

Comparison of Serum Insulin, Insulin-Like Growth-Factor-1 Concentrations and Insulin Resistance Indices in Severe Preeclamptic and Healthy Pregnant Patients

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Abstract

Objective: To compare the serum concentrations of insulin, insulin-like growth factor-1 (IGF-1) and insulin resistance indices which are fasting glucose/insulin ratio and Homeostatic model assessment-insulin resistance index (HOMA-IR) in women with severe pre-eclampsia and healthy control subjects.

Methods: In this prospective study, we investigated 20 severe pre-eclamptic, and 20 healthy pregnant women in the third trimester. Serum levels of insulin, fasting glucose and IGF-1 were measured; fasting glucose/insulin ratios and HOMA-IR indices were calculated. Serum uric acid, SGOT, SGPT, urea, creatinine, total protein, albumin, LDH were also investigated. Mann-Whitney U test was used to test the level of significance between the mean/median values of the study parameters. Spearman correlation coefficient was used for bivariate correlation analysis. p (0.05) was taken as the level of statistical significance.

Results: In patients with severe pre-eclampsia, serum levels of IGF-1 were lower than the control group ($50 \pm 103 \mu\text{gr/l}$ vs. $145 \pm 102 \mu\text{gr/l}$, $p=0.005$). There was no statistically significant difference between the fasting insulin levels, glucose/insulin ratios and HOMA-IR levels; respectively ($p=0.275$, $p=0.402$, $p=0.317$). A statistically significant correlation was found between IGF-1 and HOMA-IR levels ($r=0.406$, $p=0.009$).

Conclusion: Serum concentrations of IGF-1 was found to be lower in severe pre-eclamptic women than the healthy pregnant women but there was no difference between the groups, in terms of insulin resistance. Despite the small number of the study sample, low levels of IGF-1 detected in the pre-eclamptic patients may suggest an effective impact of implantation in the pathogenesis of disease.

Keywords: Preeclampsia, IGF-1, insulin, homeostatic model assessment (HOMA)-IR index.

Ağır preeklamptik ve sağlıklı gebelerde insulin, insulin benzeri büyüme faktörü-1 düzeyleri ve insulin direnç indekslerinin karşılaştırılması

Amaç: Ağır preeklamptik ve sağlıklı gebelerde serum insulin benzeri büyüme-faktörü (1) (IGF-1), insulin değerleri ve insulin direnç indeksleri olan açlık kan şekeri/açlık insulin oranı ve Homeostatik Model Assesment (HOMA) indekslerini karşılaştırmak.

Yöntem: Gerçekleştirilen bu prospektif çalışmada, 3.trimesterde 20 sağlıklı ve 20 ağır preeklamptik gebe araştırıldı. Açlık kan şekeri (AKŞ), İnsülin, AKŞ/insülin oranı, IGF-1, HOMA-insulin direnci (HOMA-IR) ürik Asit, SGOT, SGPT, üre, kreatinin, total protein, albumin, LDH çalışılan parametrelerdi. Çalışılan parametrelerin ortalama/ortanca değerlerinin karşılaştırılmasında, gruplar arasındaki farkın anlamlılığı Mann-Whitney U test ile değerlendirildi. Parametreler arasında yapılan korelasyon analizinde, Spearman korelasyon katsayısı kullanıldı. İstatistiksel anlamlılık düzeyi (p) 0.05 olarak kabul edildi.

Bulgular: Her iki grup arasında plazma IGF-1 düzeyleri karşılaştırıldığında ağır preeklampsi grubunda plazma seviyeleri daha düşük bulunmuştur (IGF-1 çalışma grubu : $50 \pm 103 \mu\text{gr/l}$, IGF-1 kontrol grubu : $145 \pm 102 \mu\text{gr/l}$, $p=0.005$). Plazma insülin düzeyleri ve AKŞ/insulin oranları karşılaştırıldığında ise anlamlı bir fark saptanmamıştır ($p=0.275$, $p=0.402$). Benzer olarak, HOMA-IR düzeyleri karşılaştırıldığında her iki grup arasında istatistiksel olarak anlamlı bir fark tespit edilmemiştir ($p=0.317$). IGF-1 ve HOMA-IR indeksi arasında korelasyon olup olmadığı, Spearman korelasyon katsayısı ile araştırıldığında ise anlamlı ancak orta kuvvette korelasyon olduğu ortaya konmuştur ($r=0.406$, $p=0.009$).

