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The Role of Pre-Pregnancy Body Mass Index (BMI) in Predicting Maternal Serum Leptin

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Abstract

Background: *The key role of leptin is regulation of appetite and body lipid and pregnancy is a condition associated with overeating, reduction in heating and adaptation of lipid cells, culminating in increased body fat mass. So, this study was conducted to examine the relationship between changes in pre-pregnancy BMI and leptin.*

Methods: *This Longitudinal study was conducted on 45 women in the first trimester of pregnancy using a longitudinal approach and convenience sampling method in Tehran city in 2015. The mothers in terms of pre-pregnancy BMI were divided into two groups: group A (n=22 with normal BMI) and group B (n=23 with high BMI), with maternal serum leptin being taken in 6-12 weeks and 15-20 weeks of pregnancy and measured by enzyme-linked immunosorbent assay (ELISA). The statistical data were analyzed by SPSS V.21 using Kolmogorov Smirnov, independent t-test, two-sample Chi square, Mann-Whitney, Regression, Pearson and Landa tests with P.V<0.05.*

Results: *The mean age of mothers in the present study was 27.47±5.55 years with a minimum age of 19 and a maximum age of 37 years. The mean plasma leptin of the first and second trimesters of pregnancy was significantly higher in the high BMI group than in the normal group. The correlation showed that the first trimester leptin and changes in leptin levels of pregnancy with pre-pregnancy BMI were significantly higher in the normal group (P=0.04 and P=0.003).*

Conclusions: *BMI before and during pregnancy can be a predictor of maternal serum leptin in pregnancy weight gain.*

Keywords: Leptin, Pregnancy, BMI.
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Introduction

The mother's weight as an important health index is closely associated with the growth, development, and survival of newborns in the future.[1] One of the most common methods for measuring obesity is the use of body mass index (BMI) which is the division of the body weight in kilograms by squared height in meters.[2] Infertility and menstrual disorders are often associated with obesity; the baseline levels of gonadotropins and LH responses to gonadotropin secreting hormone (GnRH) are related to weight and base metabolism, where weight loss reduces plasma leptin, androgens and as a result, LH response and ovulation in obese infertile women.[3] Pregnancy is a condition associated with overeating, reduction in heating and adaptation of lipid cells resulting in increased body fat mass. At the early stages of pregnancy, the production of fatty acids from glucose is increased and the pathways of lipogenesis prevail, which seems to be driving hormones such as insulin and leptin. On the other hand, at the late stages of pregnancy, molecular pathways of lipolysis are more active.[4,5] Adipokine changes in the maternal circulation in a normal pregnancy through changing the maternal weight gain can affect the pregnancy complications such as gestational diabetes,[6-9] preeclampsia,[10-12] other blood pressure disorders,[13,14] late fetal death, early delivery, childhood obesity,[15-18] and type II diabetes in adulthood. Adipokine produced from adipose tissue, such as leptin, adiponectin and etc. will play an important role in regulating insulin sensitivity, fat metabolism, energy stability, and inflammation.[19,20] Leptin, a long chained spiral protein, belongs to the supernal family of cytokines in group 1 of ob (obese) gene located on chromosomes 6 and 7, structurally similar to the growth hormone, prolactin, granulocyte colony-stimulating factor, oncostatin M 3, and some interleukins 4.[21,22] Adipokine has a range of biological activities at two central and peripheral levels including body weight regulation,[23] energy balance with preventing food intake, simulating energy intake,[24] satiety,[25] affecting the glucose and fatty acid metabolism,[26-28] affecting insulin sensitivity, producing glucocorticoids, osteogenesis, blood pressure, embryo development, especially in the maturity of pulmonary type II cells for the production of surfactants, onset of maturity,[29] fertility, pregnancy, and lactation[30] in different species.[22,31-34] Leptin receptor (ob-R) encoded by the diabetes gene (db)[22,32] has a long isoform Leptin receptor long (LERRL) in the hypothalamus, short isoform Leptin receptor short (LERRS) in organs and tissues[35] and soluble Leptin receptor isoform (SolLERR) only in humans.[31] Probably, soluble Leptin receptor isoforms in pregnancy are responsible for placental transfer of leptin for fetal development.[36] In this regard, in pregnancy, despite the increase in intake of food, and a reduction in insulin sensitivity and hyperlipidemia, contrary to the usual role of leptin, in order to adapt the mother to prolactin, lactose and steroid hormones, this physiological resistance is evident in leptin.[33,37,38]

