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Original Research Article

Leptin's Potential Role in the Assessment of Diabetic and Cardiac Patients in Saudi Arabia: A Cohort Study

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Abstract

The incidence of Cardiovascular Diseases (CVD) is increasing in Saudi Arabia, and so are the rates of Diabetes Mellitus (DM) and Obesity. The obesity effect on function of vascular system could be controlled by polypeptide Leptin hormone (LEP). The possible correlation between LEP with both DM and CVD is studied in this work. The present work was performed in Jeddah, Saudi Arabia. The patients were allocated into four matched groups: GI; patients with CVD, GII; patients with type 2 DM, GII: patients suffering from DM and CVD, and GIV: healthy controls. Each group was subdivided into male and female subgroups. Anthropometrics, blood pressure, lipid profile, insulin, fasting blood glucose, fibrinogen, and uric acid levels were estimated, and then correlated to LEP levels. Two hundred and one patients, (114 males) and (87 females), were included in this study. Although plasma LEP was higher in the (CVD and DM) study group when compared to normal individuals, and in females when compared to males, LEP levels showed no significant difference between groups. LEP was strongly associated with age and Systolic Blood Pressure (SBP) in all females' subgroup. Males showed a negative correlation between LEP and cholesterol levels while females showed a positive correlations between LEP with age and uric acid, and negative correlations with blood glucose and cholesterol levels. The present study indicated that LEP levels were higher in (CVD and DM) group when compared to normal individuals. Estimation of LEP might be used as a biomarker to detect early cardiovascular manifestations.

Keywords: Cardiovascular Diseases, Diabetes Mellitus, Leptin

INTRODUCTION

In the 1980s, DM was detected at (4.7%), and at the end of 2014 it doubled with an approximate (1.5) millions related deaths in 2012 (King et al., 1998). CVD are among the most worldwide significant causes of both morbidity and mortality, especially when linked with DM (Kalofoutis et al., 2007). The incidence of both DM and CVD are rapidly increasing in Saudi Arabia (Aljefree and Ahmed, 2015). Coronary Heart Disease (CHD) is considered a serious health burden in the kingdom, and represents the third most common causes of mortality in hospitals after an accidents and in aged individuals (Kumosani et al., 2011). In fact, the World Health Organization (WHO) reported that; in Saudi Arabia (35%) of all non-communicable diseases mortality were due to CVD alone (World Health Organization, 2008). These rates were strongly linked to the delayed detection of CVD, and the prolonged aggravation of atherosclerosis. Thus, there is a need for protective measures, plus extensive and thorough assessments with the appropriate biomarkers (Rainwater et al., 1997).

The major risk factor for DM and CVD is Obesity but the mechanism by which obesity inhance the risk of these two is only partially understood (World Health Organization, 1999; Laakso, 2002; Kendall et al., 2003). The polypeptide hormone Leptin (LEP) mediated the effect of obesity on vascular function, in fact LEP was originally considered as an hormone of anti-obesity as it acts as appetite suppression and can increase creases basal metabolism (Ahima and Flier, 2000). Its concentrations rise with enlarged body fat, and therefore obese individuals usually exhibit markedly elevated levels (Considine et al., 1996). Furthermore, the large spared of LEP receptors on vascular cells indicates that they may also affect vascular physiology (Parhami et al., 2001). LEP can initiate atherogenic, thrombotic, and angiogenic alterations, stimulate vascular inflammation and hypertrophy, which was attributed to type 2 DM, hypertension, atherosclerosis, and coronary heart disease (Koh et al., 2008), and although it was suggested as a strong predictor of myocardial infarction in hypertensives, there are no studies examining the role of LEP in Saudi patients suffering from DM and CVD. In this study, we focus on these patients, examine their clinical parameters including LEP and comparing differences between different patients.

MATERIALS AND METHODS

Design of the Study

A prospective cohort study, involving Saudi patients followed at King Abdulaziz University Hospital (KAUH), in Jeddah - Saudi Arabia. This study was approved from the Bioethical and Technical Research Committee, Faculty of Medicine, King Abdulaziz University, while all required approvals were secured from KAUH's administration. We targeted patients attending outpatient clinics at KAUH, where prior to recruitment study objectives and procedures were explained to these individuals, and they were reassured about confidentiality of personal information. Written informed consents were obtained.

