

Original Article

Ketone body elevation in placenta, umbilical cord, newborn and mother in normal delivery

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Abstract

Background: Low carbohydrate diets (LCD) have been recently prevalent in the medical and health field, especially in diabetes mellitus. We have applied LCD on thousands of patients with metabolic diseases and reported the clinical effect of LCD so far. Through our experience and research concerning LCD, the physiological role of glucose and ketone bodies during the pre- and post-partum period was investigated in this study.

Subjects and methods: Subjects were 60 normal pregnant woman who had a normal delivery in full-term, without an abnormal glucose intolerance. Methods included the measurement of the value of ketone bodies in the umbilical cord blood, placental tissue fluid and maternal blood, associated with the value of blood glucose. As ketone bodies, the value of 3-hydroxybutyric acid (3-OHBA, beta-hydroxybutyric acid) was measured. 3-OHBA and glucose values were measured by the electrode method using Precision Exceed Kit (Abbott) and the conventional enzymatic cycling method, with comparison investigation of the data from two kits.

Results: The average 3-OHBA levels were as follows: 2,235.0 $\mu\text{mol/L}$ in the placenta, 779.2 $\mu\text{mol/L}$ in the umbilical cord blood, in which the former is significantly higher than the latter ($p < 0.001$), 240.4 $\mu\text{mol/L}$ in the newborn after four days, and 366.7 $\mu\text{mol/L}$ after 30 days. The standard 3-OHBA level in a healthy man is less than 85 $\mu\text{mol/L}$. Glucose levels in the umbilical cord and placenta were 78.6 mg/dL vs 74.9 mg/dL, with no significant difference, and was the same as that of the pregnant woman. Accuracy management of the two kits revealed a significant correlation ($r = 0.94$, $p < 0.001$). 3-OHBA values of the maternal blood and umbilical cord blood were extremely elevated from the standard level, with a mutual significant correlation ($r = 0.724$, $p < 0.001$, $n = 416$).

Conclusion: This clinical study concerning ketone bodies during pre- and post-partum period was investigated, and revealed that 1) a clinically rapid useful kit for ketone bodies had high reliability and validity compared with conventional kit, 2) elevated values of 3-OHBA were shown in the placental tissue fluid, umbilical cord, newborn and maternal blood, 3) 3-OHBA would be a physiologically indispensable element in nutrition metabolism for fetus and newborn at least until 30 days, with further development of investigation for ketone bodies.

KEY WORDS: ketone bodies, 3-hydroxybutyric acid (β -hydroxybutyric acid), placenta, umbilical cord, newborn,

Introduction

Metabolic syndrome such as obesity and diabetes mellitus has recently increased, and low carbohydrate diets (LCD) have been noted in the medical and health field. Bernstein, Atkins and others have developed LCD^{1,2)}, and LCD has been widespread.

By the treatment of LCD, fat and fatty acid in the

body tends to burn for a long time. It causes elevated blood ketone bodies, which have sometimes been regarded as high riskfactors, because of insufficient correct differential diagnosis of hyperketonemia whether it is ketoacidosis or ketosis.

As a matter of fact, ketone diets were applied to infants with epilepsy for a long time, associated with hyperketonemia

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and without any complications. This treatment has been recommended by international guidelines such as Cochrane Library and National Institute for Health and Care Excellence (NICE) ³⁻⁵.

As for LCD and research of ketone bodies, we have continued LCD movement for more than 12 years. Ebe K. first started in Japan in 1999 with lots of books, and Bando H. developed this movement with medical presentations ⁶⁻⁹. After that, Ebe K. established the Japan carbohydrate restriction clinical promotion association, and Muneta T has broadened activity in OB/GYN and pediatrics fields ^{10,11}.

Our study has come to the next stage. Firstly we could measure the value of ketone bodies from the umbilical cord, and from the placenta tissue fluid, in which the validity of the measurement was investigated and clarified. Furthermore, the value of ketone bodies in maternal blood, placenta, umbilical cord, and newborn system was firstly investigated and argued in this report.

