ARTÍCULO ORIGINAL

Breastfeeding and metabolic indicators in Mexican premature newborns

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ABSTRACT

Background. Morbidity and mortality rates are higher among preterm infants due to physiological immaturity and greater growth demands. Nutritional intervention contributes to proper weight gain, which translates into better growth and neurological development, and prevents the onset of metabolic complications. The effect of breastfeeding duration was studied in the analytic profile at the end of the first six months of life. **Objective.** To describe the nutritional and metabolic markers effect in preterm infants at the end of the first semester of life. **Material and methods.** We performed an analytical, transversal and comparative study in 100 preterm infants, 30 to 36 weeks gestational age. Measures for weight, length and head circumference at birth were taken from the subjects' clinical files. A follow-up conducted at 6 to 9 months of age evaluated the same nutritional indicators (weight, length, head circumference) and compared them with values at birth and recommendations. Metabolic indicators (glucose, hemoglobin, cholesterol, triglycerides, insulin, urea, creatinine, gamma-glutamyl-transferase and alkaline phosphatase) were compared with the recommendations. Follow-up study in 100 preterm infants (30 to 36 weeks gestational age). Weight, length and head circumference were measured at birth and 6 to 9 months later. We measured analytic parameters related to metabolic syndrome (glucose, hemoglobin, cholesterol, triglycerides, insulin, urea, creatinine, gamma-glutamyl transferase and alkaline phosphatase). Confusing factors like income level and access to public services were also studied. **Results.** The mean age at follow-up was 7.3 ± 1.4 months. Levels of hemoglobin, creatinine and urea showed significant differences with regard to reference values (Wilcoxon ranks test, < 0.05). The average duration of breastfeeding was 4.3 months. The mean age at follow-up was 7.3 ± 1.4 months. Risk factors for hypercholesterolemia, as well as levels of hemoglobin, creatinine and urea showed significant differences with regard to reference values (Wilcoxon ranks test, < 0.05). **Conclusions.** Premature infants showed deficiencies in weight gain. Biochemical parameters could reflect metabolic risk, therefore we recommend prolonging breastfeeding as well

Lactancia materna e indicadores metabólicos en recién nacidos prematuros mexicanos

RESUMEN

Antecedentes. *Los recién nacidos prematuros presentan mayor morbimortalidad debido a una inmadurez fisiológica y una mayor demanda energética. La intervención nutricional contribuye a una ganancia de peso, crecimiento y desarrollo neurológico adecuado; disminuye el riesgo de desarrollar enfermedades metabólicas. El efecto de la duración de la lactancia materna en el perfil analítico al final del primer semestre de vida.* ***Objetivo.*** *Describir los indicadores nutricios y metabólicos en prematuros.* ***Material y métodos.*** *Estudio de seguimiento de 100 prematuros (30 a 36 semanas de gestación). Peso, talla y perímetro cefálico al nacer y a los 6-9 meses. Se midieron parámetros analíticos relacionados con el síndrome metabólico (glucosa, hemoglobina, colesterol, triglicéridos, insulina, urea, creatinina, gamma-glutamil transferasa y fosfatasa alcalina). Otros factores de contusión confundidores estudiados fueron nivel de ingresos y acceso a servicios públicos.* ***Resultados.*** *El tiempo de lactancia materna fue en promedio de 4.3 meses. Al momento del seguimiento, la edad media fue de 7.3 ± 1.4 meses. Los factores de riesgo para una hipercolesterolemia, así como la hemoglobina, creatinina y urea, mostraron diferencias significativas con los valores de referencia (Wilcoxon test de rangos, p < 0.05).* ***Conclusiones.*** *Los prematuros mostraron deficiencias en la ganancia de peso. Los parámetros bioquímicos reflejarían un riesgo metabólico, por lo que se recomienda prolongar el amamantamiento, y seguimiento del crecimiento y desarrollo de este grupo de edad, una vez que egresan del hospital.*

as extending the follow-up of these infants for monitoring their growth and development once out of the hospital.

Key words. Premature infant. Glucose. Hemoglobin. Weight gain.