Study Participants

The participants were allocated into 4 groups. All groups were matched by age and gender, and then each group was subdivided by gender to assess the latter's effect on the studied parameters. The first group included CVD patients only (mainly atherosclerosis), and the second group included only DM type 2 patients. The third group included patients suffering from both DM and CVD and the fourth and final group were healthy controls. Both CVD and DM patients were followed at outpatient clinics, designated for the Association of Diabetic Patients (ADP) in KAUH. The healthy controls were recruited from other general clinics, and all were non-smokers, with normal blood pressure at the time of the study, they were never diagnosed with DM or CVD, and they did not take any relevant medications. Patients with the following conditions were excluded; Cushing's syndrome, type 1 DM, or acute illnesses.

Materials

Automated Flex® Reagent Cartridge

Reagent kits needed for chemistry analysis were purchased from Siemens Flex® Reagent Cartridge (Newark, DE, U.S.A). It included serum measurements for: levels of cholesterol, low and high density lipoproteins, triglycerides, fasting insulin levels, fasting glucose levels, uric acid and fibrinogen. Everything was analyzed using Dimension Vista® System, at the clinical chemistry laboratory in KAUH.

ELISA Kit for Human LEP

ELISA kit for human serum was purchased from USCN Life Science Inc. Wuhan, Cat. No. E0084Hu, and it consisted of: Standard (5000 pg/ml) and standard diluents, Detection reaction A, Detection reaction B, Assay diluents A (2x concentrate), Assay diluents B (2x concentrate), Tetra Methyl Benzidine (TMB) substrate, Stop-working solution and Washing buffer (30x concentrate).

Data collection

Past Medical History, Anthropometrics and Blood Pressure Measurements

At the baseline, anthropometric parameters for all participants were measured, including height, weight, Body Mass Index (BMI) and Waist to Hip Ratio (WHR). Blood pressure readings were also reported, as well as history of cigarette smoking, use of chronic medications, osteoporosis and other heredity diseases. Measurements were performed in the morning, before breakfast, while the subjects wear light clothing and no shoes. Standing weight and height were taken using a digital scale.

Reagents Preparation and Sample Collection

A 10 ml sample of blood was taken after fasting, and collected in separate tubes as follows: (4) ml was collected into a plain vacutainer tube for chemistry and hormonal analysis, (3) ml in a blue cap vacutainer tube containing sodium citrate to measure fibrinogen levels,

and the last (3) ml in a gray cap vacutainer tube with sodium fluoride to monitor Fasting Blood Glucose (FBG) levels. Blood in the plain vacutainer tube was allowed to stand for few minutes at room temperature, and centrifuged twice. Serum was aliquoted into a clean, dry Eppendorf tubes, and kept at 80˚C for analysis.

LEP levels were determined using LEP sandwich enzyme immunoassay kit, which was effective in a range of (78 - 5000 pg/ml). Micro plates in the kit were precoated with an antibody unique to the tested polypeptide. In the kit, the Standard was reconstituted with (1) ml of standard diluent, stood for 10 minutes at room temperature, and shaken smoothly. Seven points of diluted standard were set up; 5,000 pg/ml, 2, 500 pg/ml, 1, 250 pg/ml, 625 pg/ml, 312 pg/ml, 156 pg/ml, 78 pg/ml, and the last Eppendorf tube was the blank as 0 pg/ml. Diluent A or B concentrate (2X) were briefly spun or centrifuged before use, and then (6) ml was diluted with (6) ml of deionized distilled water. Twenty ml of washing solution concentrate (30X) were diluted with (580) ml of distilled water, and (600) ml of wash solution (1 X) were prepared. The required amount of TMB substrate solution was aspirated with sterilized tips. Standards and biological samples were then added to the suitable microtiter plate wells, with a biotin-conjugated polyclonal antibody preparation. Avidin conjugated to Horseradish Peroxidase (HRP) is added into every microplate well and incubated. TMB substrate solution was also included. Only wells that contain LEP will show a change in color. The enzyme-substrate reaction was completed by addition of sulphuric acid solution, and coloration change was measured spectrophotometrically at a wavelength of 450 nm.

Procedure and Calculation

The wells for diluted standard, blank and sample were labeled and added into the suitable wells. They were protected with the plate sealer and incubated for 2 hours at 37˚C.The liquid of each well was removed and 100 µl of detection reagent A working solution were added to every well. They were incubated for 1 hour at 37˚C covered with plate sealers. Solution was aspirated and wells washed with 400 µl of (1X) washing solution, and sat for 1-2 minutes, and residual liquid was removed from wells by inverting plates onto absorbent paper. Washing was repeated three times. The plate was inverted and blotted on to absorbent paper. Then, 100 µl of detection reagent B working solution were added. They were incubated for 30 minutes at 37˚C after, and then processed and washed as above. This wash was repeated for five times. Ninety µl of substrate solution were added to each well and incubated for 15-25 minutes at 37˚C away from light, and the liquid color changed to blue, and when 50 µl of stop solution were added to each well, the liquid's color changed to yellow. The liquid was mixed by tapping plate gradually. The plate was cleaned by removing any drops of water or fingerprint on the plate's bottom with no air bubbles on the surface. The micro plate reader was run and measurements were conducted at 450 nm immediately. The concentration of LEP in samples was determined by comparing the samples' optical density to a standard curve. Readings for respectively standard, control, and serum samples were averaged, and the average zero standard (blank) optical density was subtracted. A standard curve was created using computer software proficient for creating a four-parameter logistic (4-PL) curve-fit. As an alternative, a standard curve was constructed by plotting the mean absorbance for every standard on the x-axis against the concentration on the y-axisin order to to draw the best appropriate curve.

