Correlation studies between leptin, glucose and insulin in pre- and postmenopausal Saudi

Abstract

Leptin act as a regulator of cellular energy metabolism but its role in lipid metabolism in humans is still unclear. Relation between leptin and plasma lipids in Saudi females was evaluated in this study. 126 females with age ranging from 18 to 75 years were recruited and grouped into premenopausal and postmenopausal females and then in lean, normal weight, overweight, and obese on the basis of their BMI values. Plasma samples were assessed for Leptin, Cholesterol, triglycerides, High-density lipoproteins (HDL-C), Low-density lipoproteins (LDL-C) and glucose. Significant increase in glucose, triglycerides and leptin was associated with increase weight. Insulin level was found to be significantly highest in overweight group. Cholesterol, LDL-C was found to increase with increase weight while HDL-C was decreased with increased weight. Leptin, triglycerides and glucose were significantly higher ($P<0.05$) in the postmenopausal females as compared to the premenopausal group. Remarkable increase of cholesterol and glucose was found in postmenopausal female while HDL-C, LDL-C and insulin were slightly decreased in postmenopausal females. High serum leptin levels can act as the risk factor for diabetes in obese and postmenopausal female. Regular monitoring of total leptin at pre-menopause stage could help in managing some life-threatening condition related to obesity in old age.

Key words: *Leptin, premenopausal, postmenopausal, glucose, insulin, plasma lipids, BMI*

Introduction

Leptin is a protein hormone of 167 amino acids and is synthesized and secreted from the adipose tissue [1]. The secreted leptin usually acts principally in brain and may have direct peripheral effects [2]. Within the brain, the leptin receptor is present in several nuclei with the highest expression observed in the hypothalamus particularly the arcuate nucleus [3]. Within the arcuate nucleus, two molecularly distinct neuronal populations have emerged as major targets of leptin: the stimulatory neurons expressing proopiomelanocortin (POMC) and inhibitory neurons expressing agouti-related protein (AgRP) [4]. Leptin activates anorexigenic POMC neurons while simultaneously inhibit orexigenic AgRP neurons [5,6]. Therefore, it exerts its effect of decreasing food intake and body weight, increasing fat oxidation and energy expenditure, thus favoring leanness [7].

Higher leptin levels lead to fatty acid oxidation and reduction in adipose tissue mass, whereas leptin deficiency is associated with an increase in fat deposition [8]. Leptin can affect energy balance at the gut level by reducing lipids released into the circulation [9]. In some studies, it was demonstrated that obese people have increased lipogenesis that could contribute to their excessive fat mass [10] and other studies reported that serum leptin level was significantly related to total cholesterol and triglycerides [11.12]. The leptin prevents physiological deposit of non-polar triglycerides in insulin-dependent cells. The main cause of high level of leptin in blood plasma is overeating of food physiological by content of nutrients. Increased levels of insulin are associated with obesity, Cushing's syndrome, oral contraceptives, acromegaly, insulinomas and hyperthyroidism. Decreased levels of insulin are found in some forms of diabetes mellitus (DM) and are part of a complex mechanism involving catecholamines [13]. There are two major forms of diabetes mellitus: type 1 diabetes mellitus, which is known as insulin dependent diabetes

mellitus. The other type is type 2 diabetes mellitus and most people with this form have impaired insulin action. Obesity is commonly associated with this condition and weight loss alone frequently ameliorates the hyperglycemia. Leptin modulates pancreatic B-cell function in vivo. Increased leptin levels can accompany high serum insulin levels as many studies have reported a correlation between endogenous insulin and leptin level [14] Studies have confirmed that the more obese a person is the higher are their levels of leptin [15,16] Insulin and glucocorticoids work directly on adipose tissue to upregulate levels and rates of leptin secretion in human adipose tissue over the long term.