Palabras clave. *Prematuros. Glucosa. Hemoglobina. Ganancia de peso.*

INTRODUCTION

Prematurity contributes to increase neonatal morbidity and mortality. The definition of preterm birth, according to World Health Organization (WHO), is an infant who is born before 37 weeks gestational age. Prematurity is one of the main problems in developing countries, with a prevalence of 10% of total births. 20% of these infants have some type of malnutrition.[1] Twelve million of children are born in Latin America and the Caribbean each year; 135,000 of these children die because of prematurity. One fifth of premature children born in extreme conditions die within the first year after birth; 60% of those who survive will suffer from neurological disabilities.[1,2] Mexico has an overall prematurity prevalence of 8.9%, with a prevalence of 13.7% in tertiary-level hospitals.[2]

Preterm infants have feeding problems due to insufficient development of the suck and swallow reflexes, digestive immaturity, maladaptation of gastrointestinal hormonal responses, poor absorption capacity, low tolerance to enteral feeding, and risk of developing necrotizing enterocolitis.[2-4] These factors prevent preterm infants from covering their requirements. Nutritional support (enteral or parenteral feeding) prevents malnutrition caused by prolonged fasting, and decreases morbidity and mortality. However, nutritional support causes other metabolic complications, such as hyperglycemia, hypercholesterolemia and hypertriglyceridemia. These complications must be monitored during hospital stays.[4] Monroy, *et al.*[5] studied preterm newborns in a Regional General Hospital, Guanajuato State and found that energy and macronutrient supply via nutritional support was 50% lower than the recommendations. The metabolic complications observed were hyperglycemia and elevated gamma-glutamyl-transferase and urea. It is known that tardy administration of nutritional support, insufficient energy supply and deficient surveillance hinder weight gain and prevention of metabolic complications.

The preterm neonate has immaturity of many organs and hormonal production. It is known that a steady increase in blood glucose increases insulin levels, with an elevated risk of future pancreatic damage.[6-8] Barker, *et al.*[9] described that nutrition during pregnancy has implications for fetal growth and development which can increase metabolic risks (cardiovascular, development of diabetes, dyslipidemia) early in childhood or adulthood. However, the exposure time required for these effects to occur is not yet clear.[10,11]

Adequate weight gain has been linked to better growth and neurological development when infants reach school age.[11] Low energy intake causes failure to gain weight, while food overload results in excess weight. Increases and decreases in weight induce alterations in metabolism and hormone production, and an elevated risk of early-onset metabolic syndrome, diabetes and cardiovascular disease.[10]

The health benefits of breastfeeding in infants have been well documented. International and professional organization recommend exclusive breastfeeding for the first six months of life, and breastfeeding with complementary foods for at least one year.[12] Breastfeeding is the optimal form of infant nutrition.[13] Among premature infants, formula feeding increases the risk for necrotizing enterocolitis, delayed brainstem maturation, lower scores in cognitive and developmental tests, sepsis, and delayed visual development. Many interventions are designed to increase breast milk consumption among preterm infants.[14,15]

The Ministry of Health of the State of Guanajuato reports that the primary cause of perinatal morbidity in 2005 was preterm birth, with a total of 86.5% of cases.[16] The statistics of the Mother and Child Hospital of León register 2,605 deliveries in 2006, with 458 preterm births. In 2007, 1,783 deliveries were premature (17 deliveries per week).

Increased frequency of premature births, the problem of low energy intake and deficient weight gain, poor breastfeeding practices and the lack of studies describing these variables in the first year of life motivated the authors to conduct a follow-up study in a group of preterm infants. In this study, nutritional diagnosis at birth was compared with a second evaluation performed between 6 and 9 months later. Energy and macronutrient intake, duration of breastfeeding and other metabolic indicators were also evaluated and compared with reference parameters.

MATERIAL AND METHODS

Descriptive study in 100 preterm infants of the Mother and Child Hospital of León, of the Ministry of Health of the State of Guanajuato, Mexico. The inclusion criteria were: preterm newborns 30 to 36 weeks gestational age, with complete anthropometric information from birth registered in the clinical file at (weight, length, head circumference), and the availability of anthropometric values, information about energy and macronutrient intake and metabolic indicators like hemoglobin, glucose, insulin, cholesterol and triglycerides at follow-up (6 to 9 months of age). Newborns with metabolic, infectious or congenital diseases were not included. Sample size was determined with two proportions test; according to the literature, we expected to find malnutrition in 50% of preterm infants at follow-up (with a significant difference of $\alpha < 0.05$ and $\beta = 80$). Non-probability sampling designs (consecutive sampling) were used.

