

Leptin Level in Gestational Diabetes Mellitus

Sura Zahim Hussein* (Ph.D in Biochemistry),

Abdul-Monaim Hamad Al- Samarraï** (Ph.D in Biochemistry (UK))

* Department of Laboratory /Tikrit Teaching Hospital/Iraq, **Department of Chemistry/ College of Education/Samarra University/Iraq.

Abstract

Leptin, a protein secreted by white adipocytes, plays a relevant role in the regulation of body weight and food intake. During pregnancy, leptin seem to act in an autocrine/paracrine fashion in the placenta and adipose tissue, playing a role in the maternal-fetal interface and contributing to glucose metabolism and fetal development. Leptin level, BMI, glucose and lipid profile were measured in 30 gestational diabetes mellitus and 30 non-diabetic pregnant women from January 2010 to June 2011. Blood samples were collected of the 1st, 2nd and 3rd trimester of pregnant women. Correlation measured between leptin level with BMI and lipid profile. Leptin level increased significantly ($P \leq 0.01$) in diabetic pregnant women during the three trimesters compared to the non-diabetic pregnant women. There was a positive correlation leptin level with BMI and lipid profile (except HDL-cholesterol) which increased in diabetic pregnant women. These increased in leptin level in diabetic pregnant women due to insulin resistant and hyperinsulinemia in gestational diabetes mellitus.

Introduction

Diabetes can occur temporarily during pregnancy, hormonal changes during pregnancy can lead to blood sugar elevation in genetically predisposed individuals.

Blood sugar elevation during pregnancy is called gestational diabetes (1). Gestational diabetes usually resolves once the baby is born. Leptin of human origin has a sequence of 167 amino acids, the molecular weight of leptin is around (16 kDa) and it has 67% sequence identity among diverse species (2).

Leptin is a hormone that is produced predominantly by adipose cells (3&4). Circulating leptin levels are proportional to adipose tissue mass. Thus leptin levels can be thought of as a signal to the body of its energy reserves. The placenta also produces

leptin in human pregnancy, increasing the amount in the maternal circulation. Thus maternal leptin levels are the sum of leptin secretion from adipose tissue, which is proportional to maternal fat levels, and from the placenta, which occurs at an adiposity-independent rate (5). Women who are obese and therefore more likely have decreased insulin sensitivity are at increased risk for many adverse pregnancy outcomes. Similar to what is observed in the non pregnant population, the constellation of conditions mimics the metabolic syndrome (6). The metabolic syndrome of pregnancy includes an increased risk of hypertensive, metabolic disturbances of nutrient metabolism, and inflammation. Although these pregnancy-related conditions are most likely to clinically resolve once the woman is

Leptin Level in Gestational Diabetes Mellitus

delivered, these individuals still have the subclinical underlying metabolic disorder, and are at increased risk for the metabolic syndrome in later life, particularly if there is increased postpartum weight gain (7). The decrease in insulin sensitivity in pregnancy is not limited only to glucose metabolism but is also observed in relation to lipid metabolism as well (8). There is a two- to threefold increase in basal triglyceride and cholesterol concentrations with advancing gestation (9). The increases are more pronounced in the GDM as compared with the normal glucose tolerant pregnant woman (8).

Subjects and Methods

Venous blood specimens were obtained from 60 pregnant women (30 gestational diabetic women & 30 normal pregnant women) subdivided into three groups according to pregnancy stages, 20 patients and controls for each trimester with age ranges from (25-42) year which collected from January 2010 to June 2011. The control females are non-diabetic and non-smoker with no familial history of diabetes or personal history of hypertensive, thyroid or renal diseases.

The DSL-10-23100 ACTIVE® Human Leptin ELISA (USA) is an enzymatically amplified "two-step" sandwich-type immunoassay that used in this study. Lipid profile was measured by enzymatic colorimetric method supplied (Bicon

Burbach / Germany). Body mass index (BMI) of all participants was calculated by:-
(BMI = body weight (kg)/ height (m²))

Results were analyzed statistically using (F) tests and the statistical program Minitab. Averages were compared in calculations of the characteristics of the application Duncan's Multiple Range Test by probability level $P \leq 0.05$.

Results

The leptin mean value in three trimesters of pregnancy period was [1st trimester= 13.6 ng/ml with BMI 21.72 kg/m², 2nd trimester= 24.5 ng/ml with BMI 24.78 kg/m² and 3rd trimester= 36.9 ng/ml with BMI 26.68 kg/m²] in non diabetic pregnant women (table 1), while leptin was increased in gestational diabetic women (table 2) [1st trimester= 17.9 ng/ml with BMI 22.52 kg/m², 2nd trimester= 36.4 ng/ml with BMI 24.88 kg/m² and 3rd trimester= 46.8 ng/ml with BMI 26.34 kg/m²]. These results showed that there was highly significant difference ($p \leq 0.01$) between the three trimesters across pregnancy period.