Glucose is the primarily energy source for the human body. After absorption its metabolism proceeds according to the body's requirement. This metabolism results in energy production by conversion to carbon dioxide and water, storage as glycogen in the liver or triglycerides (TG) in adipose tissue, or conversion to keto acids, amino acids or protein [17]. Leptin may play a regulatory role in glucose metabolism within adipocyte cells and may have the ability to lower blood glucose levels [18]. The objective of this study was to determine the level of leptin in Saudi females and its relation to plasma lipids in relation to pre- and postmenopausal state. Also the relationship between leptin and both of glucose and insulin was evaluated.

2. Methods and materials

This study was conducted on 126 healthy females, 94 of them were premenopausal and 32 postmenopausal. The subjects were randomly selected excluding diabetic ones. The aim of the study was explained and their consensus was taken. They were asked to come fasting for 12 hours on an agreed day. The personal information was obtained and all the information was recorded on special form together with their signature. Height (in meter) and weight (in kilograms) were recorded on a measuring scale. The data was used to calculate the BMI using

the formula: BMI = weight (Kg)/ height^2 (m^2). The hip and waist were measured using a measuring tape and waist/hip ratio was calculated. The systolic and diastolic blood pressures were measured using blood pressure gauge.

2.1 Collection of samples

Blood sample was drawn by venipuncture in plain tubes and plasma was separated from cells by centrifugation at 1000 rpm for 10 minutes. The plasma was stored frozen at –20°C until required for analysis.

2.2 Leptin and Dyslipidemia –related markers.

Leptin level was determined by radioimmunoassay using kit from Linco. Whereas Cholesterol, triglycerides, HDL and LDL, was done by using kits from United Diagnostics Industry

2.3 Glucose

Glucose was estimated using a glucose meter (one Touch II meter), which applies an enzyme method for estimation of glucose.

2.4 Insulin

Insulin was estimated by micro particle enzyme immunoassay (MEIA).

2.5 Ethical approval-

The study protocol was approved by the Ethical Committee at King Khalid University Hospital, King Saud University, Riyadh, Kingdom of Saudi Arabia (IRB no: E-14-1194). All participants attending the out-patient Clinics of the Clinical co-investigators were enrolled in the study, after taking their informed consent.

2.6 Statistics analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) program version 9.0. The mean, median, mode, standard deviation, variance skewness, kurtosis, 95% confidence interval, and parametric and non-parametric ranges were obtained. Frequency distribution histograms were obtained. The females were grouped as pre- and post-menopausal. The data was separately analyzed for the different groups. The females were also grouped into different groups on the basis of their BMI results of different groups were compared using student 't' test and Mann-Whitney test. $p<0.05$ was considered statistically significant. Correlation studies were carried out between different parameters and Pearson's correlation coefficient (r) and p values were obtained. Correlation was considered statistically significant at values of $p<0.05$`

3. Result and Discussion

Demographic characteristics of all the recruited groups in the study are shown in Table 1. Comparing demographic data of lean, normal weight, overweight and obese females is shown in Table 2. Females were grouped as lean, normal weight, overweight and obese according to their BMI. Biochemical parameters were compared on the basis of lean, normal weight, overweight and obese females as shown in Table 3. Cholesterol did not differ significantly between any of the different groups. Significant increase in glucose, triglycerides and leptin was associated with increase weight. Insulin level was found to be significantly highest in overweight group. Cholesterol, LDL-C was found to increase with increase weight while HDL-C was decreased with increased weight (Table 3).

Females were also grouped on the basis of pre- and post-menopausal stage as shown in Table 4. In the total females in this study, the mean ±S.D range for cholesterol in total group was 4.88±2.32 mmol/l whereas in pre- and post-menopausal females it was 4.85±1.84 mmol/l and

4.97±3.4 mmol/l, respectively. The cholesterol level was slightly higher in the post-menopausal females, though the difference was not statistically significant. Cholesterol is a non-essential lipid for humans and can be synthesized from acetyl CoA and acetoacetyl CoA by the formation of 3-hydroxy-3-methylglutaryl CoA by 3-hydroxy-3-methylglutaryl CoA synthase. The 3-hydroxy-3-methylglutaryl CoA is then reduced to mevalonate and after several steps results in the formation of the 27 carbon atom steroid i.e. cholesterol. The major site of cholesterol synthesis is the liver. However, cholesterol synthesis by the liver is suppressed by dietary cholesterol.