Gynecologist and neonatologists referred mothers with preterm infants for the study at the time of birth and upon discharge from the hospital. Mothers who accepted to participate in the study received an informed consent letter; the procedures were explained to them, and they were asked for a telephone number and address for contacting them at follow-up. The study was conducted in two stages. The first stage consisted of gathering anthropometric data from the newborns' clinical files, mainly weight, length and head circumference. The authors questioned the infants' mothers about breastfeeding and feeding practices at the time. At this stage, the authors didn't interfere with feeding prescriptions before or upon discharge from the hospital. The evaluation was directed towards tracking infants' evolution upon a single, subsequent measurement after 6 to 9 months. The second stage consisted of follow-up measurements at 6 to 9 months of age. Weight, length and head circumference were analyzed in order to obtain a nutritional diagnosis. This age was considered fit for evaluation because infants double their length and triple their weight during the first year of life.[17] For this stage, the infants' parents were contacted by telephone 6 to 9 months after the infants' birth. We proceeded to remind them of the study and provide a new informed consent. Once the parents accepted, they were called to the Body Composition Laboratory of the Department of Medicine and Nutrition, University of Guanajuato. The anthropometric indicators (weight, length, head circumference) were analyzed by a standardized dietitian. The weight and length were measured with SECA® brand electronic scales for babies. Head circumference was measured with SECA® brand fiberglass tape.

The Fenton growth chart for preterm infants (adaptation of the Babson-Benda curve growth charts) was used to obtain each child's nutritional diagnosis at the first stage (at birth) 18 and the preterm infants were classified as appropriate for gestational age (AGA, weight > 10th and < 90th percentile), small for gestational age (SGA, < 10th percentile) or large for gestational age (LGA, > 90th percentile); WHO growth curves were also used at this stage. At the follow-up stage, only the WHO growth curves were used. When length with regard to age, weight with regard to age, and weight with regard to length were within < 1 standard deviation or between the 3rd. and 97th percentile, the nutritional diagnosis was considered good. At > 2 standard deviations or below the 3rd. percentile, it was considered that there was some degree of malnutrition.[19] For the follow-up stage, premature infants' ages were corrected according to the following formula:[20]

- Corrected age = 40 - weeks of gestation = missing weeks of gestation.
- Chronological age - missing weeks of gestation = corrected age.

During the follow-up stage, infants' mothers were questioned about feeding practices and lactation using a 24-hour recall. This was used for analyzing children's energy and macronutrient intake (proteins, fat and carbohydrates). The intake was calculated using Nutrikcal® version 4.0 software. Food replicas NASCO® were used. The results were compared with the guidelines and recommendations of the American Dietetic Association (ADA), as these references are the most frequently used by clinicians.[21] We calculated the fitting percentage, whose normal values range from 90% to 110%. The outcomes allowed us to determine real intakes and compare them with 100% daily recommendations. A food frequency questionnaire was used for determining the food groups introduced during weaning.

As to the metabolic values, hemoglobin was analyzed in capillary blood samples drawn from the infants' fingers using HEMOCUE® equipment. A blood sample (1-3 mL), obtained from the back of the hand by a laboratory technician was used to evaluate glucose, urea, creatinine, cholesterol, triglycerides, alkaline phosphatase, gamma-glutamyl-transferase (GGT) and insulin. These markers were processed in the Clinical Laboratory of the Department of Medicine and Nutrition of the University of Guanajuato. Mothers were instructed to have the children fast before the procedure, and they were summoned in the morning. We selected these specific markers because they are considered markers of metabolic, renal and hepatic risk.

Confusing factors like family income level and access to public services were also studied.

Statistical analysis

Changes in weight, length, head circumference, energy and macronutrient intake were evaluated using the Student's t-test. Nutritional diagnoses were calculated in percentages and compared using a two-proportion test. Comparisons between laboratory test results at 6 to 9 months and reference values were performed a Student's t-test. The alpha significance level for all tests was < 0.05.

The study was approved by the Ethical and Research Committees from the Medicine and Nutrition Department and the institution where the study was conducted. All the parents of the newborns selected for the study signed an informed consent, as did the institution, granting access to clinical files. The study did not represent a health risk for the newborns; blood samples were obtained only by trained personnel and in accordance to recommended amounts. We used the statistics package NCSS®, version 2.0, 2006.

