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GPIHBP1 and Lipoprotein Lipase Level During Pregnancy

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ABSTRACT

Objective: During pregnancy, lipid metabolism is characterized by accumulation of fats during the first half of pregnancy and an increase in catabolism during the later stages. However, the underlying mechanisms for this shift are not well understood. We attempted to clarify the involvement of glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP-1), an anchor protein for lipoprotein lipase (LPL), which is a major lipid metabolism enzyme, by measuring its blood levels during pregnancy.
Methods: Blood samples were collected from non-pregnant women and from pregnant women at different stages: early pregnancy (up to 20 weeks of gestation), mid-pregnancy (21–33 weeks of gestation), late pregnancy (34–41 weeks of gestation), and puerperium (4–8 weeks after delivery). The levels of LPL and GPIHBP-1 were measured in each sample. In addition, these values were adjusted for albumin concentration to account for the effects of physiological blood dilution due to pregnancy.
Results: During pregnancy, GPIHBP-1 and LPL blood concentrations decreased transiently but returned to non-pregnant levels after delivery. When adjusted for albumin concentration, the decrease in GPIHBP-1 levels was negated, while the decrease of LPL levels was preserved.
Conclusions: During the course of normal pregnancy, the levels of GPIHBP-1 showed a transient decrease, which was thought to be due to physiological dilution. The levels of blood LPL also showed transient decrease probably due to inhibition of lipolysis.

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Key Words
lipid metabolism, lipoprotein lipase, physiological changes, pregnant women

I. Introduction

Blood triglyceride levels are known to be increased in patients with diabetes mellitus and severe obesity. It is believed that suppression of lipolytic enzymes, which are normally regulated by insulin in healthy individuals, has been the mechanism for this increase. In patients with increased insulin resistance, the control exerted by insulin is weakened, resulting in an accumulation of triglycerides that remain unmetabolized.

Lipoprotein lipase (LPL) is an enzyme responsible for degrading lipoproteins, while glycosylphosphatidylinosi-

tol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) serves as a critical scaffold for LPL on the vascular endothelium.

Lipids absorbed through the intestine are present in the blood as lipoproteins, which are complexes of lipids and proteins. To be used as energy, the triglycerides within these lipoproteins must be hydrolyzed to produce free fatty acids. Additionally, lipoproteins are converted into smaller lipoproteins and stored in the liver. LPL and GPIHBP-1 are known to play key roles in these processes [1].

It has been reported that decreased activity or genetic mutations in GPIHBP1 [2,3] and defects in LPL [4] cause abnormal elevations in blood lipid levels.

Moreover, LPL expression is known to be regulated by insulin, and LPL blood levels tend to be low in conditions characterized by insulin resistance or obesity [5].

On the other hand, blood levels of total cholesterol (TC) and triglycerides (TG) are well known to increase as pregnancy progresses through the gestational weeks.

During pregnancy, a characteristic of lipid metabolism is the increased fat assimilation and accumulation in the earlier stages, which is followed by enhanced catabolism of maternal fat in the later stages to satisfy the heightened demand as the fetus grows.

It has been reported that human placental lactogen (hPL), which a hormone derived from the placenta, has an anti-insulin effect that suppresses maternal glucose utilization [6]. Additionally, it plays a role in lipolysis in later stages of pregnancy owing to its lipolytic activity. As mentioned previously, during pregnancy, fat metabolism undergoes unique changes, but the specific alterations in lipolytic enzymes during this process have not been fully clarified.

Therefore, we decided to investigate the levels of blood GPIHBP1 and LPL throughout the course of a normal pregnancy.

II. Materials and Methods

(Subjects)

This study was approved by the Kiryu Kosei Hospital Ethical Review Board for Medical Research Involving Human Subjects.

The subject of this study included pregnant women who underwent pregnancy management at Kiryu Kosei Hospital. Excluded from this study were women with hypertension, diabetes, or endocrine disorders. In addition, women with multiple pregnancies, intrauterine fetal death, smokers, and heavy drinkers were also excluded.

Serum samples were collected from subjects at four different points: early pregnancy (defined in this study as before 20 weeks of gestation), mid-pregnancy (21–33 weeks), late pregnancy (34–41 weeks), and the puerperium (4–8 weeks after birth). During mid-pregnancy, 50 grams of glucose were administered, and blood samples were collected one hour later as a screening for glucose intolerance. Serum samples were collected without any dietary or water restrictions during the other periods.

The samples were stored at −80℃ until the following measurements after routine biochemical analyses at the hospital laboratory.

Serum samples were also collected from non-pregnant women who provided consent to participate in the study.

(Measurements)

GPIHBP-1 was measured by using the sandwich ELISA method using Anti-Human GPIHBP-CH79A4 Rat IgG monoclonal antibody and HRP-conjugated Anti-Human GPIHBP1-HE20A6 rat IgG Fab' as detection antibodies (#27279 Human GPIHBP1 Assay Kit, IBL Co., Ltd, Fujioka, Japan) [7]. The intra-assay coefficients of variation were 1.9%–5.0% and 1.7%–3.0% at 49.8–56.7 ng/L and 218.5–262.3 ng/L, respectively. The inter-assay coefficients of variation were 0.07 and 0.04% at 56.6 ng/L and 234.1 ng/L, respectively.