Statistical Analysis

We recorded clinical and laboratory data on an investigative report form, and statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 16, (SPSS Inc., Chicago, IL, USA). Descriptive data is presented as means ± Standard Deviations (SD). Associations between LEP and studies diseases (i.e. DM and CVD) was tested using Pearson correlation models. Pearson rank order correlation was used to study relationships between two non-parametric variables within the same group, and namely assessing LEP correlations with other parameters. A *P*-value < 0.05 was considered statistically significant.

RESULTS

The study group included (201) subjects, (114) males and (87) females representing (56.7%) and (43.3%) respectively. Subjects were divided into four main groups, matched by age and gender. The first group involved CVD patients, mainly atherosclerosis, and included (48) patients, (30) males and (18) females. The second group included a total of (46) DM type 2 patients, (17) male and (29) females. The third group consisted of (65) patients, (42) males and (23) females, suffering from both DM and CVD, and finally the fourth group included (42) healthy controls, (25) males and (17) females. (Figure 1) The mean age in years for each group was as follows: for the CVD group (57.88±10.07), for the DM group (59.33±10.05), for the third group (56.76±8.56), and for control group (47.98±12.15).

Physical Characteristics

Regarding mean BMI values, it was (28.3±5.57) Kg/m^2 for

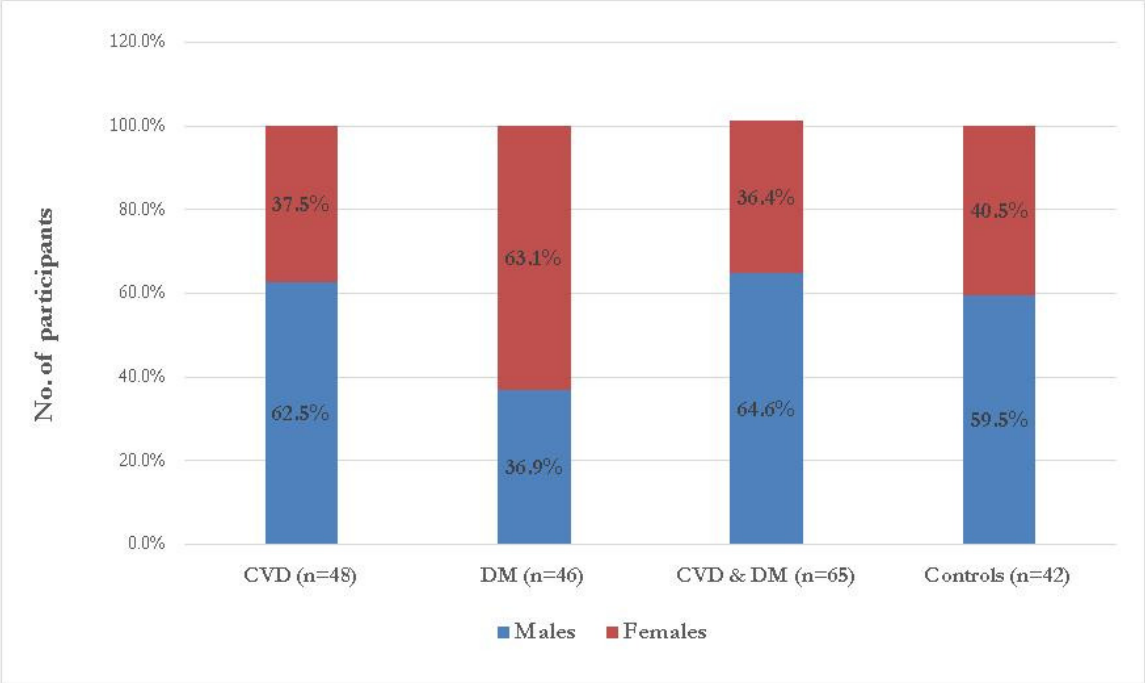

Figure 1. Gender distribution for the study groups

Table 1. Physical Characteristics & Chemical Parameters for study groups

Parameter	Study Groups				P - Value
	CVD	DM	CVD & DM	Controls	
Age	57.88±10.07	59.33±10.05	56.76±8.56	47.98±12.15	0.067
BMI	28.29±5.57	29.64±6.96	29.42±5.17	25.17±3.92	0.852
WHR	0.96±0.08	0.95±0.10	0.93±0.14	0.90±0.08	0.141