Cholesterol plays essential roles in the humans and is a component of all eukaryotic plasma membranes. In addition to its role in the biosynthesis of steroid hormones, vitamin D and bile acids, it is essential for the growth and viability of cells in higher organisms. However, in human's high serum levels of cholesterol are associated with several serious conditions, some leading to disease and death by contributing to the formation of atherosclerotic plaques in arteries throughout the body[19]. Several studies have shown that an increase in the body mass index is associated with adverse changes in the plasma lipids and lipoprotein profiles resulting in elevated total cholesterol, LDL-C and TG levels and a decrease in HDL-C level [20].

Table 5 shows the correlations between the biochemical parametersand Table 6 shows the correlations between leptin, lipids, Glucose, Insulin with demographic parameters.

Correlation between cholesterol with demographic data showed a positive correlation between cholesterol and hip circumference, waist circumference, waist/hip ratio and diastolic blood pressure The significant correlation between cholesterol and hip circumference, waist circumference, waist/hip ratio may explain the association of body fat distribution with cardiovascular risk factors. There was a positive correlation between cholesterol and blood

pressure. This correlation did not exist in lean or normal weight group but existed in the overweight (systolic BP and cholesterol) and obese groups (diastolic BP and cholesterol), hence we conclude that cholesterol possibly relate to blood pressure indirectly through increase in body weight. A positive correlation was also found between cholesterol and TG. This correlation did not exist in lean or normal weight females, but existed in overweight and obese females. These results confirm that weight increases can result in increase of cholesterol, triglycerides which can directly or indirectly result in the increase in blood pressure. Finally, cholesterol was found to correlate positively with LDL-C. This was expected, since LDL-C is the major carrier of cholesterol in the blood.

Triglycerides showed several interesting correlations with the different demographic parameter. It correlated positively with age, weight, BMI, waist circumference, hip circumference, waist/hip ratio and systolic blood pressure. Positive correlation was found with diastolic blood pressure in the overweight group. Correlation between TG and waist/ hip ratio has been reported in previous studies. Rendell et al [21] concluded that the amount of the intra-abdominal fat strongly influences plasma triglycerides levels in early postmenopausal women, whereas Tai et al [22] reported that the distribution of fat between subcutaneous fat depots may be important in the metabolic syndrome given the correlation of fasting TG with waist/ hip ratio but not with abdominal fat.

Leptin levels showed a highly significant positive correlation with the triglycerides level in the total studied females. Correlation between leptin and TGs has been reported previously Martini et al [23] Kavazarakis et al [24] concluded that there is independent association between leptin and TG after controlling for any known cofounder. The TG levels were higher in the post-menopausal group and the difference between the two groups was statistically significant. The

increase in TG level in the post-menopausal females could be due to increase in age. Some studies report that as age increase TG levels increase. However, Pasquali et al [25] reported that the age-adjusted values of TG were similar in all age groups they studied. The correlation of TG with age may be due to an indirect correlation with BMI. This study and those reported earlier have shown that BMI increases significantly with age. Similarly, when the females were divided to lean, normal weight, overweight and obese groups according to their BMI, TG levels were found to be significantly different between most of the groups, except no difference was found in the TG level between lean and normal weight females.

With the other biochemical parameters TG correlated positively with cholesterol, and LDL-C, but negatively with HDL-C. When the correlation studies were carried out between the different BMI groups (i.e. lean, normal weight, overweight, and obese) several differences were obvious. In the lean group TG correlated negatively with HDL-C. This indicated that as triglycerides will increase in normal weight people, HDL-C the 'good' cholesterol would decrease. In the overweight and obese females, TG correlated positively with cholesterol and LDL-C. Decrease in HDL-C and increase in cholesterol and LDL-C are all risk factors for the development of cardiovascular disease and as shown by the results of this study, these correlate positively with weight gain and increase in BMI. Hence overweight and obesity can be considered as major risk factors for cardiovascular diseases. Interestingly, correlation with blood pressure did not exist in lean or normal weight group but did exist in the overweight females. We further conclude that as weight and BMI increase TG increases and this may play a role in increasing in blood pressure.