LPL was also measured by using the sandwich ELISA method using Anti human LPL N3A1 Mouse IgG monoclonal antibody and HRP-conjugated anti-human LPL 88B8 mouse IgG as detection antibody (#27268 Human Lipoprotein Lipase (LPL) Assay Kit, IBL Co., Ltd, Fujioka, Japan) [8].

Blood levels of TG and TC were measured by using the GP-HPLC method (LipoSEARCH®, IBL).

Concentrations of total protein and albumin were measured at LSI Medience.

(Analysis)

Statistical analysis was carried out using the Mann–Whitney U test, and a P-value of <0.05 was considered statistically significant.

III. Results

A total of 67 pregnant women were recruited for the study. However, 11 of them were diagnosed with glucose intolerance during pregnancy and were excluded from the study. Hence, the final group consisted of 56 pregnant women.

The following are the number of blood samples collected at each stage: 29 during early pregnancy, 39 during mid-pregnancy, 47 during late pregnancy, and 17 during the puerperium. 16 blood samples were collected from non-pregnant women.

Table 1 presents the background of the subjects. The

distribution of age and weight was nearly identical between the non-pregnant women group and the pregnant women group.

First, we measured total protein and albumin at each stage of pregnancy as indicators of physiological blood dilution resulting from pregnancy. Total protein levels decreased to 80.6% as expected of those in non-pregnant women during the mid-pregnancy, while albumin levels decreased to 67.3% of those in non-pregnant women during the late pregnancy (**Fig. 1**).

As shown in **Figure 2**, the level of GPIHBP-1 transiently decreased to a statistically significant level during pregnancy; then it recovered to the level seen in non-pregnant women. However, the decrease was only slight and not statistically significant after adjusting for albumin concentration.

On the contrary, the level of LPL showed a statistically significant decrease during late pregnancy transiently, and then it recovered to a level that exceeded that of non-pregnant women, even after adjusting for albumin concentration.

IV. Discussion

The changes in the levels of GPIHBP-1 and LPL during the course of a normal pregnancy were clarified. The levels of GPIHBP-1 showed a transient decrease and then returned to the level observed in non-pregnant women, but this effect was nullified when corrected for albumin levels.

Consequently, it is most likely that this decrease was the result of a dilution caused by increased blood volume during pregnancy. As a result, it is difficult to state that GPIHBP-1 plays a significant role in metabolism of lipids during pregnancy.

Conversely, the levels of LPL transiently decreased during late pregnancy. As already known, as the placenta grows during pregnancy, levels of hPL increase, resulting in increased insulin resistance within the physiological range. The reduction in blood LPL concentration is probably linked to the suppression of lipolysis, similar to the insulin resistance observed in obesity and diabetes.

In the puerperium, the level of LPL/Alb exceeded the level of nonpregnant woman. It is thought that LPL expression increased with the increased demand for lipid utilization associated with breast milk production during the postpartum period.

V. Limitations

・LPL is anchored to the vascular endothelium by proteoglycans and is released into the blood with the admin-

Table 1 Characteristics of the subjects

	non-pregnant women		pregnant women	
n	16		56	
Age (y)	35	(22 - 42)	31	(19 - 42)
Prepregnant BMI (kg/m^2)	21.5	(21.5 - 28.4)	21.6	(17.2 - 37.9)
Number of primigravida			6	(10.7%)
Gestational age at delivery (weeks)			39.4	(36.7 - 41.4)
Body Weight of the newborn (g)			2969	(2044.0 - 3962.0)
Number of cesarean section			6	(10.7%)

Numbers are average (range)

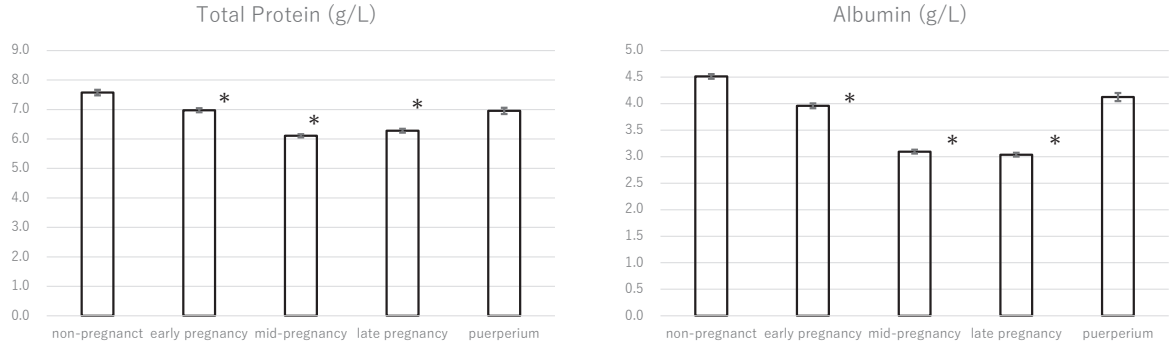

Figure 1 Blood Levels of total protein and albumin

Blood levels of total protein and albumin in non-pregnant women and at each point of pregnancy. Data are presented as average ± standard error. *$p<0.05$ vs. non-pregnant women.