Leptin correlates directly with the total body fat mass such that it grows twice in the first trimester of pregnancy.[9] According to the results of Considine and Caro study, serum leptin showed a high correlation with lipid mass, and with other lipid indicators such as body lipid percentage and body mass index.[39] Also, the results of Mohammadzadeh et al. study revealed a direct and significant correlation between serum leptin levels and pelvic, and leptin, and BMI.[40] Also, in a study by Samolis et al. (2010) in Greece entitled "the relationship between serum leptin and BMI of pregnant" pre-pregnancy BMI was associated with leptin levels in both groups.[41]

Since serum leptin theory has been suggested for weight gain during pregnancy in some studies and leptin studies on pregnancy in Iran have generally been conducted under pathophysiological conditions such as gestational diabetes and preeclampsia, therefore, we decided to take a step in identifying predictive factors to prevent the occurrence of overweight complications during pregnancy by studying the relationship between BMI at the beginning of pregnancy and leptin.

Materials and Methods

This longitudinal study was conducted on two groups of normal BMI (BMI=19/8-26 kg/m2) and overweight mothers (BMI=25-29/9kg/m2) in the first trimester who were referred for prenatal care in Tehran in 2015. The research site included Prenatal Clinic of Mahdieh Hospital, Public Health Centers Covered by Shahid Beheshti University of Medical Sciences in northern, eastern and southern parts of Tehran such as Shobeir, Pourhedayat, Behesht Al-Nabi, Nader, Kadous, Sahib Al Zaman, Imam Hasan Mojtaba, Azgul, ImamzadehQasem and Chizar. Normal and overweight mothers were taken separately through convenient sampling. Serum leptin of the mother's blood samples was measured at Endocrine and Metabolism Center Laboratory of Shahid Beheshti University of Medical Sciences. The study inclusion criteria included: 1) age: 18-40 years old, 2) singleton pregnancy, 3) lack of systemic diseases such as lupus, diabetes mellitus and thyroid, heart disease, kidney disease, coagulation, epilepsy, asthma, hepatitis and high blood pressure, 4) the absence of psychological problems, death of loved ones and history of using psychiatric drugs, 5) no smoking, drug and alcohol abuse, 6) the first trimester of pregnancy, and 7) being Iranian. The study exclusion criteria included: 1) the presence of any complication of pregnancy such as preeclampsia, moles, ectopic pregnancy, diabetes, placenta previa and placental abruption, 2) use of any drugs other than pregnancy supplements and 3) special diets such as vegetarianism and proteinuria. The present study was extracted from a Master's thesis which was financially supported by Tarbiat Modarres University of Medical Sciences under the ethical code of 5059/52d.

The sample size was estimated according to Kim's survey (2008) in South Korea and Castecano Filho (2013) in Brazil on the measurement of leptin in pregnancy[42,43] and calculated using the formula for measuring the sample size with 95% confidence level and test power 0.8:

S1= Standard deviation of leptin levels in pregnant women with normal BMI

S2= Standard deviation of leptin levels in pregnant women with abnormal BMI

μ1= Mean leptin level in pregnant women with normal BMI

μ2= Mean leptin level in pregnant women with abnormal BMI

Since the sample size at the end of the period is important in a cohort study, the sample size was obtained from the following formula and estimated as 45 cases taking into account the phenomenon of loss to follow up rate (% 59):

According to previous studies, we knew that the probability of loss to follow up was very considerable and as such, the study sampling was conducted on 110 pregnant women who were eligible to enter the study. During the sampling, the mothers were divided into two groups: "the mothers with pre-natal normal body mass index" (group A) and "the mothers with high pre-natal body mass index (overweight and obese)" (group B). Due to a large drop rate (two cases of blood sampling, immigration or traveling at blood sampling, abortion and unwillingness to continue cooperation) in the samples during the present longitudinal study, finally the remaining 45 mothers of the initial number of mothers were studied, with 22 mothers were being the normal group and 23 in the abnormal group. The gestational age was calculated using the first day of the last menstruation and if the date was uncertain, the date of the first ultrasound in the first trimester of pregnancy was used.