Sonuç: Ağır preeklamptik gebelerin serum IGF-1 düzeylerinin, sağlıklı gebelere göre daha düşük olduğu ortaya konmuştur. Buna karşın, preeklamptik gebelerde insulin direncine rastlanmamıştır. Her ne kadar olgu sayımız az olsa da, implantasyonda önemli bir rolü olan IGF-1'nin preeklamptik hastalarda literatürle uyumlu olarak düşük seviyelerde bulunması, bu hastalığın etyopatogenezinde bulunan implantasyon başarısızlığının bir kanıtı olabilir.

Anahtar Sözcükler: Preeklampsi, IGF-1, insulin, homeostatik model assessment (HOMA)-insulin direnç indeksi.

Introduction

Preeclampsia is a syndrome characterized by maternal hypertension, proteinuria, edema and insufficient placenta invasion. It is thought that it has an important role for implantation by limiting trophoblast invasion of insulin-like growth factor binding protein-1 (IGFBP-1) which is synthesized by endometrial stroma in maternal deciduas.^{1,2} Also in several sectional works, it is reported that IGFBP-1 levels increased and insulin-like growth factor-1 (IGF-1) levels decreased in preeclampsia and intrauterine growth restriction (IUGR), maternal circulation at 2nd and 3rd trimesters of gestation.³⁻⁵ Thus, it is thought that IGFBP-1 slows down fetal growth by limiting the activity of IGF-1 and decreases trophoblast invasion.^{6,7}

On the other hand, it is known that insulin resistance occurs in preeclampsia. But it could not being explained how and when insulin resistance occurs. Insulin is major negative regulator of IGFBP-1 in healthy pregnancies and except pregnancies. It is seen that the relation between insulin and IGFBP-1 becomes reverse in preeclampsia.⁸ It is observed that insulin levels of cases growing preeclampsia show more increase at third trimester than cases not growing preeclampsia.⁹ Moreover, it is stated that some metabolic abnormalities exist in insulin resistance seen at gestational hypertension and/or preeclampsia cases.^{10,11} However, there are many publications in recent years stating that insulin resistance has a role in etiology of gestational hypertension, not in preeclampsia.^{12,13}

In this work, we compared preeclamptic pregnant with healthy pregnant and evaluated HOMA-IR index, FBG (high fasting blood glucose) / Insulin rate, Insulin and IGF-1 levels and determined the relationship between these values.

Methods

20 pregnant that had heavy preeclampsia and eclampsia diagnoses at third trimester as a result of examinations who applied polyclinic in between 01.10.2003 – 01.03.2004 and 20 healthy pregnant who did not have any maternal illness at third trimester were included to this work (Table 1).. Detailed anamneses of all pregnant were taken and systematic examinations and gestational controls as ultrasonographic were done. Blood, bio-

chemical and full urine scrutinizes or protein amount in urine of 24 hours of patients were asked. Preeclampsia was defined as that astolic blood pressure was higher than 90 mmHg in every four or more hours or 110 mmHg in a single measurement and proteinuria was 0.3 g/day or 1+ by the dipstick method providing that no urinary infection. All pregnant in work group were diagnosed as “heavy preeclampsia” (20 cases) as to criteria within ACOG classification.¹⁴ Data of 2 cases which had eclampsia and 1 case which had HELLP syndrome were included into heavy preeclampsia group. All patients in work group were applied magnesiumsulfate (MgSO₄) treatment and all of them were applied Nifedipine treatment as an anti-hypertensive agent at least 1 time. Magnesiumsulfate treatment was applied as 1.5 gr intravenous continuation infusion per hour following 4.5 gr intravenous given in 20 minutes. Blood product was given by erythrocyte suspension to only 2 patients in work group. These medications were not applied to any patient in control group (Table 2).

