities were positively associated with hypertension.

On the other hand,Table4. and Figure4. shows There was a linear correlation between the increase of gdf-15 concentration there was a linear correlation between the increase of GDF-15 concentration in patients with diastolic blood pressure which correlation coefficient was(r= 0.53) and with systolic blood pressure was(r=0.62) and with BMI which correlation coefficient was(r=0.23) this results agree withSökmen E, Uçar C, Sivri S, Çelik M [49], who elevated serum GDF-15 levels in non-dipper HT patients compared with both dippers and healthy controls Additionally, GDF-15 level and nighttime diastolic BP were revealed to be independently associated with a non-dipping BP pattern. and the result before agree with[50] T. Kempf, A. Guba-Quint, J. Torgerson et al . who found level of GDF-15 was strongly correlated with BMI in addition to thatconcerning obesity and GDF-15 level, it was found that GDF-15 level were higher in obese group than in non-obese group . In this study found positive correlation between GDF-15 and GOT enzyme which correlation coefficient was(r=0.231)and between LAP and GOT which correlation coefficient was(r=0.266) There was no previous studied of their relationship.

Table 4. Simple Stepwise Regression Analyses for the LAP activity with GDF-15 Level and other biomarker in the Entire Cohort

Variables	r	SEM	*P* Value
GDF-15	0.68	0.012	<0.001
Diastolic blood pressure	0.184	0.028	<0.001
Systolic blood pressure	0.243	0.003	<0.001
BMI	0.23	0.002	<0.001
Magnesium (mg\dl)	0.065	0.030	0.04
Calcium (mg\dl)	0.061	0.026	0.05
Zinc	0.47	0.026	<0.001
Cholesterol(mg/dl)	-0.043	0.037	0.12
HDL-C (mg/dl)	0.065	0.037	0.057

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VLDL(mg/dl)	0.034	0.041	0.06
LDL(mg/dl)	-0.189	0.041	0.176
TG(mg/dl)	-0.191	0.044	0.131
Total Protein(mg/dl)	0.17	0.025	<0.001
Albumin (mg/dl)	0.194	0.033	<0.001
Globulin(g/dl)	0.047	0.026	0.02
Potassium	0.038	0.026	0.01
Sodium	0.198	0.006	0.121
Chloride	0.02	0.037	0.01
phosphorus	0.078	0.037	0.03
GOT	0.266	0.041	<0.001
GOT with systolic blood pressure	0.42	0.035	<0.001
GOT with diastolic blood pressure	0.33	0.024	<0.001
GDF-15 with GOT	0.231	0.028	<0.001
GDF-15 with diastolic blood pressure	0.53	0.034	<0.001
GDF-15 with systolic blood pressure	0.62	0.029	<0.001
GDF-15 with BMI	0.23	0.023	<0.001

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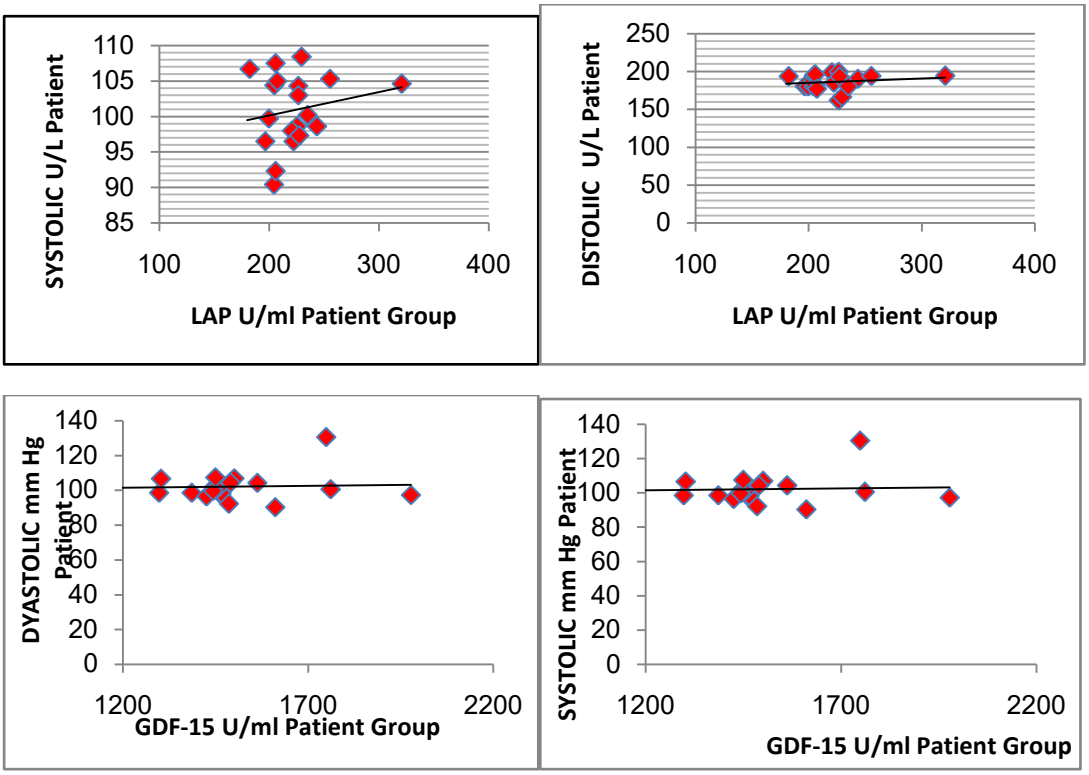

Figure3. Correlation between LAP activity and GDF-15 level with diastolic and systolic blood pressure

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