Leptin did not show any correlation with HDL-C, though a slight decrease occurred in HDL-C as the leptin level increased, but the results were not statistically significant. It is well documented

that elevated plasma HDL-C level is protective against coronary heart disease whereas decreased levels increase the risk of coronary heart disease.

When the correlation studies were carried out separately in the lean, normal weight, over weight and obese groups several interesting differences came to light. Within normal BMI female group there was a negative correlation between weight and HDL-C. This means that as weight increases (although still within normal range), HDL-C decreases, and this is a bad sign. Also within normal BMI female group there was a negative correlation between HDL-C and hip circumferences, waist circumference, and waist/hip ratio. No correlation was obtained between leptin and LDL-C. LDL-cholesterol is the major carrier of cholesterol in the blood, from the liver to the tissues. It is considered as the 'bad' cholesterol and elevated level is associated with increasing risk of CHD.

A highly significant positive correlation was seen between LDL-C and hip circumference and waist circumference. The correlation with hip and waist circumferences, and not weight and BMI, suggests the importance of body fat distribution as a risk factor for development of CHD. It is well believed that androgenic obesity is much greater risk factor compared to the pear shape obesity, as there appear to be a higher chance of metabolic abnormalities [26]

Soderberg et al [27] concluded that leptin is an important link in the development of cardiovascular disease in obesity. In addition, Chu et al [28] concluded that plasma leptin plays a role in CVD through independent effects on lipid metabolism.

Leptin correlated positively with glucose and insulin. Glucose is the primary fuel for the brain. However, elevated levels are associated with diabetes mellitus and can be dangerous, as well as a risk for development of CHD. Glucose correlated positively with age, weight, BMI, hip circumference, waist circumference, waist/hip ratio, triglycerides, insulin and leptin but

negatively with cholesterol, HDL-C, and LDL-C. Insulin correlated positively with weight, height, BMI, hip circumference, waist circumference, waist/hip ratio, triglycerides, glucose, and leptin and correlated negatively with HDL-C. Studies have shown that glucose infusions, which increase endogenous insulin secretion, also increase plasma leptin in human[29,30].

German et al [31] study concluded that Leptin action in the brain potently suppresses hepatic glucose production while increasing tissue glucose uptake despite persistent, severe insulin deficiency. This leptin action is distinct from its previously reported effect to increase insulin sensitivity in the liver and offers compelling evidence that the brain has the capacity to normalize diabetic hyperglycemia in the presence of sufficient amounts of central nervous system leptin.

Thus, leptin along with insulin, which also has direct actions in the CNS to regulate food intake and energy expenditure, functions as a negative feedback signal to the CNS to regulate energy balance. They act as medium to long-term regulators of energy balance, and not as short-term satiety signals [32]. Leptin infusion improved hyperglycemia and hyperinsulinemia in mice [33]. Leptin infusion acutely enhanced hepatic insulin sensitivity [34] Together, these results suggest that the effects of insulin, which increases leptin production, could be mediated through increase in glucose utilization by adipocytes [32]

4.Conclusion High serum leptin levels can act as the risk factor for diabetes in obese and postmenopausal female. Regular monitoring of total leptin at pre-menopause stage could help in managing some life-threatening condition related to obesity in old age.

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Table 1: Demographic characteristics in Saudi females

Parameter	Group	Mean ± S.D.	P value
Age (years)	Premenopausal group	30.53 ± 7.28	0.0001
	Postmenopausal group	58.34 9.16	
	Total	37.6 14.42	
Weight (Kg)	Premenopausal group	66.39 ± 14.31	0.054
	Postmenopausal group	70.87 9.92	
	Total	67.53 ± 13.44	
Height (m)	Premenopausal group	1.57 0.06	0.0001
	Postmenopausal group	1.54 ± 0.07	
	Total	1.56 0.06	
BMI (Kg/m)	Premenopausal group	27.01 5.45	0.001
	Postmenopausal group	29.85 3.63	
	Total	27.73 5.19	
Waist circumference (cm)	Premenopausal group	105.62 9.9	0.088
	Postmenopausal group	111.3 10.06	