We explained the process and ensured the mothers about having free-cost testing, then after checking entering criteria and gaining their written consent, blood sample was taken. The mothers were also assured of their personal information confidentiality and the researcher's personal contact number was given to them by name and position for any midwifery telephone counseling. Then, through a standard questionnaire form of the prenatal care of the Ministry of Health, demographic characteristics, pregnancy history and medical history of the mothers were taken with a direct interview with them and recorded without mentioning the mother's name as encoded information. The maternal weight was recorded by the center unit's mechanical scale, while the blood pressure and embryo's heart rate were recorded by a digital barometer and calibrating Sonicaid by a person respectively. More specialized maternal examinations, including thyroid and dental health were taken by a specialist of the center and registered in the file. BMI was also calculated through dividing the weight (kg) by squared height (m^2). The pregnant women's nutrition was registered using the recommended dietary protocol of the ministry of health and training on proper nutrition for prenatal care was planned according to the usual method. In each prenatal visit, weight, height, BMI and other criteria for prenatal care were reviewed such as blood pressure, fetal heart sounds and etc. to confirm maternal health. Pregnancy food pyramid groups were trained according to the ministry of health protocol and According to mothers' reports, those who did not follow the protocol were excluded and only mothers

with normal blood pressure were assessed. At the end of each visit, the next visit was reminded according to the gestational age and, if necessary, Tel follow-up was made to communicate more in depth for working with mothers during the study.

The mother's venous sample was taken in sitting position, in two first and second trimesters, preferably left hand antecubital vein and rarely from back hand vein and midwifery, in order to measure their serum leptin in 6- 12 weeks of

Gestation between 9 and 11 AM. The samples were sent to the laboratory within 48 hours. In the center laboratory, the samples were centrifuged with 3000 rpm for 10 minutes and plasma was separated, with the serum frozen at low temperatures (20 to 70 °C) until the experiment. After completing the required sample size in the study, the samples were simultaneously measured by ELISA method by a leptin specific kit.

In the present study, a special human leptin kit of Mercodia Uppsala (Intraassay CV%: 7.1 with sensitivity of 0.024 ng / ml) was purchased from P Teb Co to be employed through ELISA method. In accordance with the kit's instructions, the samples were diluted 11 times and then the results were multiplied by 11. The raw data were collected by SPSS V.21 and after encoding, they were analyzed by Kolmogorov-Smirnov, Regression, Fisher exact test, Independent t-test, Chi-square, Pearson and Mann-Whitney and Landa statistics (for RA correlation coefficients' comparison with RB obtained from each group at a significance level of P<0.05) tests.

Results

The mean age of mothers (n=45) in the present study was 27.47±5.55 years with a minimum age of 19 and a maximum age of 37 years (24.5±5.718 in group A and 29±5.198 in group B, P=0.603). A total of 54.5% of the studied mothers were between 21 and 30 years of age. Also, 55.5% of mothers had diploma and higher education, while 53.3% of spouses had diploma and higher education. Further, 95.6% of the mothers were housewives, which included all mothers in group A and 91.3% of the mothers in group B. Most spouses (82.2%) were self-employed (86.4% in group A and 78.3% in group B). The monthly income of 6.7% of the subjects was poor, 80% was average and 13.3% was satisfactory. Also, 31.1% of the subjects' family had 2 members, 60% had three members and 8.9% had four or more members. Further, 55.6% of the mothers had normal delivery and 44.4% had cesarean delivery. Finally, 33.3% of the subjects were nulligravida and 66.7% of them were multigravida with 17.8% of the mothers having also a history of abortion.

The homogeneity of the two groups was confirmed by statistical tests in terms of background and demographic variables such as age, education and occupation, number of households, gender, fertility status, income and type of delivery (table 1).

The normal distribution of variables in each group was verified by Kolmogorov-Smirnov statistical test. If the distribution was normal, for quantitative variables, independent t-test and for qualitative data 2-sample Chi-square test are used. For abnormal distribution, Mann-Whitney test was used to confirm the homogeneity of the above-mentioned variables.