Subjects and methods

Subjects were 60 normal pregnant women who had a normal delivery in full-term, without any abnormal glucose tolerance or gestational diabetes mellitus. As ketone bodies, the value of 3-hydroxybutyric acid (3-OHBA, beta-hydroxybutyric acid) was measured. Methods included the measurement of the values of 3-OHBA in umbilical cord blood, placental tissue fluid and maternal blood, associated with the value of blood glucose.

The measurement of 3-OHBA and glucose was performed from the placental tissue fluid obtaining by slow and soft pressure for placenta without circulating blood. We used the Precision Exceed Kit (No. 44562003, registration 22300

AMX00567000; Abbott Japan, Kashiwa, Chiba, Japan) for measurement of 3-OHBA. The standard value of 3-OHBA in the blood of a healthy man is less than 85 $\mu\text{mol/L}$, and its measurement range is 30 to 8,000 $\mu\text{mol/L}$. The detail of this kit can be obtained in the HP of Abbott Co., Inc. ^{12,13}.

The data of 3-OHBA obtained from the Precision Exceed Kit was compared with those from the conventional enzymatic cycling method at usual professional laboratories, and the validity of Precision Exceed Kit was investigated.

Furthermore, we had 4 types of specimen including the umbilical blood, placental tissue fluid, mother blood and newborn blood, and 2 measure kit for 3-OHBA which are Precision Abbott and conventional enzyme cycling method. The summarized protocol is shown in [Table 1](#).

Ketone bodies include three chemicals, 1) acetoacetate (AcAc), the source of the two other ketone bodies, if not oxidized to form usable energy, 2) acetone, not an energy source, but instead exhaled or excreted as waste, 3) 3-hydroxybutyric acid (3-OHBA, beta-hydroxybutyric acid), not technically a ketone, but reversibly produced from AcAc, with useful energy ^{14,15}. In this study, we have measured 3-OHBA levels as ketone bodies.

Statistical analyses

Data were shown as the mean \pm standard deviation. For statistical analyses, correlation coefficients were calculated according to the Mann-Whitney U test in the comparison of two groups. We used two apparatuses for statistical analyses, which were the JMP (Version 8) statistical analysis software (JMP Japan Division of SAS Institute Japan Ltd., Minato-ku, Tokyo, Japan) and the Microsoft Excel analytical tool.

Table 1. 3-OHBA and glucose values in the umbilical cord, placenta, and newborn.

	Range	Average	Median	n	Kit
3-OHBA ($\mu\text{mol/L}$)					
Umbilical cord (delivery)	300 ~ 2,500	779.2	729.5	60	a)
Placental tissue fluid	1,200 ~ 5,200	2,235.0	2,114.5	60	a)
Newborn (4 days)	100 ~ 800	240.4	200.0	99	a)
Newborn (30 days)	200 ~ 700	366.7	400.0	24	a)
<hr/>					
Umbilical cord (delivery)	30 ~ 1,900	254.6	161.0	416	b)
Mother blood	30 ~ 4,400	285.4	65.0	416	b)
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Glucose ($\mu\text{mol/L}$)					
Umbilical cord (delivery)	35 ~ 136	78.6	79.0	55	c)
Placental tissue fluid	20 ~ 189	74.9	68.0	57	c)

Values of 3-OHBA are measured by a) Precision Exceed, Abbott and b) the conventional enzyme cycling method kit. c) Glucose values are simultaneously measured by the same kit as a). 3-OHBA: 3-hydroxybutyric acid, beta-hydroxybutyric acid.

Ethical considerations

The present study was conducted in compliance with the ethical principles of the Declaration of Helsinki (Note of Clarification added at the 2004 World Medical Association General Assembly in Tokyo) and Japan's Act on the Protection of Personal Information, and with reference to the Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs (Ordinance of Ministry of Health and Welfare No.28 of March 27, 1997) and the Ethical Guidelines for Epidemiological Research established by Japan's Ministry of Health, Labour and Welfare, and Ministry of Education, Culture, Sports, Science and Technology. The present study was conducted after examination and approval for the ethics and appropriateness of the study at a meeting of the Muneta OB/GYN Clinic Ethics Committee for Scientific Research Involving Human Subjects, including several experts (Approval number #105-2).