High fasting blood glucose (FBG), insulin, IGF-1, uric acid, SGOT, SGPT, urea, creatinin, total protein, albumin, lactate dehydrogenase (LDH) were parameters which were worked on. Insulin resistance was measured indirectly as FBG/Insulin rate and HOMA-IR (Homeostatic Model Assessment Insulin Resistance Index) = [FBG (mmol/l) x high fasting insulin (mIU/l)] ÷ 22.5. Blood samples of working and control groups were taken from antecubital venous at a hungry state in post partum first day in between 07:00 – 09:00 in the morning. Blood samples were studied immediately for all parameters except IGF-1 just after serum was separated by centrifuge. All bloods collected for IGF-1 were frosted in -20°C after being centrifuged at 450 rpm for 5 minutes. After collecting all blood samples for IGF-1, 40 blood samples were dissolved at 18-25°C for 10 minutes and they were worked on by IGF-1 RADIOIMMUNASSAY kit (IGF-1 ELISA, HAMBURG, GERMANY).

Plasma glucose was determined by glucose oxidase method. Plasma insulin determination was measured by radioimmunoassay (RIA) method.

Statistical analyzes were performed by using program of SPSS (Statistical Package for Social Sciences) 10.0 for Windows.

For comparing average/middle values of working parameters, significance of difference between groups was evaluated by Mann-Whitney U test. Spearman correlation coefficient was used for correlation analyze between parameters. Statistical significance level (p) was accepted as 0.005.

Results

Demographic data belonging to 40 cases which are formed of twenty healthy pregnant and twenty heavy preeclamptic pregnant are shown in Table 1. While there was statistically no difference between two groups in terms of age, gravida, parity; a significant difference was found in terms of gestational week (p= 0.001). No significant difference was found when groups were compared as to birth types (Table 3).

Table 1. Demographic qualities of cases..

	Working group (n=20)	Control group (n=20)	P
Age (year)	28.21 7.2	26.55 5.22	0.542
Gravida	2.3 2.1	2.2 1.3	0.11
Parity	1.2 2.0	0.7 0.7	0.07
Gestational week	35.390 3.35	38.475 1.73	0.001

Table 2. Medications applied to groups.

	Working group (n=20)	Control group (n=20)	P
MgSO4	20 (%100)	0 (%0)	< 0.001
Nifedipine	20 (%100)	0 (%0)	< 0.001
Blood and blood products	2 (%10)	0	< 0.001

Table 3. Data of birth type of groups.

	Working group (n=20)	Control group (n=20)
Birth by spontaneous vaginal way	8 (%40)	12 (%60)
Birth by vaginal way by oxytocin induction	9 (%45)	6 (%30)
Cesarean	3 (%15)	2 (%10)

* Multi-eyed ki-square test, X2-1.6, p=0.049

Averages of values of plasma hemoglobin, hematocrit, thrombosis, FBG, urea, creatinin, uric acid, AST, ALT, LDH, total bilirubin, total protein, albumin and comparison between two groups are

shown in Table 4. Significant difference was observed between levels of ALT, AST, LDH of groups but no significant difference was found between hematological values. Comparison of difference between values of plasma IGF-1 and insulin belonging to 40 cases which are formed of twenty healthy pregnant and twenty heavy preeclamptic pregnant are shown in Table 5.

Table 4. Demographic qualities of cases.

	Working group (n=20)		Control group (n=20)		P
Hb (g/dl)	10.57	1.80	10.94	1.2	0.498
Htc (%)	32.05	4.29	33.34	3.28	0.358
plt	172650	90323	204850	50032	0.291
FBG (mg/dl)	90.8	24.4	93.95	24.75	0.626
Urea (mg/dl)	27.65	14.61	15.21	5.88	0.001
Creatinin (mg/dl)	0.785	0.236	0.742	0.851	0.291
Uric acid (mg/dl)	5.91	1.37	5.18	1.05	0.121
AST (U/l)	47.34	30.75	24.95	20.02	0.017
ALT (U/l)	30	25.95	13.40	5.63	0.003
LDH (U/l)	890.45	443.12	496	99.37	0.001
T. Bilirubin (mg/dl)	0.46	0.314	0.487	0.222	0.465
T. Protein (g/dl)	6.35	0.85	6.13	0.571	0.176
Albumin (g/dl)	3.3	0.50	3.35	0.42	0.935

Table 5. Insulin, IGF-1 levels, FBG/insulin rates and HOMA-IR indexes of cases.