SBP	143.67±19.36	139.54±21.58	138.78±19.05	123.90±17.09	0.519
DBP	75.67±12.759	77.50±12.171	76.09±11.451	76.74±10.537	0.636
Insulin	12.37±7.95	15.98±21.97	10.69±4.67	10.82±4.78	0.000
FBG	5.99±1.61	8.13±3.35	9.15±3.51	5.45±0.42	0.069
Uric Acid	322.81±76.20	300.37±140.07	298.42±99.83	300.55±116.52	0.012
Fibrinogen	405.61±103.37	447.75±119.81	426.99±127.99	304.40±89.44	0.083
Cholesterol	4.001±1.039	4.751±1.481	4.116±1.150	4.008±2.305	0.000
HDL	2.25±1.07	2.72±1.20	2.08±1.04	2.73±1.80	0.000
LDL	1.18±0.31	1.35±0.48	1.18±0.39	1.06±0.80	0.000
Triglycerides	1.48±0.95	1.95±1.61	1.69±1.11	1.82±1.16	0.000
Leptin	87.43±64.51	83.14±85.60	63.12±59.11	94.54±53.51	0.269

BMI=Body Mass Index, WHR=Waist to Hip Ratio, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, FGB=Fasting Blood Glucose, HDL= High Density lipoproteins, LDL=Low Density Lipoproteins, OPG= Osteoprotegerin

the CVD group, (29.64±6.96) Kg/m^2 for the DM group, (29.45±5.17) Kg/m^2 for the DM & CVD group, and for the control group, it was (25.17±3.92) Kg/m^2. There was a significant difference in BMI values between the control group and all other study groups, and between males and females. (P<0.05). The mean WHR measurements were; in CVD group (0.96±0.08) m, in DM group (0.95±0.10) m, in DM & CVD group (0.93±0.14) m, and in the controls, it was (0.90±0.08) m. No significant difference was detected between the groups. (Table 1). Mean Systolic Blood Pressure (SBP) readings recorded for the GIV; CVD, DM, CVD & DM and controls were: (143.67±19.36) mmHg, (139.54±21.58) mmHg, (138.78±19.05) mmHg, and (123.9±17.09) mmHg. A significant difference was detected in SBP readings between the control group and the remaining study groups (P<0.05). On the other hand,

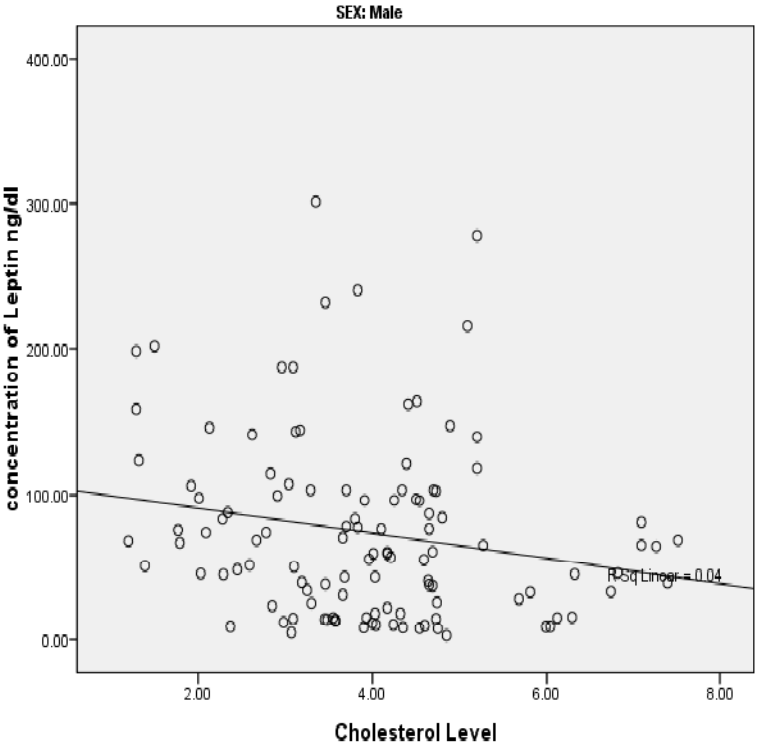

Figure 2. Scattered plot for significant negative correlation between LEP and Cholesterol levels in males' subgroups