RESULTS

The gestational age range of all 100 infants was 30 to 36 weeks (mean 33.4 gestational weeks); 28% were female and 72% were male. At follow-up, the mean age was 7.3 ± 1.4 months (range 6 to 9 months), corrected for prematurity.

First stage: at birth

The average weight was 2007 g (range 659 to 3,750 g); the average length was 43.7 cm (range 30 to 52 cm), and the average for head circumference was 32.4 cm (range 28 to 35.5 cm). The weight, length and head circumference at birth showed differences of 400g, 2.4 cm and 0.9 cm, respectively, regarding the recommendations, and there were no significant differences (> 0.05) (Table 1). According to the Fenton charts, 57% of infants were appropriate for gestational age (AGA), while the rest were small for gestational age (SGA). According to the WHO growth charts, 41% of the infants had some degree of malnutrition, and 59% had adequate nutritional diagnosis at birth.

Table 1. Comparison between anthropometric characteristics at birth and at follow-up, and recommendations (N = 100).

Variable	Birth			Follow-up		
	Study outcomes Mean ± SD (range)	Recommendation* Mean ± SD (range)	p †	Study outcomes Mean ± SD (range)	Recommendation** Mean ± SD (range)	p †
Weight (kg)	1.8 ± 0.7	2.2 ± 0.4	0.075	6.8 ± 1.3	8.8 ± 0.6	0.012
Length (cm)	45.0 ± 3.5	46.4 ± 1.9	0.135	68.1 ± 6.1	71.5 ± 2.0	0.058
Head circumference (cm)	30.1 ± 2.6	31.0 ± 1.4	0.265	43.9 ± 2.4	44.6 ± 1.2	0.338

SD: standard deviation. *Comparison with Fenton growth charts (Student's t-test, p < 0.05). **Comparison with WHO growth charts (Student's t-test, p < 0.05). † Student's t-test.

Table 2. Comparison between energy and macronutrient intake at follow-up and recommendations.

Variable	Follow-up Mean ± SD	Recommendations* Mean ± SD	Fitting percentage‡	P
Energy (Kcal/kg)	822.2 ± 168.6	847 ± 156.6	97.1	0.690
Proteins (g)	20.1 ± 4.0	23.1 ± 4.3	87.1	0.067
Fat (g)	22.8 ± 4.1	33.1 ± 6.1	68.9	0.001§
Carbohydrates (g)	82.3 ± 22.0	115.5 ± 21.4	71.2	0.1§

SD= standard deviation. *American Dietetic Association recommendations.[21] ‡Fitting percentage refers to the percentage in which the amounts of energy and macronutrients supplied to the infants are similar to the recommended values; its normal range is 90-110%. §Fat and carbohydrate intake was significantly different from ADA recommendations (Student's t-test, p < 0.05).

Second stage: follow-up

The infants were measured at between 6 to 9 months of age. When compared with the recommendations of the WHO growth charts, they showed deficits of 1,100 g, 3.4 cm and 0.7 cm for weight, length and head circumference respectively. A significant difference was observed only in weight (Table 1). Regarding of the nutritional diagnosis, 71% of children had an adequate nutritional status and 29% showed some degree of malnutrition.

No significant differences were observed by comparing this nutritional diagnosis with nutritional diagnosis at birth. At this moment, 31% of infants were malnourished and the rest had normal nutrition. Out of 59% of children with adequate nutritional diagnosis at birth, 18% changed to some degree of malnutrition. Of those children who had some degree of malnutrition at birth, only 14% had reached an adequate nutritional diagnosis at follow-up. The remaining 27% continued to show some degree of malnutrition.

Dietetic characteristics

86% of children received exclusively breastfeeding during an average of 4.3 months (range 1.6 to 5.1). The rest of the children received different types of commercial formulas for premature infants. Weaning (the introduction of foods other than breast milk) began at 4.3 months of age. Mothers' decisions regarding weaning were made according to their own beliefs in 36% of cases, following family and friends' advice in 35% of cases, and according to physician counseling in 29% of them. The first food groups introduced were fruit, cereals and sugars. The foods were mainly mashed, and preparations included raw, for some fruits, and cooked. As to the food frequency questionnaire, the sugar group was represented mainly by industrialized juices, soft drinks and candy.