	Working group (n=20)	Control group (n=20)	P
IGF-1 (gr/l)	50±103	145±102	0.005
Insulin (IU/ml)	14.40±7.76	16.050±21.91	0.275
FBG/Insulin	6.15±6.93	6.29±4.21	0.402
HOMA-IR	3.16±2.35	3.72±7.79	0.317

When comparing plasma IGF-1 levels of two groups, it was found that plasma levels were lower in high preeclampsia group and the difference is significant (p=0.005).

No significant difference was found when plasma insulin levels of work and control group were compared (p=0.275). No significant difference was found when comparing FBG/insulin rates and HOMA-IR indexes which were performed in order to determine insulin resistance (p=0.402; p=0.317).

Correlation between IGF-1 and HOMA-IR indexes was researched by Spearman correlation and a correlation was found which was positive, significant but having middle strength (rall work group: 0.406, p=0.009, n=40 and rpreeclampsia group: 0.668, p=0.001, n=20).

Discussion

Preeclampsia/eclampsia which was first defined more than 100 years continues to be one of the major reasons of maternal and fetal mortality and morbidity. Though the intensive researches, our information about pathophysiology and etiology are still limited.

In recent years, it is shown that IGF-1 has a role as facilitating molecule for implantation of endometrium embryo during IVF (in vitro fertilization).¹⁵ A good and entirely formed implantation is required for a healthy pregnancy. It is known that a defect during implantation causes gestational complications such as spontaneous abortus and preeclampsia. Thus, IGF-1 is a good determinant for a healthy pregnancy. It is reported that preeclampsia has a relationship with levels of low estrogen and IGF-1 and increased progesterone, androgen, HCG, IGFBP-1, cortisol and insulin.¹⁶ Also, Giudice et al found in their work that heavy preeclampsia patients had increased IGFBP-1 expression in syncytiotrophoblast, cytotrophoblast and decidual cells. It was also reported that this binding protein may also has a role in placentation disorder in preeclampsia pathogenesis.⁷ It was thought that low IGF-1 levels and increased IGFBP-1 levels may cause restricted placental and fetal growth. On the other hand, Halhali et al evaluated IGF-1 levels of 40 pregnant which were normotensive during their pregnancies and 10 women having preeclampsia longitudinally at 20.7, 27.6 and 35.5 gestational week in their work.¹⁷ It was showed in this work that physiological increase in IGF-1 levels decreases in preeclamptic patients. It was also showed in this work that increase in IGF-1 levels of preeclamptic patients was not 30% as normotensive women but 5% and it was decided that changes of IGF-1 synthesis in early period might be effective in etiopathogenesis of preeclampsia.

When we compared serum median IGF-1 levels of preeclamptic pregnant with normal healthy control group, we found lower levels as statistically significant level. But our work and control

groups statistically showed significantly difference in terms of gestational week. Difference between groups in terms of gestational week reminds us whether difference between serum IGF-1 levels occurs due to a change related with gestational week or not. Difference between serum IGF-1 levels as to gestational week is showed in limited numbers of researches. Insulin-like growth factor-1 may be regulated by growth hormone (GH). But due to the fact that growth hormone secretion is inhibited from maternal hypophysis during gestation, IGF-1 production is regulated by placental growth hormone. Levels of insulin-like growth factor-1 do not change up to the third trimester but show increase beginning from third trimester in normal pregnancies.¹⁸ However, it is thought that it causes low IGF-1 levels by limiting placental growth hormone in heavy preeclamptic women in which placental invasion was limited.⁷

Caufriez et al researched change in IGF-1 levels occurring in normal gestation period and postpartum period in their work.¹⁹ It was seen that IGF-1 levels did not change up to 29th-30th gestational weeks and they stayed as in levels before pregnancy. It was observed that IGF-1 levels began to increase in 29th-30th gestational weeks and it reached its maximum value at 35th-36th gestational weeks. It was proved that average IGF-1 level was still high in 39th - 40th gestational weeks and did not statistically show difference to value in 35th-36th gestational weeks.¹⁹ Even this work was performed 17 years ago, it is an important work in terms of researching IGF-1 changes during gestation. In our work, average gestational week of work group was found as 35.3 and average gestational week of control group was found as 38.4. Consequently, when data of physiological change of serum IGF-1 levels occurred in gestation are taken into consideration, it could be thought that both groups in our work are suitable group in terms of gestational week for comparison of IGF-1 levels. Consequently, the question that the difference between groups is occurred whether due to difference between gestational weeks or due to preeclampsia will be the subject of next studies.