Results

1) The 3-OHBA value in the umbilical cord, placenta and newborn, with glucose value shown in [Table 1](#). The 3-OHBA level in the placental tissue fluid was 2,235.0 $\mu\text{mol/L}$ on average, and was 779.2 $\mu\text{mol/L}$ in the umbilical cord blood; the former was significantly higher than the latter ($p < 0.001$).

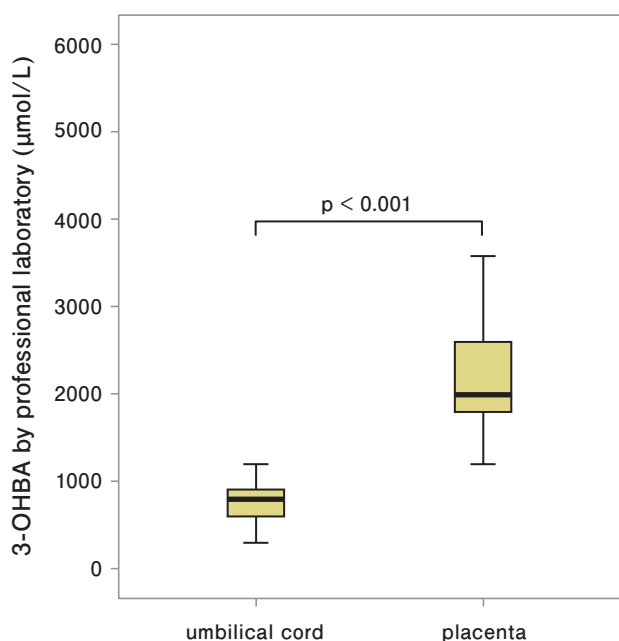


Fig. 1. 3-OHBA values in the umbilical cord and placenta tissue.

Results are expressed as mean \pm standard deviation ($n = 60$ each). The mean 3-OHBA value in the placental tissue is significantly higher than that in the umbilical cord by the Mann-Whitney U test ($p < 0.001$). 3-OHBA: 3-hydroxybutyric acid, beta-hydroxybutyric acid.

The 3-OHBA value in the newborn (4 days and 30 days) was much higher than the standard level. Furthermore, glucose level in umbilical cord and placenta was almost the same with no significant difference.

2) The 3-OHBA value in placental tissue fluid was significantly higher than that of the umbilical cord ($p < 0.001$, [Fig. 1](#)). The former was revealed to be about three times higher than the latter, and was 20 ~ 30 fold higher than the standard blood level (less than 85 $\mu\text{mol/L}$).

3) The glucose level in the placental tissue fluid was 75 ~ 80 mg/dL, which was not significantly different than the umbilical cord of all pregnant woman ([Fig. 2](#)).

4) Accuracy management of 3-OHBA by precision exceed was investigated. [Figure 3](#) showed the correlation of 3-OHBA data by two measurements via the electrode method (Precision Exceed, Abbott) and the enzymatic cycling method (conventional kit in professional laboratory), with significant correlation ($p < 0.001$).

5) The 3-OHBA values of maternal blood and umbilical cord blood are shown in [Fig. 4](#), with significant correlation ($p < 0.001$, $n = 416$). These data were from the enzymatic cycling method, which has been used as the standard method in usual professional laboratories.

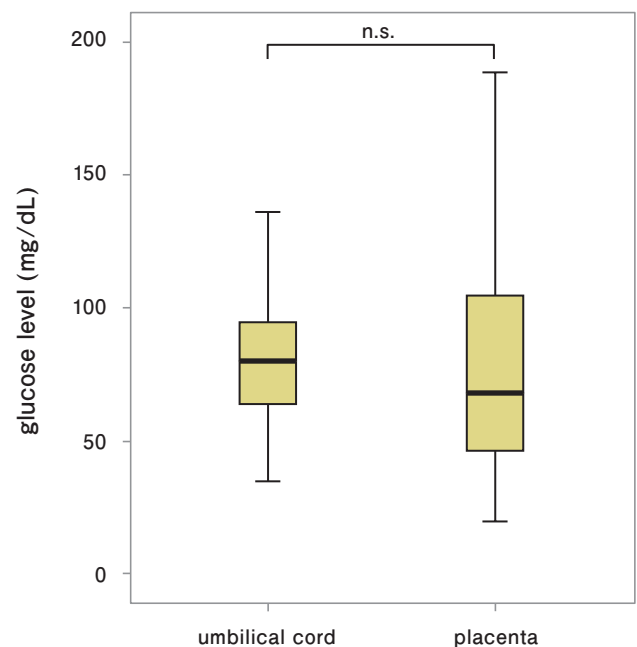


Fig. 2. Glucose level in the umbilical cord and placenta tissue.