Diastolic Blood Pressure (DBP) readings for the groups CVD, DM, CVD & DM and controls were; (75.67±12.76) mmHg, (77.5±12.17) mmHg, (76.09±11.45) mmHg and (76.74±10.54) mmHg respectively, however we found no significant difference between the groups. (Table 1)

Chemical Parameters

The mean serum insulin levels for the CVD group were (12.37±7.95) µIU/ml, for DM group (15.98±21.97) µIU/ml, for the CVD & DM group (10.68±4.67) µIU/ml, and for the control group levels were (10.82±4.78) µIU/ml. Serum insulin concentrations showed no significant difference between groups. FBG concentrations were (5.99±1.61) mmol/L for CVD group, (8.13±3.35) mmol/L for DM group, (9.15±3.51) mmol/L for DM & CVD group, and for the controls (5.45±0.42) mmol/L. Serum FBG concentrations in both the DM and the DM & CVD groups (both main and gender subgroups) were significantly higher when compared to the controls ($P<0.05$). Uric Acid levels recorded for the CVD group were (322.81±76.20) µmol/L, for the DM group (300.37±140.07) µmol/L, for the DM & CVD (298.42±99.83) µmol/L, and they were (300.55±116.52) µmol/L for control group. We found no significant difference between groups. For fibrinogen levels, the following readings; (405.61±103.37) mg/dl, (447.75±119.82) mg/dl, (426.99±127.99) mg/dl and (304.41±89.44) mg/dl were reported for CVD, DM, DM & CVD and control groups respectively. Serum fibrinogen concentrations for all main and subgroups were significantly higher when compared to the corresponding control groups ($P < 0.05$).

Regarding lipid profile, thetotal cholesterol concentrations estimated for the CVD group were (9.13±12.48) mmol/L, (4.75±1.48) mmol/L for DM group, (4.12±1.15) for the DM & CVD group mmol/L, and (4.01±2.31) mmol/L for the control group. Serum High Density Lipoprotein (HDL) levels recorded for the CVD group were 2.25±1.07 mmol/L, 2.72±1.2 mmol/L for DM group, 2.08±1.03 mmol/L for DM & CVD group, and 2.73±1.8 mmol/L for the control group Serum Low Density Lipoprotein (LDL) concentrations reported for the four main groups; CVD, DM, DM & CVD and controls were (1.17±0.32) mmol/L, (1.35±0.48) mmol/L, (1.17±0.40) mmol/L, and (1.06 ± 0.80) mmol/L respectively. Finally, serum triglycerides concentrations for the four groups; CVD, DM, DM & CVD and controls were as follows: (1.82±1.16) mmol/L, (1.95±1.61) mmol/L, (1.69±1.11) mmol/L and (1.81± 1.15) mmol/L respectively. When compared to the controls, serum HDL, LDL and triglycerides concentrations in other main and subgroups were significantly higher ($P\leq0.05$).

As to serum LEP levels, the CVD group reported (87.43±64.51) ng/dl, the DM group levels (83.14 ± 85.6

