Maternal Status of Trace Elements in Normal Pregnancy and in Gestational Diabetes Mellitus

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ABSTRACT

Adequate nutrition is critical in pregnancy, because both the fetus and an infant are dependent on adequate maternal stores of micronutrients. The current study aimed to assess statuses of the essential micronutrient (iron, copper and zinc) in normal pregnancy and in pregnancies complicated with gestational diabetes mellitus (GDM). The study included three groups: non-pregnant (n = 44), healthy normal pregnancy (n = 47) and pregnancy complicated with GDM (n = 42). Results revealed significant variations in iron status as indicated by decreased serum iron and elevated TIBC, both in normal pregnancy and in GDM. Serum copper was higher in normal pregnancy and in GDM, while ceruloplasmin was elevated only in normal pregnancy compared to non-pregnant. Serum zinc showed a trend towards decrease in normal pregnancy and no change in GDM compared to non-pregnant group. No significant correlations were obtained between each of iron, copper, zinc and their related markers with markers of insulin resistance in pregnancy. It could be concluded that normal pregnancy and GDM are associated with imbalance in iron, copper and zinc status, however, the imbalance in trace elements has no significant role in the decreased insulin sensitivity associated with pregnancy, especially in GDM.

Key Words: Trace Elements; Pregnancy; Gestational Diabetes Mellitus; Insulin Resistance Markers.

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INTRODUCTION

Trace elements (iron, copper and zinc), needed in minute quantities, encompass minerals essential for normal human development and functioning of the body. These are known to be limited in the diet, particularly of the socioeconomically weaker and physiologically vulnerable sections of the population in developing countries. There is an increased requirement for these nutrients in normal pregnancy, not only due to increased demand, but also increased loss. Similarly, GDM is associated with excessive nutrient losses which might be due to glucosuria [1]. Therefore, an inadequate supply of these micronutrients will compromise the health and growth of both mother and conceptus, which can be detrimental to the fetus [2].

During the first two trimesters of pregnancy, iron-deficiency anemia increases the risk for preterm labor, low-birth weight babies and infant mortality and predicts iron deficiency in infants after 4 months of age [3]. Many authors suggested that the iron overload can lead to ß-cell toxicity and dysfunction as well as impaired glucose metabolism [4]. Increased accumulation of iron affects insulin synthesis and secretion in the pancreas and interferes with the insulin-extracting capacity of the liver so that hepatic gluconeogenesis suppression might be implicated [5]. Also, excess iron deposition in the muscle might decrease glucose uptake [4]. In addition, iron may also impair insulin action and may interfere with the glucose uptake in adipocytes [6]. Iron has a role in diabetes development via three mechanisms: decreased insulin production, increased resistance to insulin and causing liver dysfunction [7].

Copper is an essential micronutrient required for the formation of many enzymes, with important role in the human body [8]. Copper is involved in the function of several cuproenzymes, such as Ceruloplasmin [9],

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that catalyses the conversion of ferric ion to the ferrous form, favoring the absorption of iron from the gastro-intestinal tract. It also plays a role in the mobilization of iron to plasma from the tissue stores [10]. Copper has an important role in pregnancy for the formation of a wide variety of enzymatic and other processes within the developing fetus. During pregnancy, many changes occur in copper levels and transport in both mother and fetus [8]. Copper deficiency; during embryonic and fetal development; results in numerous gross structural and biochemical abnormalities [11].

Zinc is an important trace element necessary for metabolic regulation of cellular growth and cell differentiation [12]. High prevalence of zinc deficiency is evident in regions with a high consumption of plant-based diets and limited access to rich food such as animal, oysters and other shellfish [13]. Zinc deficiency in pregnancy results in complications, ranging from infertility and fetal death to intrauterine growth retardation, and include preterm birth and other anomalies [14]. Moreover, potential postnatal complications are possible, such as neurobehavioral abnormality and impaired immunocompetence. It is suggested that GDM is closely related to an unbalanced zinc trace element [15]. Zinc is an important component of the body's antioxidant system, such as catalase and superoxide dismutase, which retards the oxidative process particularly related to diabetes mellitus [16].

The aim of this study was to assess iron, copper and zinc status in normal pregnancy and in gestational diabetes mellitus compared to non-pregnant women. The correlations between levels of the studied micronutrient and markers of insulin resistance parameters were also investigated.