Results are expressed as mean \pm standard deviation (umbilical cord, $n = 55$; placenta, $n = 57$). Neither level has any significant difference by the Mann-Whitney U test. n.s.: not significant.

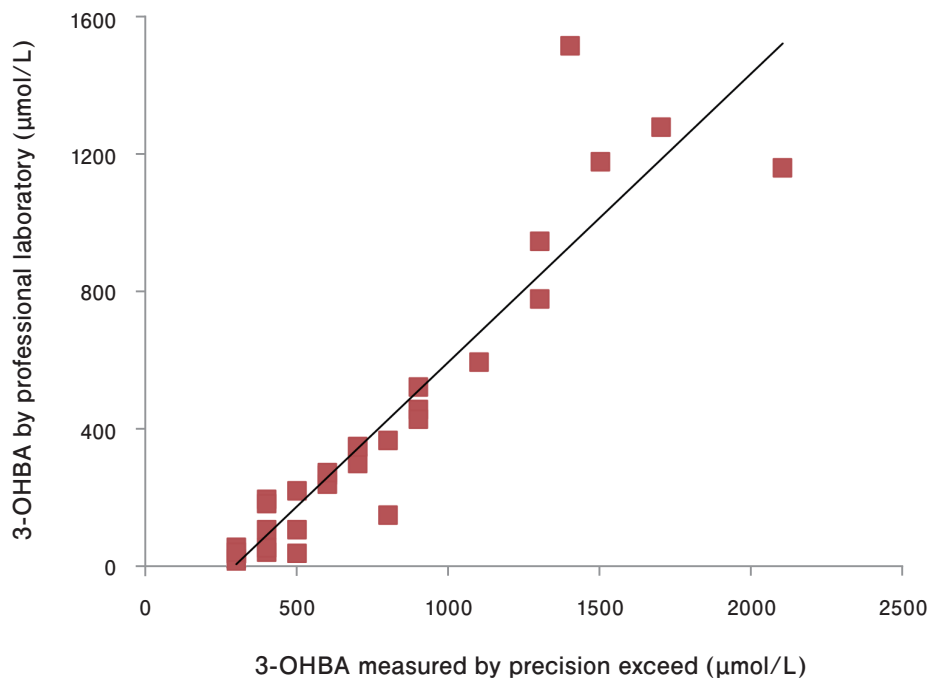


Fig. 3. Accuracy management of 3-OHBA by precision exceed.

Correlation of 3-OHBA data between two measurements, electrode and enzymatic cycling methods are shown. Significant correlation is observed ($r = 0.94$, $p < 0.001$, $n = 31$). 3-OHBA: 3-hydroxybutyric acid, beta-hydroxybutyric acid.