Parameter	Group	Mean ± S.D.	P value
	Total	106.18 10.01	
Hip circumference (cm)	Premenopausal group	81.38 ± 12.4	0.0001
	Postmenopausal group	96.7 ± 7.2	
	Total	82.88 ± 12.81	
Waist/ hip	Premenopausal group	0.77 0.06	0.0001
	Postmenopausal group	0.87 ± 0.07	
	Total	0.78 ± 0.07	
Systolic blood pressure (mm/Hg)	Premenopausal group	111.1 ± 11.42	0.0001
	Postmenopausal group	124.72 ± 18.98	
	Total	114.56 ± 14.89	
Diastolic blood pressure (mm/Hg)	Premenopausal group	72.3 ± 10.10	0.271
	Postmenopausal group	74.66 ± 11.35	
	Total	72.9 ± 10.43	

Table 2: Comparing of the demographic data of lean, normal weight, overweight and obese females

Parameter	**Group**	**Mean**	**Std. Deviation**	**Significance**
Age (Yrs)	Lean	25.75	5.15	b, c, d, e
	Normal	30.40	9.94	
	Overweight	40.23	15.71	
	Obese	42.02	14.05	
Weight (Kg)	Lean	47.29	3.93	a, b, c, d, e, f
	Normal	57.53	4.86	
	Overweight	65.33	7.51	
	Obese	80.22	11.59	
Height (m)	Lean	1.57	0.06	e
	Normal	1.58	0.06	
	Overweight	1.56	0.07	
	Obese	1.55	0.06	
BMI (Kg/m^2)	Lean	19.18	0.59	a, b, c, d, e, f
	Normal	23.02	1.40	

	Overweight	26.92	1.24	
	Obese	33.31	3.71	
Hip (cm)	Lean	90.88	4.29	a, b, c, d, e, f
	Normal	99.32	4.15	
	Overweight	106.66	4.77	
	Obese	115.77	9.49	
Waist (cm)	Lean	68.58	4.50	a, b, c, d, e, f
	Normal	73.11	7.72	
	Overweight	82.69	7.51	
	Obese	95.65	10.84	
Ratio	Lean	0.75	0.03	c, d, e, f
	Normal	0.74	0.06	
	Overweight	0.76	0.06	
	Obese	0.83	0.07	
Systolic (mm/Hg)	Lean	112.75	12.74	e, f
	Normal	107.43	12.87	
	Overweight	112.89	13.81	
	Obese	121.41	15.13	
Diastolic (mm/Hg)	Lean	73.75	11.11	e
	Normal	69.47	8.58	
	Overweight	71.93	10.32	
	Obese	76.05	10.99	

**The difference is significant at 0.05 levels: *'a' is used when the difference between groups 1and 2 is significant, 'b' when 1,3 significant, 'c' when 1,4 significant, 'd' when 2,3 significant, 'e' when 2,4 significant, 'f' when 3,4 significant*

Table 3: Comparing the biochemical parameters of lean, normal weight, overweight and obese females

Parameter	Group	Mean	Std. Deviation	Significance
Glucose (mmol/l)	Lean	4.45	.342	c, e, f
	Normal	4.51	.459	
	Overweight	4.69	.474	
	Obese	4.98	.831	
Cholesterol (mmol/l)	Lean	4.58	1.12	-
	Normal	4.78	0.80	
	Overweight	4.80	1.15	
	Obese	5.08	1.38	
TG (mmol/l)	Lean	0.83	0.28	a, b, c, d, e, f
	Normal	0.90	0.34	
	Overweight	1.11	0.48	
	Obese	1.41	0.52	
HDL-C (mmol/l)	Lean	1.1	0.36	-
	Normal	0.91	0.28	
	Overweight	0.98	0.32	
	Obese	0.92	0.26	
LDL-C (mmol/l)	Lean	3.13	1.0	-
	Normal	3.46	0.84	
	Overweight	3.32	1.08	
	Obese	3.53	1.21	