Table 1. Distribution of demographic and clinical characteristics of the samples

Variable		Normal BMI n(22)	High BMI n(23)	P.V
Education*				
– Elementary school		4 (44.4)	5(55.6)	
– High school		5(45.5)	6(54.5)	P=0.89
– Diploma and Higher education		13(52)	12(48)	
Job**				
– Employed		22(51.2)	21(48.8)	P=0.16
– Housewife		0(0)	2(100)	
Number of households**				
– 2 members		9(64.3)	5(35.7)	
– 3 members		11(40.7)	16(59.3)	P=0.36
– 4 and more members		2(50)	2(50)	
Month salary** (Iran's Rial)				
– Less than 500,0000		1(33.3)	2(66.7)	
– 600,0000-1,000,0000		16(44.4)	20(55.6)	P=0.18
– More than 1,000,0000		5(83.3)	1(16.7)	
Infant sex*				
– Boy		8(40)	12(60)	P=0.28
– Girl		14(56)	11(44)	
Delivery mode*				
– Normal		12(48)	13(52)	P=0.89
– Cesarean		10(50)	10(50)	
Fertility status**				
– Number of pregnancies	۱	8(53.3)	7(46.7)	P=0.54
	۲	8(40)	12(60)	
	≥ ۳	6(60)	4(40)	
– Number of deliveries	0	9(56.3)	7(43.8)	P=0.37
	1	9(31.9)	14(60.9)	
	2	4(66.7)	2(33.3)	
– Number of abortions	0	18(48.6)	19(51.4)	P=0.94
	≥ ۱	4(50)	4(50)	
– Number of living born	0	9(52.9)	8(47.1)	P=0.9
	1	11(45.8)	13(54.2)	
	2	2(50)	2(50)	

Chi-square* and fisher exact test**

Table 2. Plasma leptin level (ng/ml) during 1stand 2ndtrimester in both groups

Group	Group A	Group B	P.V
SerumLeptin (ng/ml)	mean±SD	mean±SD	
1st trimester Leptin	27.05±17.17	38.7±15.43	P=0.01
2nd trimester Leptin	43±17.22	25.05±17.7	P=0.01
Leptin changes	4.2±7.77	3.2±8.3	P=0.719

Independent t-test

The mean plasma leptin of the first and second trimester of pregnancy was significantly higher in group B than in group A. The lowest plasma leptin concentration in the first trimester was 5.8 ng / ml while its highest serum concentration was 76.1 ng / ml in the second trimester.

A positive correlation was observed between the first trimester leptin level and pre-pregnancy BMI in both groups, and this relationship was statistically significant. With an increase in pre-pregnancy BMI (kg/m²), leptin concentration in the control group was 5.53 ng/ml in the control group and 2.59 ng/ml in the case group. The correlation of leptin level in the first trimester with pre-pregnancy BMI in the control group was significantly higher than in the case group.

Table 3. The relationship between serum leptin levels and pre-pregnancy BMI

Serum Leptin (ng/ml)	pre-pregnancy BMI		Lambda test
	Pearson correlation		
	Group A	Group B	
	R (P.V)	R (P.V)	Lambda statistics (P.V)
1st trimester Leptin	0.79 (<0.001)	0.66 (0.001)	1.98 (0.04)
2nd trimester Leptin	0.63 (0.02)	0.68 (<0.001)	-0.63 (0.53)
Leptin changes	-0.30 (0.174)	0.08 (0.70)	-2.95 (<0.01)

A positive correlation was observed between the second trimester leptin level and pre-pregnancy BMI in both groups, and this relationship was statistically significant. With an increase in pre-pregnancy BMI (kg/m²), the second trimester leptin level in the control group was 4.52 ng/ml and 2.75 ng/ml in the case group. Lambda test indicated that the correlation between the second trimester leptin level and pre-pregnancy BMI was not significantly different between the two groups. No significant relationship was found between pre-pregnancy BMI and changes in leptin levels in each study group. However, the correlation between leptin changes and pre-pregnancy BMI in the control group was significantly higher than in the case group (tables 3).