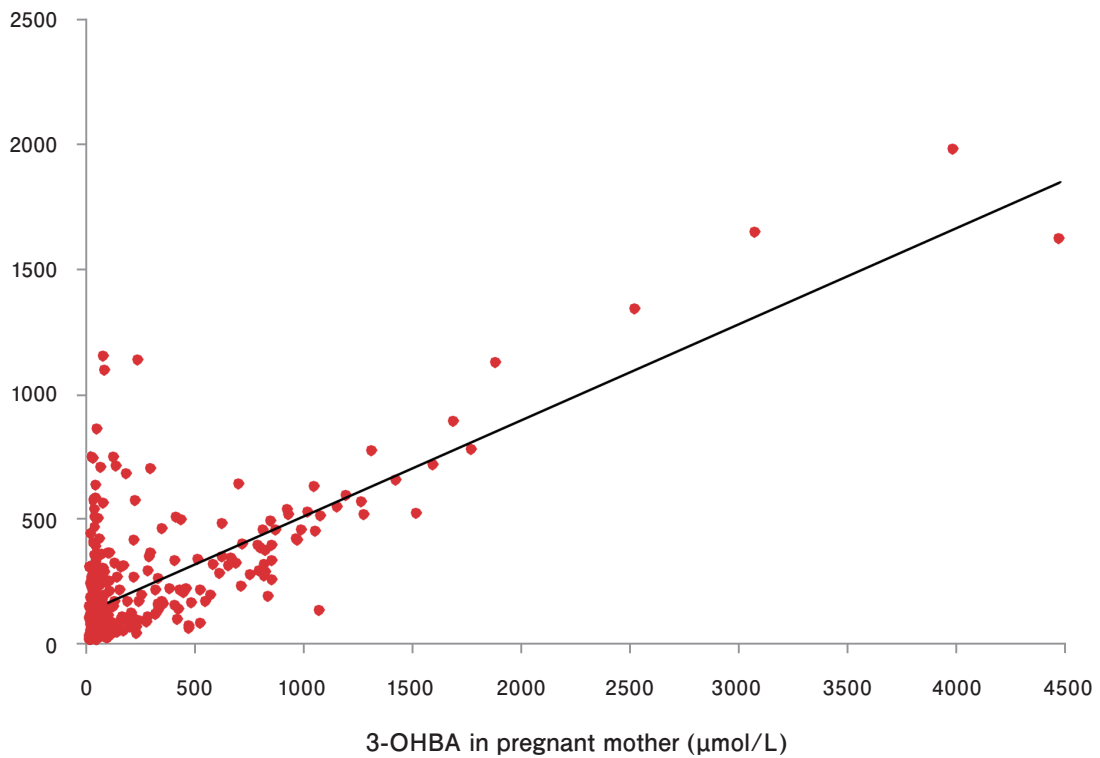


Fig. 4. 3-OHBA values in the maternal and umbilical cord.

Maternal and umbilical cord values of 3-OHBA are measured by enzymatic cycling method, in which a significant correlation is observed ($r = 0.724$, $p < 0.001$, $n = 416$). 3-OHBA: 3-hydroxybutyric acid, beta-hydroxybutyric acid.

Discussion

1) Low carbohydrate diet (LCD)

According to a Dietary Intervention Randomized Controlled Trial (DIRECT) study in Europe, LCD without calorie restriction (CR) was compared to a Mediterranean diet with CR and fat restriction with CR, in which LCD showed the predominance effect^{16,17}. In Japan, the coauthors have vigorously treated thousands of patients with obesity, metabolic syndrome and other diseases⁶⁻¹¹. Further development would be expected through Japan's low carbohydrate restriction clinical promotion association in the future¹⁸. As LCD has become more popular, the correct understanding concerning hyperketonemia and differential diagnosis of ketosis and ketoacidosis become more widely spread.

2) Ketone bodies

From an evolutionary perspective, ketosis has been considered the physiological response to fasting in *Homo sapiens*¹⁹⁻²¹.

Ketone bodies and glucose metabolism, we can consider for vertebrae evolution²². The eggs of oviparous animals, such as amphibian and birds species, contain no carbohydrates, but have fat and protein, which can feed and grow up to embryo. This evolution was transmitted to mammal species. At first, a fertilized egg was implanted, and after that, huge nucleated red blood cells have been seen, during yolk sac hematopoiesis. This phenomenon indicates that metabolism may be possible without carbohydrates.

Recently, the physiological role of ketone bodies has been clarified, including various beneficial functions^{20,23}. Ketone bodies have provided non-glucose substrate to the hypertrophied brain, sparing muscles from destruction for glucose synthesis. It has a protective role for epileptogenesis by preventing both after-discharge generation and propagation in kindling seizures^{24,25}. Furthermore, it has a protective role for nerve cells and neurons, and a prophylaxis effect for Alzheimer's and Parkinson's disease²⁵⁻²⁸. Thus, ketone bodies may aggressively become a protective energy source for brain in several reports^{14,15}.

3) Clinical application

This study has spread the clinical application for the measurement of ketone bodies.

Data obtained from the Electrode method (**Fig. 3**) revealed extremely high significant correlation with those by enzyme cycling method ($p < 0.001$), suggesting its rapid usefulness in clinical setting.