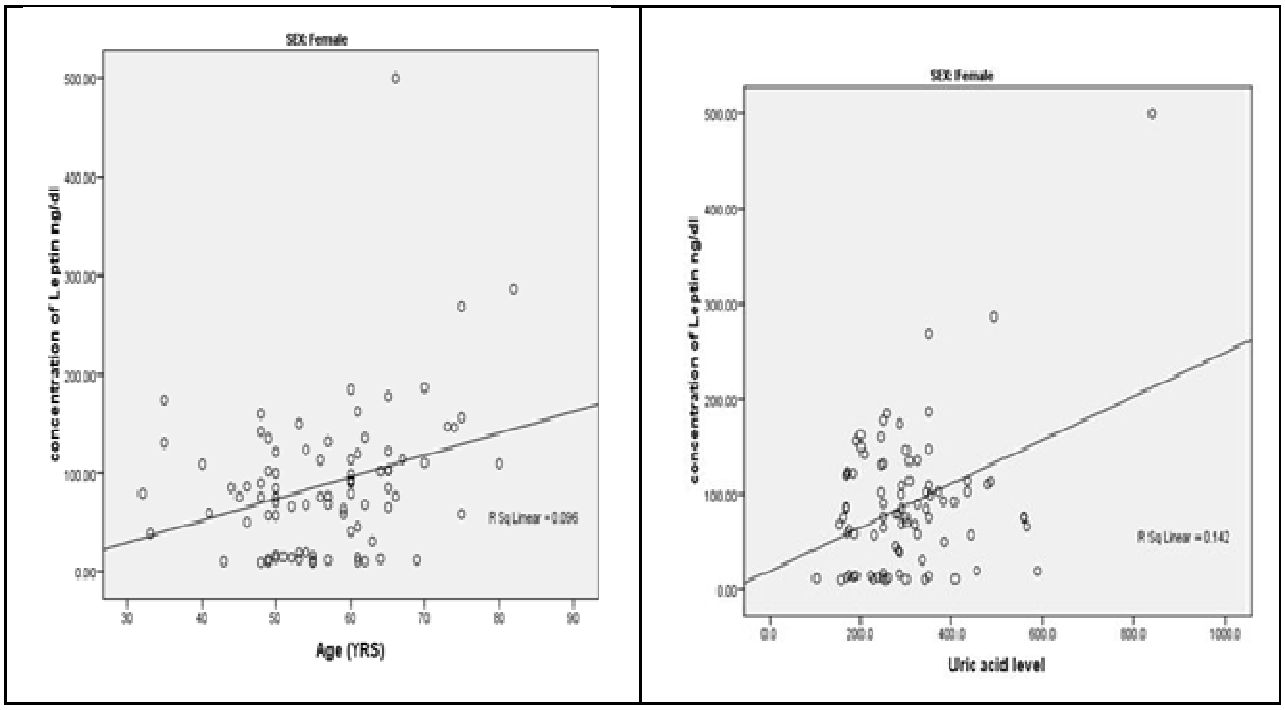

Figure 3. Scattered plot for moderate positive correlations between LEP and Age & Uric Acid levels in females' subgroups

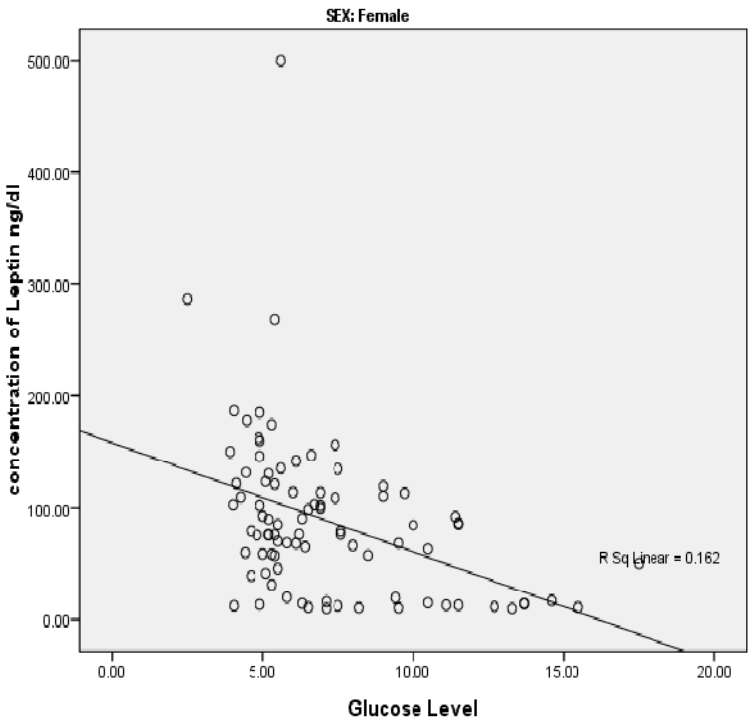

Figure 4. Scattered plot for moderate negative correlation between LEP and FBG levels in females' subgroup

ng/dl), for the DM & CVD group levels were (63.12±59.11) ng/dl, and finally for the control group mean LEP levels were (94.54±53.51) ng/dl. Although we detected no significant difference in LEP levels between the main four groups, when tested for associations with other parameters, all females' serum LEP levels were