Across all pregnancy period, the leptin mean value was (25.0 ng/ml with BMI 24.39 kg/m²) and (33.7 ng/ml with BMI 24.58 kg/m²) in control and diabetic pregnant women respectively. These results showed that there was highly significant difference ($p \leq 0.01$) between three trimesters across pregnancy period. These results indicated that there was positive correlation between

Leptin Level in Gestational Diabetes Mellitus

leptin with BMI in control and diabetic pregnant women ($r=0.556$) and ($r=0.201$) respectively (Fig 1).

Cholesterol, triglyceride, VLDL and LDL was increased, while HDL was slightly decreased in diabetic pregnant women rather than control (table (1&2)). There was a positive correlation between leptin with (cholesterol, triglyceride, VLDL and LDL-cholesterol) ($r=0.664, 0.391, 0.391$ and 0.64) and ($r=0.484, 0.446, 0.446$ and 0.396) in control and diabetic pregnant women respectively, but there was a negative correlation with (HDL-cholesterol) ($r=-0.538$) and ($r=-0.257$) in control and diabetic pregnant women respectively (Fig 1).

Discussion

Leptin in pregnant women was increased progressively during three trimesters of pregnancy, while the elevation of leptin in diabetic pregnant women was more than it because of insulin resistant and hyperinsulinemia in gestational diabetes mellitus. There was a positive correlation between leptin and BMI; therefore, BMI was increased progressively with leptin in all trimesters. The appetite of most pregnant women increases after the fourth month of gestation when symptoms of nausea and vomiting disappear because leptin resistance was occurred (10). Therefore, in addition to uterine content, systemic organs including subcutaneous adipose tissue, omentum, blood volume and breasts increase in size with

advancing gestation. Leptin is one of the proteins produced by syncytiotrophoblasts in the placenta (11&12). The amount of leptin synthesized by the placenta should increase due to the increased size of the placental mass with advancing gestation, these results were agree with (Reitman *et al* (5), Kautzky-Willer *et al* (13), Al-Atawi *et al* (14) and Khan *et al* (15)) but in contrast with that found by Kennedy *et al* (16). Hassink *et al* (17) found similar or higher amounts of leptin mRNA in placental tissue than in abdominal fat tissue and speculated that placenta might be the major source of leptin production for the fetus. The increase in plasma leptin concentration during pregnancy might be attributable to transfer of placental leptin to maternal circulation.

Lipid profile parameters for all three trimesters were progressively increased in diabetic pregnant women rather than control, except HDL-cholesterol which decrease in comparison with control. The previous results may be due to the explanation done by Butte (18) who stated that the higher concentrations of estrogen and insulin resistance were thought to be responsible for the hypertriglyceridemia of pregnancy. Cholesterol was used by the placenta for steroid synthesis and fatty acids were used for placental oxidation and membrane formation. Changes in total cholesterol concentration reflect changes in the various lipoprotein fractions. Changes in lipid metabolism promote the accumulation of maternal fat stores in early and mid pregnancy and

enhance fat mobilization in late pregnancy (18).

References

- 1-American Diabetes Association. Gestational diabetes mellitus (Position Statement). *Diabetes Care* 2004;27 (Suppl 1):88-90.
- 2-Yang J, Zhao XQ, Guo SC, Li HG, Qi DL, Wang DP, et al. Leptin cDNA cloning and its mRNA expression in plateau pikas (*Ochotona curzoniae*) from different altitudes on Qinghai-Tibet Plateau. *J Biochem Biophys Res Commun* 2006;345(4):1405-13.
- 3-Zhang Y, Proenca R, Maffei M, Barone M, Leopold L & Friedmann JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* Dec1994;372:425-32.
- 4-Ahima RS & Flier JS. Adipose tissue as an endocrine organ. *Trends Endocrinol Metab* 2000; 11(8): 327-32.
- 5-Reitman ML, Bi S, Marcus-Samuels B & Gavrilova O. Leptin and its role in pregnancy and fetal development - an overview. *Biochem Soc Trans* 2001; 29(2):68-71.
- 6-World Health Organization .Definition, Diagnosis and Classification Of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, Switzerland: World Health Organization 1999.
- 7-Villamor E & Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. *Lancet* 2006; 368:1164-70.
- 8-Catalano PM, Nizielski SE, Shao J, Preston L, Qiao L & Friedman JE. Downregulated IRS-1 and PPAR γ in obese women with gestational diabetes: relationship to free fatty acids during pregnancy. *Am. J. of Physiology Endocrinology and Metabolism* 2002 ; 282:522- 33.
- 9-Knopp RH, Chapman M, Bergelin RO, Wahl PW, Warth MR & Irvine S Relationship of lipoprotein lipids to mild fasting hyperglycemia and diabetes in pregnancy. *Diabetes Care* 1980; 3: 416- 20.
- 10- Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: a prospective study of its frequency, intensity, and pattern of change. *Am J Obstet Gynecol* 2000; 182:931-7.
- 11- Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, Nishimura H, et al. Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. *Nat Med* 1997; 3:1029-33.
- 12- Senaris R, Garcia-Caballero T, Casabiell X, Gallego R, Castro R, Considine RV, Dieguez C, et al. Synthesis of leptin in human placenta. *Endocrinology*. 1997;138:4501-4.
- 13- Kautzky-Willer A, Pacini G, Tura A, Biegelmayer C, Schneider B, Ludvik B, et al. Increased plasma leptin in gestational diabetes. *Diabetologia* 2001;44:164-72.
- 14- Atawi F, Addar M, Warsy AS & Babay Z. Leptin concentration during different trimesters of pregnancy & its relation to other pregnancy hormones. *Saudi Med J* 2004;25(11);1617-22.