Before this report, we came to know that Abbott Co., Ltd. had no experience or no data to measure the serum or plasma of a newborn. Therefore this is the first report of the level of 3-OHBA in the blood of newborns at 4 and 30 days by rapid procedure using a small amount of blood, as well as in the placenta, umbilical cord and mother.

Accuracy management was successful, as a highly significant coefficient was found ($r = 0.97$) with reliability and validity. The standard value of 3-OHBA in the blood for a normal healthy man is less than 80 $\mu\text{mol/L}$, and the measurement range is 30 ~ 8,000 $\mu\text{mol/L}$ ^{12,13}. Using these kits, further data and speculation would be expected in future investigation. For clinical application of this kit, pregnant women with nausea and vomiting in emergency treatment were utilized, with successful rapid and adequate

diagnosis²⁹.

Historically speaking, the measurement of 3-OHBA in blood had been used for the management of diabetic ketoacidosis, and after that rapid enzymatic methods were developed^{30,31}. The first of these systems is marketed by GDS Diagnostics (Elkart, IN, USA), which needs only 2 min to work, with dilution of serum at a specific temperature.

A second generation system was introduced by Abbott Laboratories (Bedford, MA, USA). The Precision XtraTM needs a finger stick blood specimen (5 μL) within 30 seconds, and is accurate for 3-OHBA from 30 ~ 8,000 $\mu\text{mol/L}$ ³².

These environments allowed users to obtain 3-OHBA and glucose values immediately in clinical settings. That is why we could investigate and summarize this report.

4) Data Analysis

The authors have begun to develop LCD for patients including pregnant women, infants and newborns, with continuous research of glucose and ketone bodies. Based on several previous investigations on LCD and ketone bodies^{11,12}, we summarized this study. This is the first report to clarify the physiological metabolism of glucose and ketone bodies in the placenta, umbilical cord, mother and newborn.

Firstly, **Table 1** and **Fig. 1** showed that the ketone bodies' value was extremely high in the placental tissue fluid, approximately 20 ~ 30 fold higher than the standard level (85 $\mu\text{mol/L}$), and three times that of the umbilical cord. By contrast, the glucose values in the umbilical cord and placenta were almost the same with no significant difference, and the glucose levels were same as that of a healthy man (**Fig. 2**). These results would suggest that nutrition metabolism in a fetus may depend on the fatty acid metabolism.

Successively, the 3-OHBA value in a newborn at 30 days was still high (366.7 $\mu\text{mol/L}$ in average, **Table 1**), suggesting that ketone bodies may be involved in the energy production for the growth process of a newborn until at least one month. Future investigation on nutrition balance (glucose, protein, lipid), glucose intake amount, element of breast milk or artificial milk and energy in/out would be necessary to further clarify.

5) Newborn and ketone bodies

3-OHBA data ($n = 416$) of a mother and umbilical cord on delivery were measured by conventional enzymatic cycling method (**Fig. 4**), with mutual significant correlation. When we observe 3-OHBA values in the mother blood, about 70% of them were elevated from the standard level (85 $\mu\text{mol/L}$).

The average values of ketone bodies were 2,235 $\mu\text{mol/L}$ in the placenta, 779.2 $\mu\text{mol/L}$ in the umbilical cord, 366.7 $\mu\text{mol/L}$ in a newborn of 30 days, 240.4 $\mu\text{mol/L}$ in a newborn of 4 days, and less than 85 $\mu\text{mol/L}$ in normal adults (**Table 1**). Elevated 3-OHBA in the newborn would suggest that newborns may start producing ketone bodies in the liver, formerly given from the placenta.

Furthermore, two more factors would be involved in the growth of newborns, which are preparation for starvation after delivery due to rapid growth of fat tissue of the fetus in the third trimester, and the high amount of fat in breast milk supporting lipid metabolism.

Our results are compatible with the report of Akram *et al.*³³ for elevated ketone bodies in newborns and mothers. There is some possibility and speculation concerning the

metabolism of newborns. Fukao T *et al.* reported that the FFA/total ketone body ratio is useful for evaluation of ketone body metabolism and that defects in ketogenesis include mitochondrial hydroxymethylglutaryl-coenzyme A (HMG-CoA) synthase (mHS) deficiency and HMG-CoA lyase (HL) deficiency³⁴.