All children received at least one food consider allergenic, including wheat products like soup, bread, cookies and industrialized cereals. Other such foods were chocolate bars or chocolate powder, whole eggs, sausages, oatmeal, orange juice, whole milk and dairy products.

Regarding the outcomes of the 24-hour recall, a significant difference was observed when comparing actual intake the recommendations for fat and carbohydrates ($p < 0.05$), but this difference was not observed for energy and protein (Table 2).

Metabolic indicators

50% of children had low hemoglobin levels, while 7% had hyperglycemia, hypercholesterolemia, and elevated levels of GGT and urea; 64% had hypertriglyceridemia.

Creatinine levels were within the normal range for 100% of the children. Low values of serum alkaline phosphatase were observed in 26% of the children (Table 3). The values for urea, creatinine and hemoglobin showed significant differences with reference values.[22]

Family income and access to public services

The income was an average of 1,000 to 4,000 Mexican pesos in most cases. The services of drinking water and electricity were rarely available. Most patients did not have access to drinking water or electricity, and their economic resources were very limited.

Table 3. Comparison of metabolic parameters with reference values.*

	Follow-up (mean ± SD)	$p^{‡}$
Hemoglobin (g/dL)	11.2 ± 1.2	0.001
Glucose (mg/dL)	100 ± 18	NS
Urea (mg/dL)	17.3 ± 4.8	0.029
Creatinine (mg/dL)	0.3 ± 0.05	0.010
Cholesterol (mg/dL)	128 ± 32	NS
Triglycerides (mg/dL)	95.4 ± 29.8	NS
Alkaline phosphatase (U/L)	191.2 ± 64.2	NS
High gamma-glutamyl-transferase, GGT (U/L)	13.5 ± 1.7	NS
Insulin (mcU/mL)	3.3 ± 0.8	NS

SD: standard deviation. * Reference values for premature infants according to Perlman.[22] ‡ Wilcoxon ranks test, $p < 0.05$.

DISCUSSION

Current advances in obstetrics and neonatology have substantially contributed to improving the survival of preterm infants and children with low birth weight, a population at elevated risk for developing metabolic complications.[9]

During the follow-up stage, we observed significantly different weight loss after comparing initial weight with weight at follow-up. This is explained by the fact that preterm birth not only disrupts fetal nutrition, but also affects weight gain. Recent studies indicate that the degree of postnatal weight loss and the time needed to regain weight may have implications for metabolic and neurological diseases later in life.[4,23]

Moreover, evolution is different for children born at term and those born prematurely. One study showed that 89% of such children had stunted growth when assessed at 36 weeks (corrected age), while 40% did at 18-22 months' follow-up. More than half did not follow a normal growth curve during the first two years of life. These children also have more growth retardation problems.[1,6-7] It has been reported that both birth length and average height of parents are related to the extent of growth in preterm infants. During the first 6 months of life, the extent of growth is explained by size at birth.[7,8] Preterm infants are commonly at higher risk of short stature. Approximately 50% of children who fail to grow by the age of two retain short stature in adulthood.[6,7,24,25]

The availability of growth curves adapted to our population would contribute to better nutritional diagnoses. For this study, we had to consider the Fenton charts,[18] which are designed for preterm infants, and then make the necessary adjustments for applying the WHO curves.

A follow-up study of preterm infants showed that they were 3 cm shorter and 2 kg lighter at the age of four than children born at term. The same pattern prevailed by the age of 7 years.[8,26]

The growth in head circumference was similar to the recommendations. We have also found that these parameters are significantly lower for preterm infants in early childhood.[6,8] It is known that adequate growth during the first year of life leads to higher IQ values in childhood and through adulthood, compared to the values from children whose head circumference remains small.[6,14]

Preterm infants suffer significant nutrient deficits during hospitalization. At the time of discharge, many preterm infants suffer a moderate to severe deficiency in growth which varies according to factors such as birth weight, gestational age, height of parents, adaptation to growth retardation, neurological impairment and low nutrition.[3] It has been demonstrated that children with growth impairments between the ages of 0 and 2 show higher obesity rates and increased central fat distribution at 5 years old. In addition, children who were born prematurely were found to have more visceral fat than children born at term. The increase in fat may be related to an increased incidence of cardiovascular disease, diabetes and metabolic syndrome in adulthood,[4] as Barker's hypothesis explains.[9]