Leptin Level in Gestational Diabetes Mellitus

15- Khan MH, Khan JA, Mahood F & Bagum N. Hormonal profile in pregnant women. Pak J Med Res 2002;41(4):159-61.

16- Kennedy A, Gettys TW, Watson P, Wallace P, Ganaway E, Pan Q, et al. The metabolic significance of leptin in humans: gender-based differences in relationship to adiposity, insulin sensitivity, and energy expenditure. J Clin Endocrinol Metab 1997;82:1293-300.

17- Hassink SG, de Lancey E, Sheslow DV, Smith-Kirwin SM, O'Connor DM, Considine RV, et al. Placental leptin: an important new growth factor in intrauterine and neonatal development? Pediatrics 1997 Jul;100(1):1-7.

18- Butte NF. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. Am J Clin Nutr 2000;71:1256-61.

Table 1:-The Mean $\pm$ SD of all parameter in non diabetic pregnant women

Tests	1 st trimester	2 nd trimester	3 rd trimester	All pregnant Period
Leptin ng/ml	13.6 $\pm$ 4.69	24.5 $\pm$ 4.79	36.9 $\pm$ 6.41	25.0 $\pm$ 11.0
BMI kg/m ²	21.72 $\pm$ 4.36	24.78 $\pm$ 2.88	26.68 $\pm$ 3.41	24.39 $\pm$ 4.05
Glucose mg/dl	90.9 $\pm$ 13.64	86.1 $\pm$ 17.05	83.9 $\pm$ 20.2	87.0 $\pm$ 16.9
Cholesterol mg/dl	166.2 $\pm$ 19.4	182.8 $\pm$ 19.25	215.0 $\pm$ 25.62	188.0 $\pm$ 29.3
Triglyceride mg/dl	133.1 $\pm$ 39.52	154.7 $\pm$ 40.76	174.3 $\pm$ 36.37	154.0 $\pm$ 41.3
HDL mg/dl	45.82 $\pm$ 4.44	42.85 $\pm$ 4.15	41.25 $\pm$ 5.22	43.31 $\pm$ 4.87
VLDL mg/dl	26.62 $\pm$ 7.9	30.94 $\pm$ 8.15	34.86 $\pm$ 7.27	30.81 $\pm$ 8.26
LDL mg/dl	93.76 $\pm$ 19.11	109.01 $\pm$ 19.17	138.89 $\pm$ 30.07	113.9 $\pm$ 29.5

Table 2:-The Mean $\pm$ SD of all parameter in diabetic pregnant women

Tests	1 st trimester	2 nd trimester	3 rd trimester	All pregnant Period
Leptin ng/ml	17.9 $\pm$ 4.93	36.4 $\pm$ 7.7	46.8 $\pm$ 10.49	33.7 $\pm$ 14.4
BMI kg/m ²	22.52 $\pm$ 3.85	24.88 $\pm$ 3.07	26.34 $\pm$ 2.82	24.58 $\pm$ 3.55
Glucose mg/dl	109.5 $\pm$ 13.98	135.8 $\pm$ 14.89	169.2 $\pm$ 20.59	138.2 $\pm$ 29.6
Cholesterol mg/dl	184.9 $\pm$ 15.53	209.2 $\pm$ 22.65	217.8 $\pm$ 30.0	204.0 $\pm$ 26.9
Triglyceride mg/dl	134.7 $\pm$ 42.43	173.0 $\pm$ 38.6	195.0 $\pm$ 38.94	167.6 $\pm$ 46.2
HDL mg/dl	44.36 $\pm$ 4.07	40.0 $\pm$ 5.31	40.82 $\pm$ 4.85	41.73 $\pm$ 4.99
VLDL mg/dl	26.94 $\pm$ 8.48	34.6 $\pm$ 7.72	39.0 $\pm$ 7.78	33.51 $\pm$ 9.24
LDL mg/dl	113.6 $\pm$ 10.26	134.6 $\pm$ 21.63	137.98 $\pm$ 34.39	128.7 $\pm$ 25.8