Newborns from the high glucose mother group revealed higher 3-OHBA ($p = 0.040$), lactate ($p = 0.040$), and triglyceride ($p < 0.001$), suggesting that pregnancy state would influence the metabolism of carbohydrate, lipids and the degradation pathways of amino acids, inducing to metabolism transportation from the mother across the placenta³⁵.

Moreover, lactate may become the focus of lipid and glucose metabolism in the future. Babies which were ≥ 35 weeks, ≤ 48 hours old and at risk of hypoglycemia, were investigated by measurement of plasma glucose, β -hydroxybutyrate, lactate and insulin concentrations³⁶. Glucose and β -hydroxybutyrate levels were low, but lactate level varied widely. Infants of diabetics had lower β -hydroxybutyrate and higher insulin concentrations. These findings suggest that lactate, rather than ketones, may provide alternative cerebral fuel in hypoglycemic newborns³⁶. Platt MW *et al.* also stated the paradigm shift for metabolism of newborn brains into lactate instead of glucose³⁷.

6) Pregnancy and ketone bodies

We cannot find previous reports for the relationship of ketone bodies values in the umbilical cord and mother on delivery with a large sample size (**Fig. 4**). Furthermore, these data were from the conventional professional laboratory with high validity. As a result, elevated 3-OHBA levels in the umbilical cord and maternal blood with mutual correlation were observed for the first time in this study.

Maternal 3-OHBA value had significant correlation with that of the umbilical cord, and showed about half level (**Fig. 4**). Influencing factors are considered to be as follows: 1) the transition of ketone bodies from placenta to maternal blood vessel, 2) the ratio of the transition and gradient, 3) metabolism difference between newborn and mother, 4) carbohydrate intake of mother in a few days of delivery, and dehydration, 5) relationship with hyperlipidemia in third trimester, 6) fetus environment and metabolism concerning ketone bodies, fat and glucose.

Metabolite profiles of arterial and venous umbilical cord plasma and maternal plasma were obtained by 1H nuclear magnetic resonance (NMR) spectroscopy³⁸. As for 3-OHBA concentration, mother vs umbilical cord plasma showed 2.87 vs 0.91 $\mu\text{mol/L}$ in normo-ponderal full-term (FT) delivery, and 1.06 vs 0.57 $\mu\text{mol/L}$ in very-low-birth-weight (VLBW) delivery.

These data seem to be consistent with our results for concentration and ratio from mother and umbilical cord. The measured number was 8 in Tea I *et al.*³⁸ and 416 in our study, indicating that our data would become the fundamental comparison of 3-OHBA between mother and umbilical cord (**Fig. 4**).

The placenta has been known to transaminate amino acids such as leucine, isoleucine and valine to their respective α -ketoacids, which are released into the umbilical and uterine circulation and contribute to placental ammonia production, consistent with the high level of β -hydroxybutyrate in maternal plasma. Further evaluation would be expected with our fundamental data of this study.

7) Fetus and ketone bodies

There have been some reports concerning ketone bodies and fetuses/newborns.

Firstly, Rizzo T *et al.*³⁹ reported that elevated 3-OHBA during pregnancy attenuated intelligence quotient after several years. This is one of the causes for the prevalent misunderstanding that elevated ketone bodies would be risky in clinical settings.

This report, however, has several questionable points, such as: 1) slightly elevated level of 3-OHBA of 100 ~ 180 $\mu\text{mol/L}$, 2) probable unstable blood glucose profile, 3) possible elevated postprandial glucose and mean amplitude of glycemic excursions (MAGE), 4) existing oxidative stress risk associated with factors 1)-3) influencing intelligence quotient.

On the other hand, our research has clarified the following: 1) in Pregnant women with morning sickness have ketone body levels more than 3,000 $\mu\text{mol/L}$, 2) placental tissue fluid always contains ketone bodies no lower than 2,000 $\mu\text{mol/L}$, 3) newborns from 4 to 30 days have elevated 3-OHBA, approximately 240 ~ 367 $\mu\text{mol/L}$. From these data, the decreased intelligence quotient due to hyperketonemia found by Rizzo's³⁹ seems to have no relation to ketone bodies.