Change analysis indicated that one unit increase in BMI before pregnancy in the normal group caused one unit decrease in changing the leptin level (2nd trimester leptin minus the 1st leptin trimester), while in the abnormal group changes in the leptin level caused by one unit increase in BMI was 0.15 increase (table 4). Regression analysis revealed that the BMI before pregnancy had no effect on 2nd trimester leptin (regression coefficient= 0.16, 95% CI= (-0.76, 1.08), P.V=0.72), but leptin in the 1st trimester was strongly associated with leptin levels in the 2nd trimester (regression coefficient= 0.94, 95% CI=0.72, 1.16), P.V<0.0001).

Discussion

The present study examined the relationship between changes in serum leptin levels and BMI. The importance of maternal BMI during pregnancy is associated with maternal-fetal outcomes and post-natal obesity and even childhood of neonates of overweight and obese mothers during pregnancy.

Leptin, as a hormone secreted from adipocytes, is secreted by placenta during pregnancy and in many studies, it was significantly correlated with maternal pre-pregnancy weight and BMI. However, these studies were conducted outside of Iran and to some extent reported contradictory results. Most studies in Iran have dealt with the relationship between leptin and obesity, diabetes, and preeclampsia of mothers; except for the present systematic review, no empirical study was found on maternal BMI and leptin levels in Iran.

The mean maternal weight at the first turn of serum leptin sampling was 67.25±11.98 kg and 1.33±1.79 kg in the first trimester.

In a study by Gashtasbi et al. in Lolagar and Mahdieh hospitals in Tehran, the mean weight gain of the mother was 13±4.5 kg. In the group of mothers with normal initial BMI, this was 13.5±4.1 kg, 13.5±4.1 kg in the overweight group and 10.8±5.3 kg in the obese group.[44]

In a study by Sharifirad et al. (2012) in Isfahan, the mean weight gain in pregnancy was 11.73 kg, 13.24±4.34 kg in the normal group, 12.76±5.13 kg in the overweight group and 10.22±7.51 kg in the obese group.[45] In a study by Kohdani et al. (2010), this mean was 10.1 kg in the case group and 13.9 kg in the control group.[46,47] In a study by Nasrabadi et al. in north and east of Tehran, the mean weight gain during pregnancy in the low weight group was 10.1±5.3 kg, 9.1±5.2 kg in the normal group and 9.9±6 kg and 9.6±6.3 kg in the overweight and obese group, respectively.[48]

The mean serum leptin level in the first trimester of the mothers of the present study (n=45) was 33.97±17.43 ng/ml.

In a study by Safdarian (2006) in Tehran, the serum leptin level in the beginning of pregnancy by ELISA method was 14.09±2.2 ng/ml. Also, Khosrobeigi et al. (2013) study in Lorestan on 30 healthy pregnant women and 30 women with diabetes reported a mean serum non-fasting serum leptin level during 24-28 weeks by ELISA method as 30.38±31.56 ng/ml. This study was one of the studies with the highest structural and study similarity, which reported plasma leptin plasma levels close to those of the present study.[49,50] In a study by Maqboli et al. (2006) in Tehran during 28-42 weeks for diabetes screening 527 healthy mothers' serum leptin by ELISA method, it was 20.35±15.15 ng/ml.[9] In a study by Dabiri (2011) in Zanjan with the aim of evaluating serum leptin of 60 preeclampsia pregnant women and normal in preterm delivery blocks, the mean level of leptin by ELISA method was 45.8±34.6 ng/ml.[14] In a study by Schubring et al. in the United States, non-fasting serum leptin of 57 mothers in 38-42 weeks, amniotic fluid and umbilical vein as well as artery of the infant during the delivery were measured by Radio-Immuno-Assay (RIA) method. The serum leptin (20±13.2 ng/ml) was significantly higher than amniotic fluid leptin (3.7±0.8 ng/ml) and artery (9.7±9.4) and vein (8.9±8.6) of the umbilical cord.[4] In a study by Heland et al. in the United States, serum leptin levels in pregnant women in 18 and 35 weeks and in their newborns were measured by RIA. They observed that that the serum leptin level was 15.5±9 in 18 weeks, 17.7±10.7 µg/l in 35 weeks, which also showed a positive correlation with pre-pregnancy BMI of mothers.[51] Elsewhere, in Lea's study in USA, the that leptin in the umbilical cord after overnight fasting before cesarean delivery was measured by ELISA method in 49 women in 35-41 weeks, with mean levels found in the normal group (1.75 ng/ml).[52] The study by Butte et al. in California was conducted to measure the serum leptin in pregnant and lactating women on 65 pregnant women in 36 weeks and 3 to 6 months after delivery and the mean serum leptin with 12-hour fasting by ELISA method was 29.8±17 ng/ml 36 weeks, 18±15.2 ng/ml 3 months and 18±15 ng/ml 6

months after delivery, with serum leptin being significantly correlated with pre-pregnancy weight.[3]