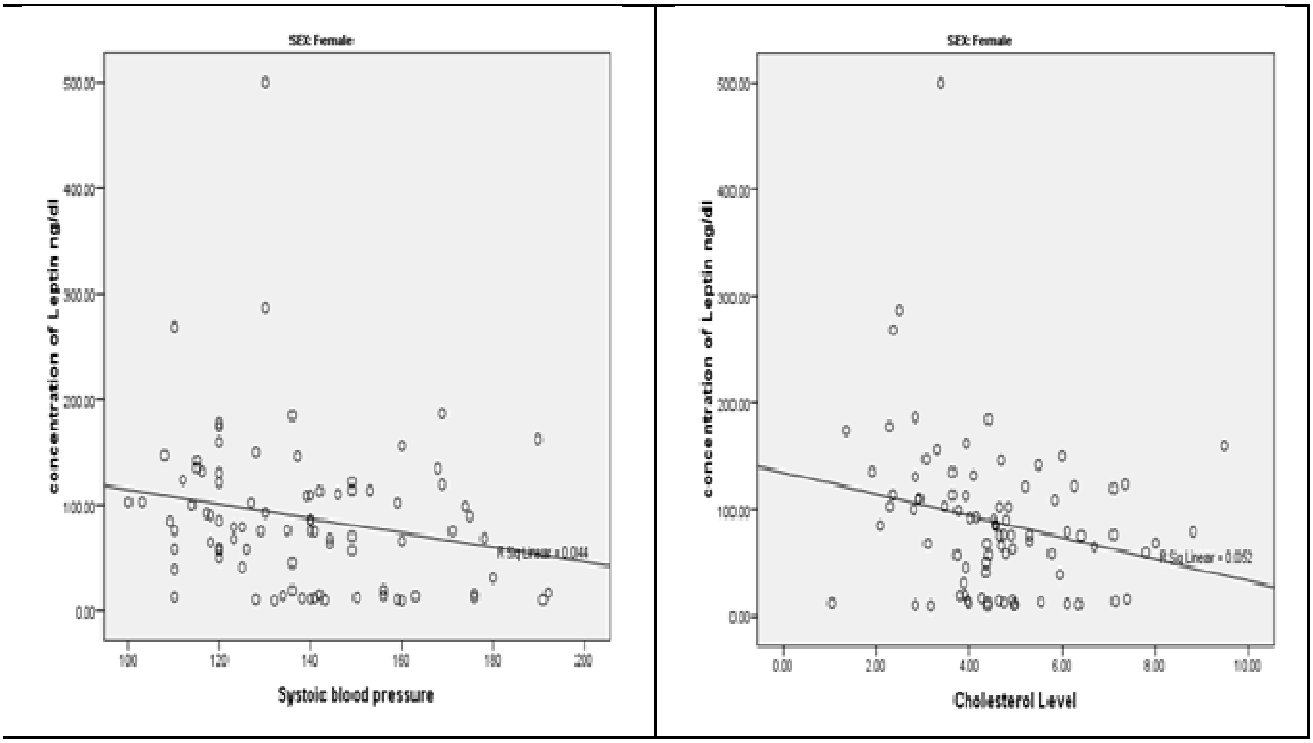

Figure 5. Scattered plot for weak negative correlations between LEP and SBP & Cholesterol levels in females' subgroups

associated with SBP readings (P=0.05), and strongly associated with age (P=0.004), especially after menopause. Surprisingly, and except for the DM & CVD group, LEP was not associated with BMI in the other study groups. Finally, LEP was negatively associated with cholesterol levels in both males and females (P=0.033).

Correlation of LEP levels with Other Parameters

The correlations between LEP and other parameters were further assessed, and more specifically for the males and females' subgroups, using the bivariate Pearson rank order correlations. For all males' groups, there was a significant negative weak correlation between LEP concentrations and cholesterol levels (Figure 2). On the other hand, in females were moderate positive correlations between LEP with both age and uric acid levels (Figure 3), moderate negative correlation between LEP and glucose levels (Figure 4), and weak negative correlations between LEP with SBP as well as cholesterol levels (Figure 5).

DISCUSSION

Obesity significantly increases the risks of developing DM, Hypertension (HTN), dyslipidemia, and CVD. overweight constitute one-third of the Saudi individuals, and this is increasing despite raising public awareness. Females usually report higher rates of obesity, and thus they are at higher risk of developing those diseases (Daghestani et al., 2007). one of the main reason of mortality is CVD (Venuraju et al., 2010), and type 2 DM patients have a two to six folds' higher risk of developing CVD (Kannel and McGee, 1979), thus the latter is considered a common and aggravating cause of morbidity and mortality among DM patients (Willerson and Ridker, 2004). LEP is a polypeptide hormone secreted by several tissues, which was strongly associated to obesity (Simonet et al., 1997). The study aimed to determine LEP levels in a Saudi population suffering from DM and CVD, compare those levels with values of normal individuals, and then assess its relationship to other parameters.

Serum LEP and the Physical Characteristics

Anthropometrics and other physical measurements are important parameters in the prediction of metabolic disorders. In this study age, BMI, and SBP were associated with high LEP values in the three diseased groups; CVD, DM, and CVD & DM, which could be related in general to role played by LEP in the food intake regulation, expenditure of energy (Lauderdale, 2000). For females' serum LEP was associated with age, which was

confirmed before in many studies (Ruhl and Everhart, 2001; Ding et al., 2003; Yamauchi et al., 2001). Although initially some studies reported no association of age and LEP after BMI adjusting, a positive association was found (Ruhl and Everhart, 2001; Ding et al., 2003; Yamauchi et al., 2001). This could be explained by the noted increase of mean body weight and BMI with age, along with the decreased mobility. An “apple figure”, with an increase in central fat distribution that strongly indicates elevated LEP concentrations (Martini et al., 2001). This should be further assessed and confirmed by measuring the body fat mass.