Consequently, LCD often induces elevated ketone body levels, but it is not risky in light of the intrauterine environment of a fetus. Currently, ketone bodies can produce energy efficiently in the environment without enough oxygen, and give positive effects on cranial nerves²⁶. Ketone bodies in the placenta were proved to exist in such high concentration physiologically, indicating that ketone bodies may be not risky, nor lower the intelligence quotient nor have teratogenicity.

Secondly, pregnant mice were investigated by being given two types of food: an ordinary diet (9.3 ~ 15.5 kcal/day, fat 5%, carbohydrate 76.1%, protein 18.9%) and a ketogenic diet (20.1 ~ 33.5 kcal/day, fat 67.4%, carbohydrate 0.5%, protein 15.3%)^{40,41}.

However, this report seemed to have a fundamental problem in research design. Muridae species such as mouse and rat originally eats seeds of grass that are equal to cereal or low fat food. Animal experimentation with food is completely different from study in medicine giving oral or venous administration. Everyone knows the famous and incorrect medical report of about 100 years ago wherein an experiment of giving high fat food to rabbits caused extreme arterosclerosis in the carotid artery, which was of a similarly incorrect design. Therefore, the results of Sussman^{40,41} would be difficult to apply to that of human.

Furthermore, special food for humans with only 0.5% of carbohydrate cannot be prepared or made in ordinary situations.

Thirdly, Japan Society of Obstetrics and Gynecology has been responsible for the diagnosis and treatment of pregnant women in Japan. In relation to this association, Japan Gynecologist Association press conference was held in February, 2016, with the comment "Pregnancy and nutrition – Do not deliver small babies, nor grow them too big –"⁴². Their presentation included a series of medical study on mice experiment by Sussman^{40,41}. However, this seemed not to be appropriate educational content for ordinary expecting women. The desirable slogan should include adequate knowledge and advice about nutrition.

In contrast, there is a reliable medical review concerning

pregnancy and diabetes⁴³⁾. The influence of gestational diabetes mellitus was investigated by meta-analysis of twelve studies involving 6,140 infants. The results were that infants aged 1~2 years from diabetic mothers had significantly lower scores of mental and psychomotor development compared to control infants. Consequently, we should consider not ketone bodies, but glucose and glycative changes from now on.

8) Limitation and future of study

Previous reports for the relationship of ketone body values in the umbilical cord and mother on delivery have not included so great a sample size, indicating our data would become the fundamental and useful report in this field.

From the axis of mother – placenta – umbilical cord – fetus, concentration of gradient and movement of ketone bodies would be considered. Value of 3-OHBA in the placenta is extremely elevated, about three times that of the umbilical cord, and maternal value is half that of the umbilical cord. These data would indicate that the placenta may produce ketone bodies and supply its energy to the fetus. On contrast, even if maternal ketone bodies might move to placental tissue, the influence is subtle because of 1/6 of 3-OHBA level in maternal blood compared to the placenta.

Consequently, we speculate that the limitation of this study would be a lack of data from fetuses, so we have planned to investigate the fetus in detail.

Another major problem seems to be glucose and glycative influence^{20,21)}. The prevalence of gestational diabetes mellitus (GDM) seems to be 12.08% in Japan according to the guideline⁴⁴⁾, and the ratio of pregnant women with obesity and/or metabolic syndrome would be around 8%. Then, in our OB/GYN clinic, about 20% of subjects would probably be advised to be on LCD treatment, and others would have no particular health problems.

Our results showed that elevated 3-OHBA was seen in 70% of subjects. Associated with statistical data, probably 50~60% of the pregnant mothers without any complications may show elevated 3-OHBA. Therefore, we plan to investigate the difference between diabetic and non-diabetic groups in future research.

Conclusion

We investigated clinical study concerning ketone bodies during pre- and post-partum period, and concluded that 1) a clinically rapid useful kit for ketone bodies had high reliability and validity compared with conventional kits, 2) the elevated values of 3-OHBA were shown in the placental tissue fluid, umbilical cord, newborn and maternal blood, 3) 3-OHBA would be a physiologically indispensable element in nutrition metabolism for fetus and newborn at least until 30 days, with further development of ketone body research.

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Statement of conflict of interest

Non contributory.

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