Insulin (µU/ml)	Lean	8.38	3.13	c, e, f
	Normal	6.83	4.47	
	Overweight	7.53	4.58	
	Obese	11.62	7.02	
Leptin (ng/ml)	Lean	8.30	3.28	b, c, d, e, f
	Normal	11.37	4.05	
	Overweight	16.8	6.65	
	Obese	25.64	11.01	

* **The difference is significant at 0.05 levels:

'a' is used when the difference between groups 1and 2 is significant, 'b' when 1,3 significant, 'c' when 1,4 significant, 'd' when 2,3 significant, 'e' when 2,4 significant, 'f' when 3,4 significant

Table 4: Levels of leptin, plasma lipids, Insulin, and Glucose in Saudi female

Parameter	Group	Mean ± S.D.	P value
Leptin (ng/ml)	Premenopausal group	16.4 ± 7.24	0.001
	Postmenopausal group	22.91 14.46	
	Total	18.06 9.95	
Cholesterol (mmol/l)	Premenopausal group	4.85 ± 0.92	0.611
	Postmenopausal group	4.97 ± 1.7	
	Total	4.88 ± 1.16	
TG (mmol/l)	Premenopausal group	1.03 ± 0.43	0.0001
	Postmenopausal group	1.49 ± 0.52	
	Total	1.14 ± 0.5	
HDL-C (mmol/l)	Premenopausal group	0.95 ± 0.29	0.897
	Postmenopausal group	0.94 ± 0.32	
	Total	0.95 ± 0.3	
LDL-C (mmol/l)	Premenopausal group	3.43 ± 0.91	0.704
	Postmenopausal group	3.35 ± 1.46	
	Total	3.41 ± 1.07	
Glucose (mmol/l)	Premenopausal group	4.62 ± 0.49	0.0001
	Postmenopausal group	5.08 ± 0.88	
	Total	4.73 ± 0.64	

Parameter	Group	Mean ± S.D.	P value
Insulin (µU/ml)	Premenopausal group	9.27 ± 5.62	0.05
	Postmenopausal group	7.59 ± 6.22	
	Total	8.84 ± 5.8	

Table 5: Correlations between the biochemical parameters in the total female population

	Leptin	**CHOL**	**TG**	**HDL-C**	**LDL-C**	**Glucose**	**Insulin**
Leptin	1.000	.012	.244	-.080	-.017	.382*	.413*
CHOL	.012	1.000	.514*	.075	.958*	-.235*	.022
TG	.244*	.514*	1.000	-.200	.403*	.228	.335*
HDL-C	-.080	.075	-.200	1.000	-.153	-.341*	-.184
LDL-C	-.017	.958*	.403*	-.153	1.000	-.209	.004
Glucose	.382*	-.235	.228	-.341*	-.209	1.000	.243*
Insulin	.413*	.022	.335*	-.184	.004	.243*	1.000

* considered statistically significant

Table 6: Correlations between leptin, lipids, Glucose, Insulin and demographic parameters

	Leptin	Cholesterol	TG	HDL-C	LDL-C	Glucose	Insulin
Age	0.236*	0.172*	0.495*	-0.074	0.102	0.338*	-0.111
Weight	0.572*	0.127	0.364*	-0.165	0.107	0.282*	0.382*
Height	0.001	-0.095	-0.034	-0.272*	-0.020	0.034	0.190
BMI	0.600*	0.176	0.400*	-0.063	0.125	0.288*	0.307*
Hip	0.722*	0.243	0.384*	-0.216	0.236	0.346*	0.374*
Waist	0.672*	0.291	0.538*	-0.146	0.230	0.372*	0.409*
Waist/hip	0.364*	0.231	0.503*	-0.033	0.139	0.271*	0.297*
Systolic BP	0.243*	0.140	0.283*	0.155	0.050	0.161*	0.062

Diastolic BP	0.175	0.215	0.134	0.138	0.167*	-0.010	0.072

* considered statistically significant