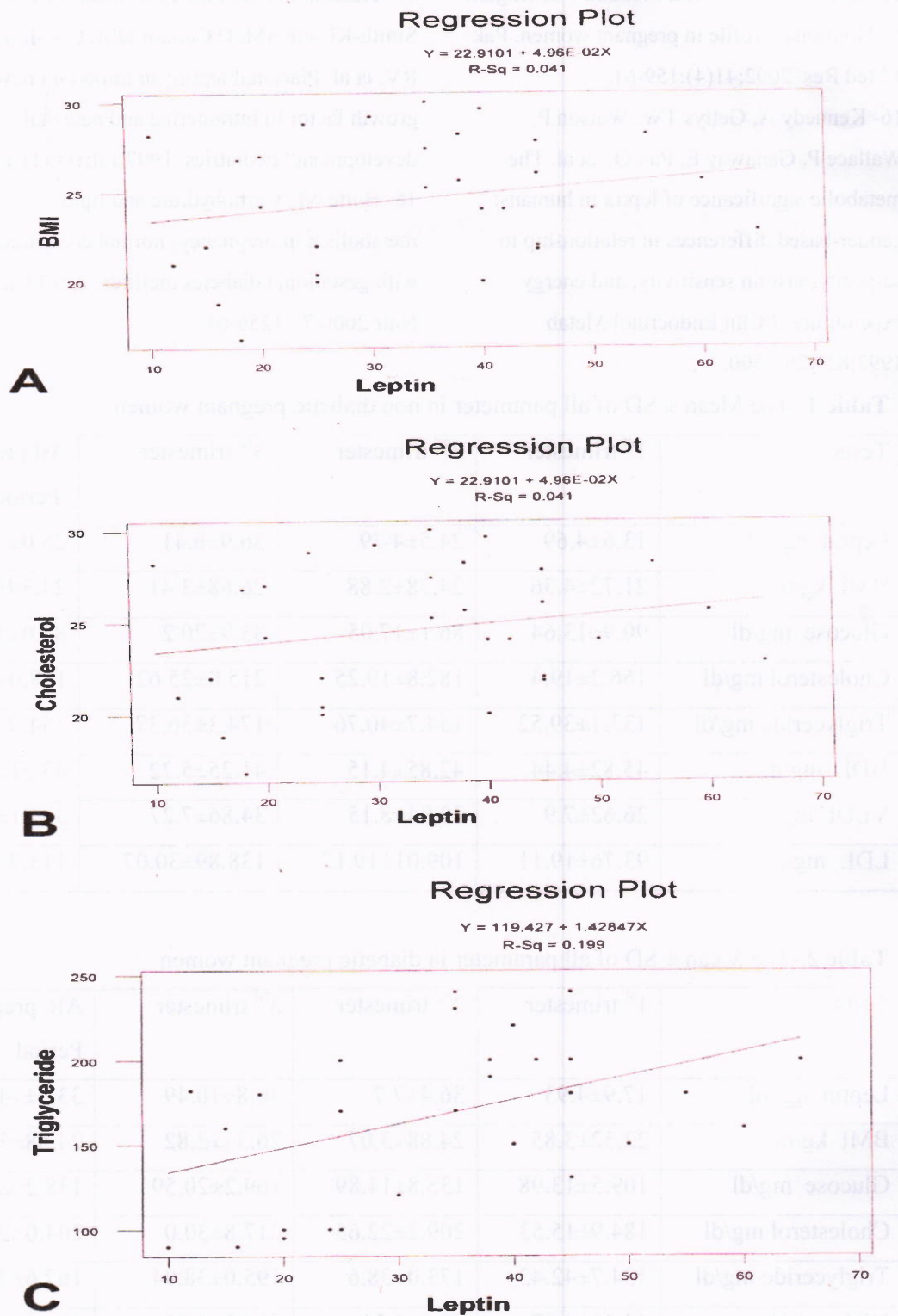


Fig 1:- Regression plot of correlation between leptin with (A):- BMI (B):-cholesterol and (C):- triglyceride in diabetic pregnant women.