This study found that more than 80% of children were exclusively breastfed, which gives them the benefit of breast milk as the optimal nutritional support for improving growth and development.[6] Lucas, *et al.*,[14] found that preterm infants who received breast milk showed higher weight gain and improved bone mineralization in the first year of life. Lucas, *et al.*, also published several articles reporting that preterm infants who were breastfed in the early neonatal period had lower blood pressure and lower LDL:HDL ratios at the ages of 13 to 16 than children fed with formula.[13,14]

The age of weaning was within the recommended range and food preparations were adequate. However, we found that the food groups introduced were predominantly fruit, grains and sugars, in the form of industrialized porridge, industrialized juice, soft drinks and candy. It is known that industrialized juices and carbonated drinks are high in fructose syrup, which promotes increased abdominal fat and weight gain.[27] This in turn is associated with increased risks of chronic degenerative diseases, as well as the risk of developing unhealthy habits.[28]

It is important to consider that most decisions regarding weaning were based on empirical knowledge, which is not always accurate. The introduction of allergenic foods can be explained by this lack of professional orientation.

Energy and macronutrient intake differed significantly from recommended allowances. Fat and carbohydrate supply was lower than recommended, but carbohydrates were supplied mainly in the form of simple sugars, from foods high in fructose syrup. Energy intake influences weight gain and body composition, whereas length and head circumference are influenced by dietary protein. Despite these differences, we observed that the diagnosis in almost 20% of the children changed from SGA to AGA. More studies are needed to promote long-term follow-up of dietary factors.

Regarding metabolic indicators, there were significant differences with reference values for hemoglobin, urea and creatinine. This could be explained by energy and protein imbalances, but insofar as other biochemical parameters show values within normal range, it is suggested that long-term follow-ups evaluate the relationships between these markers and energy intake in these children.

The hormones that influence growth before birth are primarily insulin-like growth factors I and II (IgF-I/II), structural proteins and insulin. In the postnatal stage, in addition to IgF-I/II and structural proteins, tyrosine becomes an important growth factor.[4]

The income was average $1,000 to $4,000 Mexican pesos in most cases. Potable water services and electricity were scarce. Most patients did not have potable water services neither electricity, as well as low economic contribution. Feeding practices were inadequate both in quality and type of food. These situations will impact the growth and development of preterm infants.[29]

Follow-up during the early stages of childhood is necessary and must be individualized in accordance with each child's requirements. Health professionals must provide the family with help and orientation at least until school age, perhaps even up to adolescence.

We suggest that more follow-up studies be conducted, and that these include more evaluations during the first year of life. We also suggest considering the inclusion of other metabolic and nutritional markers, such as nitrogen balance, total protein, albumin and pre-albumin levels.

CONCLUSIONS

At birth, no statistically significant differences were observed between the weight, length and head circumference of the studied infants and the recommendations for that age. Upon a follow-up evaluation, statistically significant differences were observed. Out of 59% of children with adequate nutritional diagnosis at birth, 18% developed some degree of malnutrition. Out of those with some degree of malnutrition at birth, only 14% reached an adequate nutritional diagnosis at follow-up. The remaining 27% continued to show some degree of malnutrition. 86% of children received exclusively breastfeeding during an average of 4.3 months. There were significant differences between actual fat and carbohydrate intake and recommendations. Energy and protein intakes were within the recommended ranges. Weaning was mostly guided by empirical practices, without guidance from health professionals, and the foods introduced were mainly sugars in the form of industrialized products (juice, soft drinks, and candies) and foods considered allergenic.

According to the references, statistically significant differences have been observed for hemoglobin, urea and creatinine. These may be associated with the onset of metabolic diseases such as diabetes, hypertension and metabolic syndrome. Better dietary surveillance and closer monitoring of these children are needed in order to avoid the above-mentioned complications and improve the children's quality of life. Health professionals must offer better counseling for the mothers of preterm infants and consider economic and demographic aspects. So we recommend prolonging the period of breastfeeding, and monitoring premature infants' growth and development following discharge from the hospital.

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