In a study by Mumtaz et al. (2008) in Pakistan on non-fasting serum leptin of 40 normal mothers and preeclampsia in the third trimester of pregnancy, the mean leptin of the normal group of the study with RIA method was 27.82±1.05 ng/ml.[10] A study by Stein et al. on 103 normal pregnant women in the United States reported leptin, for the first trimester as 19±1 and 28.6±1.1 µg/l for 28-week leptin, respectively.[53] In a study by Samolis (2010) in Greece, leptin of the first trimester (up to 13 weeks) on 37 pregnant women a mean level was 2.502 ng/ml.[41] In a study by Colcimea (2015) in Turkey on plasma non-fasting leptin of 30 normal pregnant women during 34-42 weeks by ELISA method, the mean serum leptin concentration was 3.1±3.1 ng/ml.[54] In a study by Saylik et al. (2009) in Turkey, again the serum leptin of mothers who were hospitalized for delivery after 6-8 hour fasting, using EASIA method in the normal group was 8.5±6.9 ng/ml.[55]

Many differences were observed in the results of pregnancy-related leptin concentration in studies and no single definite reason can be mentioned. Nevertheless, their examination in various fluids in the body, such as plasma, umbilical cord, cerebrospinal fluid and even follicular fluid, can be explained as reasons for the differences. For example, the concentration of leptin in the cerebrospinal fluid was 100 times lower than the plasma leptin.[56] The differences in the design and collection time, leptin measurements in different weeks of pregnancy, various methods and brands of assay kits in leptin analysis, differences in inclusion and exclusion criteria of samples, sample size differences, non-fasting and fasting status of mothers, breasts, geographic climates and even the type of mothers' diet in the studies can be the possible reasons for the different reported means.

In the present study, serum leptin levels of the first and second turns with maternal pre-pregnancy BMI were statistically significant. With comparing the two groups, it was found that the correlation between the first trimester leptin and pre-pregnancy BMI showed a significant difference between the two groups. A study by Kim et al. (2008) in South Korea examined plasma leptin of 75 pregnant women in the first and third trimesters of pregnancy and 6 months after delivery with a 12-hour fasting by ELISA method. According to the results, the first trimester leptin showed a significant correlation with BMI and was a predictor of birth weight.[42] A study by Lu et al. in China on 50 pregnant women between 37 and 38 weeks of gestation showed a significant relationship between leptin, weight, and BMI, with the mean serum leptin concentration being 13.62±3.68 µg/l.[57]

Filho performed a two-group cohort study in Brazil, with a similar research structure to the present study on 42 low-risk pregnant women. The serum non-fasting leptin was measured by ELISA method and a significant relationship was found between serum leptin changes and BMI before the maternal pregnancy.[43] Aguilar-Moreno study (2015) in Spain tested 71 pregnant women aged 18-24 years old. The serum leptin levels in adolescent mothers were not statistically significant compared to older mothers. Leptin was significantly associated with all anthropometric indicators of the samples such as the body weight, body fat percentage, BMI, hip circumference and wrist circumference.[58]

In the present study, due to the significant correlation between prenatal BMI, leptin of the first trimester and its serum changes between the two groups, the serum leptin levels of mothers during pregnancy can be attributed to pre-pregnancy body fat mass, which is due to the endocrine role of adipose tissue to secrete leptin.

According to the results of the present study, the first trimester plasma leptin of pregnant women had a significant correlation with pre-natal BMI. It can be concluded that the determinant factor in maternal plasma leptin hormones in pregnancy is pre-pregnancy BMI. This BMI can be a predictor of maternal serum leptin and subsequently weight gain during pregnancy.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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