Another subject in our work that should be emphasized is why serum IGF-1 levels are worked on postpartum first day. It is logical to work on these levels before pregnancy is terminated; however, both insulin-like growth factor-1 and insulin and FBG are parameters when the patient is hungry. Heavy preeclamptic patients are individuals who urgently applied to our hospital and who were interfered. All these patients came to our hospital in paroxysm states. So, these parameters are decided to be worked on postpartum first day, which is the most convenient condition for hospital, in terms of reflecting gestation situation and performing them in a hungry state. Also, change pattern in serum IGF-1 levels following birth are put forth by Caufriez et al.¹⁹ It was proved that IGF-1 levels began to decrease after birth and statistically reached a significant level on third day. By considering the information of literature, it is thought that IGF-1 levels being worked on postpartum first day still reflect changes occurring in gestation even on the first day of puerperium.

Another difference between work and control groups is medications being applied. All patients in work group were applied magnesium sulfate (MgSO₄) treatment and all of them were applied Nifedipine treatment as an antihypertensive agent at least 1 time. These medications were not applied to any patient in control group. MgSO₄ from these medications does not have any maternal metabolic effect such as hyperglycemia or hypoglycemia. A temporary and light effect of Nifedipine is mentioned in some publications.²⁰ However, there is no data that these medications whether affect IGF-1 values or not. Also, another result which was thought that it occurred from difference of medications applied to groups is that there is no difference in terms of hemoglobin, hematocrit, thrombosis, and total protein and albumin parameters. Reason of this situation may be fluid taking together with magnesium by preeclampsia patients up to birth and blood sample taking after application to hospital. But, the effect of applied fluid treatment on serum IGF-1

levels is not known. Thus, this is one of the limiting factors for determination of results in our work.

Moreover, we researched the existence of insulin resistance in preeclamptic pregnant by comparing high fasting blood glucose values, FBG/insulin rates and HOMA-IR in preeclamptic and healthy pregnant due to the fact that it was reported that insulin resist grows at preeclampsia. It was also reported that some metabolic abnormalities seen in insulin resistance in gestational hypertension and/or preeclampsia cases exist.^{10,11} But in recent years, some publications reported that insulin resistance has a role only in gestational hypertension etiology not in preeclampsia.^{12,13} In 2002, Bartha et al proved that insulin resistance increases in gestational hypertension and it does not exist in preeclampsia.²¹ In addition, they found that insulin resistance did not show statistically a significant correlation with IGF-1. There is a relation between IGF-1 and insulin sensitivity. It is known that IGF-1 cures the tissue effect of insulin. It was reported that IGF-1 in the circulation of essential hypertension is an important factor for regulation of insulin sensitivity.²² We observed that FBG level was not different in preeclamptic pregnant when comparing with normal healthy pregnant. We could not found statistically any significant difference when comparing FBG/Insulin rates of groups. Thus, we found that there was no increased insulin resistance in heavy preeclamptic patients as to control group.

We could not found any significant difference between groups when we compared median values of HOMA-IR indexes which is accepted as more standard measurement technique in recent year for determining peripheral insulin resistance. Even we could not found statistically any significant difference between high fasting blood glucose, FBG/insulin and HOMA-IR indexes of two groups; we found statistically a significant correlation between IGF-1 and HOMA-IR indexes of all groups. Obtained correlation coefficients are positive and show a relation having middle power. Correlation in heavy preeclampsia group is more

powerful and is statistically significant. Thus, it is thought that there is a significant relation between serum IGF-1 levels and peripheral insulin resistance.

Consequently, it is put forth that that serum IGF-1 levels of heavy preeclamptic pregnant are lower than healthy pregnant. Though, no increased insulin resistance was found in preeclamptic pregnant. Having in preeclamptic patients lower levels of IGF-1 which has an important role for implantation may be deemed as a proof of implantation failure in etiopathogenesis of this illness.

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