An association between hyperleptinemia and HTN was detected in obese subjects at risk of metabolic syndrome (Sudi et al., 2000; Kunz et al., 2000; Laivuori et al., 2000), and notably most studies investigating hormonal involvement in HTN pathogenesis involved obese subjects (Kennedy et al., 1997). In this study, and namely for females, we found a negative association of LEP with SBP when adjusted for general obesity. Another study reported similar results, in obese African females suffering from HTN (El-Gharbawy et al., 2002). These findings agreed with another study conducted in Saudi Arabia, and which identified LEP levels as strong predictors of HTN in obese females (Hazimi-Al and Syiamic, 2004). It is probable that associations of LEP and HTN are due to the concomitant elevation of insulin in obese subjects (Asakawa et al., 2001). This was reinforced in this study by the significant correlation detected between the two, and again in agreement with other studies conducted in both non-diabetic (Haffner et al., 1999), and diabetic subjects with normal BMI (Asakawa et al., 2001).

Surprisingly, we found no association between LEP and BMI in most of the studied groups, except for significantly decreased LEP levels in the CVD & DM group, indicating higher BMI levels for this group. This supports what was suggested previously about LEP being an important link between obesity and development of CVD. This link could also be related to the various other LEP effects on; HTN (Menendez et al., 2000; Cooke and Oka, 2002), aggregation of platelet (Chaldakov et al., 2001), arterial thrombosis formation (Beltowski et al., 2002) and vascular response to inflammatory reactions (Konstantinides et al., 2001; Bodary et al., 2002). High LEP levels are associated with lower arterial distensibility, an index of circulatory function, and thus it may be involved in the pathogenesis of atherosclerosis through mechanisms other than vascular relaxation (Chu et al., 2000). Moreover, through its receptor mechanism, LEP were shown to enhance angiogenesis, osteoblastic differentiation regulation, promote vascular cells calcification and potentiate the aggregation of pro-thrombotic platelet (Sierra-Honigmann et al., 1998; Parhami et al., 2001; Chaldakov et al., 2001). Individuals with Obesity has higher levels of plasma of pro-thrombotic factors such as fibrinogen, similar to our study findings, as well as Von Willebrand factor, factor VII and plasminogen activator inhibitor–1 (PAI-1). All the later can lead to a higher risk of thrombosis and atherosclerosis, and the above pro-thrombotic factors are directly correlated to fat composition, and therefore LEP levels (Singhal et al., 2002).

Serum LEP and the Lipid Profile

Our study demonstrated that LEP correlated negatively with cholesterol in both males and females, and with no correlated with LDL, HDL and TG (Lundasen et al., 2003). In normoglycemic, conditions, LEP protect macrophages from cholesterol overload, and in fact, an inverse relationship between LEP and HDL, cholesterol and/or apolipoprotein A–I was reported before (Lundasen et al., 2003). The LEP with plasma lipids relationship and lipoproteins was reported by several studies in both healthy and diseased individuals, yet to the best of our knowledge, no study documented the levels of LEP in Saudi patients with CVD and DM thus far. According to previous studies, there is no agreement on a clear relationship between LEP and serum lipids, or between LEP and lipoproteins. Some studies observed no correlation between LEP and serum lipid parameters (Al-Shoumer et al., 1997), while other studies reported a positive correlation between LEP and HDL (Rainwater et al., 1997; Couillard et al., 1998; Chapman et al., 1997) or between LEP and TG (Leyva et al., 1998). In our study, we found a negative correlation between LEP and cholesterol, and no association between LEP and the lipoproteins or TG levels. While we cannot present explanations for these results, the latter contradicts with what was reported by others, and must be further research in large scale prospective studies.

The following limitations must be acknowledged; due to resources constrains, our sample size was relatively small, and thus we could not confirm the predictive value of LEP in DM & CVD patients. Our study also lacked a direct assessment of the body fat mass distribution and *in vivo* insulin action. These are important parameters, and their measurement could have enhanced the findings.

CONCLUSION

LEP was higher in (CVD and DM) study groups when compared to normal individuals, and in all females’ subgroups when compared to males. LEP correlated strongly with cholesterol levels in both males and females. More studies are needed to assess LEP as a potential biomarker for CVD.

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