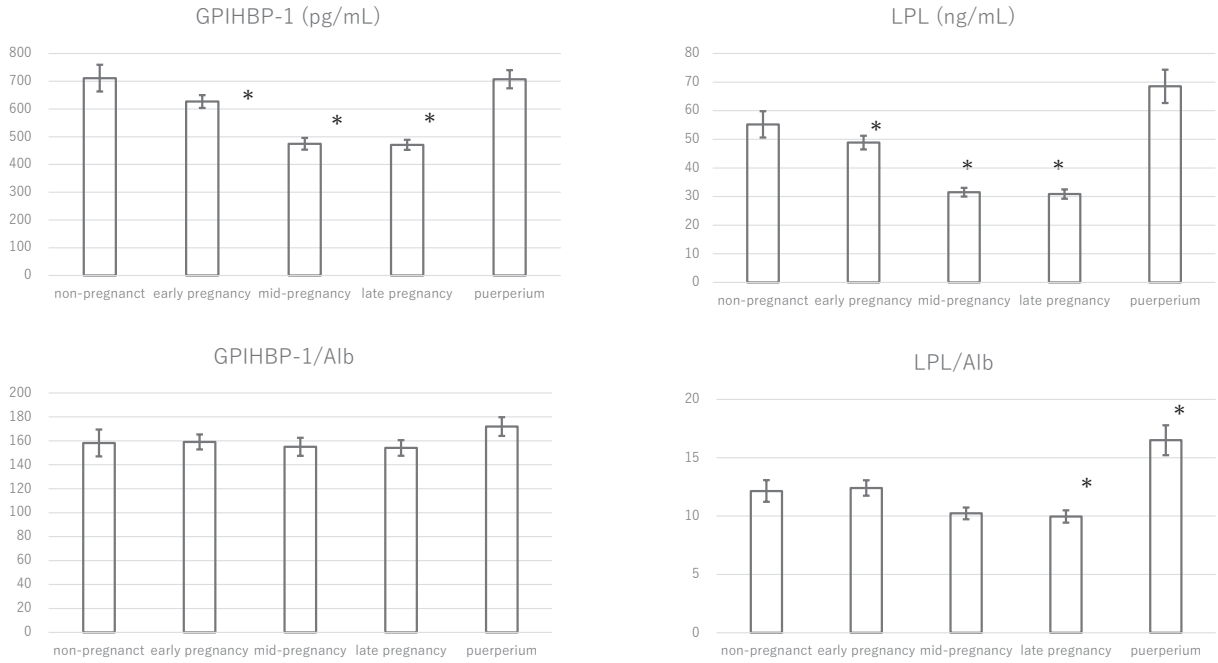

Figure 2 Blood levels of GPIHBP-1 and LPL

The levels of GPIHBP-1 and LPL, both uncorrected and corrected for albumin, in non-pregnant women and at each point of pregnancy. Data are presented as average ± standard error. *p<0.05 vs non-pregnant women.

istration of heparin [8]. In the past, blood samples taken after heparin administration (post-heparin) has been used to measure the level of LPL. However, in recent years, there have been reports indicating that LPL can be adequately assessed even from blood samples without heparin administration (pre-heparin) [9][10].

Since administering heparin to pregnant women is not advisable, it was not done in this study. Although blood samples were collected without the administration of heparin, we think that the measured LPL protein level reflects LPL expression.

・Blood samples were collected without any dietary or water restrictions, except for those from mid-pregnancy, which resulted in significant variations in the time since feeding. The reliability of the data can be affected by these variations.

・Only the blood samples from mid-pregnancy were taken after glucose loading. While there are no reports indicating that glucose loading affects lipid-metabolizing enzymes, the possibility cannot be entirely ruled out.

VI. Conclusion

During the course of normal pregnancy, the levels of blood GPIHBP-1 showed transient decrease to statistically dominant levels, but the decrease was believed to be due to physiological blood dilution that occurs during pregnancy. The levels of blood LPL also showed transient decrease probably due to inhibition of lipolysis.

Authorship Contribution

H.Sadakata, K.Nakajima, I.Kagami and Y.Abe designed the research.

K.Miyashita carried out the measurement of the data.

Y.Kajita collected the samples.

H.Sadakata analysed the data.

M.Murakami made critical reading.

All authors read and approved the final version of the paper.

Disclosure of Conflicts of Interest

The Authors declare that they have no conflict of interest

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