MATERIALS & METHODS

This study was approved by Directorate of Health Affairs, Jeddah, Saudi Arabia. Blood samples were collected from Maternity and Children's Hospital, Al-Mesadiah and from King Abdulaziz University Hospital, Obstetrics and Gynecology Clinic. Each participant signed an informed consent. All pregnant women complicated with Gestational diabetes mellitus (GDM) were requested to perform oral glucose tolerance test using 75 g % glucose solution. GDM was diagnosed according to World Health Organization.

I. **Subjects:** The study included 133 subjects, divided into three groups: healthy non-pregnant women group (n = 44), normal pregnant women group (n = 47) and GA 13 – 38 weeks) and GDM group (n = 42). All subjects had no history of diabetes; type 1 or type2. All pregnant women, either normoglycemic or GDM, had a regular follow up visits and were diagnosed by hospital physicians. All pregnant women were supplemented with 15 mg/day iron and 100 mg/day calcium. Body mass index (BMI) was calculated at sampling time (BMI= weight/height2, kg/m2). The exclusion criteria for pregnant volunteers were: presence of hypertension, preeclampsia, urinary tract infection, fever (>37.5°C), fetal/placental abnormalities, remarkable previous medical - surgical- and gynecological maternal history, and alcohol intake. GDM women included in the study were treated with nutrition therapy except four cases were treated with insulin therapy.

II. **Methods:** Each participant was subjected to a single withdrawal of blood sample after overnight fasting. Sera were used for determination of:

A. Fasting blood glucose (FBG) was carried out using glucose hexokinase method, and a kit provided by Siemens Healthcare Diagnostic Limited, Germany (Cat. # K1039).

B. Markers of insulin resistance (IR): Including
   1. Fasting serum insulin (FI) was determined using a kit provided by Bio-Inteco Diagnostic limited, UK (Cat. # 10801), based on a solid phase enzyme-linked immunosorbent assay technique.
   2. Calculation of glucose/insulin ratio (G/I), fasting insulin resistance index (FIRI), homeostasis model assessment (HOMA), HOMA-IR, Log (HOMA-IR) and HOMA1 - %B were performed as described by Singh & Saxena (2010).

C. Serum iron (Fe) and related markers: Fe was determined by flam atomic absorption technique (Savant AA, GBC Scientific Equipment). Serum ferritin was determined using a kit provided by Chemux Bio Science Incorporation, USA (cat. # 10601), based on a solid phase enzyme-linked immunosorbent assay technique. Serum total iron binding capacity (TIBC) was determined using a kit provided by CE, USA (Cat. # 0370), based on colorimetric method.

D. Serum copper (Cu) and related markers: Cu was determined by flam atomic absorption technique. Serum ceruloplasmin was determined using a kit provided by the Binding Site Ltd, Birmingham, UK (Cat. # RN045.3), based on radial immunodiffusion.

E. Serum zinc (Zn) was determined by flam atomic absorption technique.

III. **Statistical analysis:** Statistical analysis was performed using SPSS 22.0 for windows (SPSS Inc, USA). Descriptive statistics were shown as means ± standard error of means and percentages to describe the continuous data. Cohen's d test was used to estimate the effect of size that describe the proportion of total variability attributable to a variable. One-way ANOVA was performed for comparing more than two groups, using Bonferroni test as a post hoc test to compare the means of two groups. Independent-samples T test (t) was performed for comparing means GA & MA for pregnancy and GDM Groups. Pearson

correlation was used to measure the relationships between parameters. P value smaller than 0.05 was considered statistically significant.

RESULTS

I. Subjects' Characteristics: Both normoglycemic and GDM groups were matched for GA & BMI, however the mean value of MA in GDM was significantly higher than non-pregnant and normal pregnant groups (Table 1).

II. Fasting blood glucose and markers of insulin resistance: In relation to non-pregnant woman group, normal pregnant woman group had matched FBG, FI and markers of insulin resistance. On the other hand, pregnancies complicated with GDM had higher FBG, FI, FIRI, HOMA-IR and log HOMA-IR compared to non-pregnant group. It is worth noting to point out to the existence of significantly higher FBG mean value in GDM compared to normoglycemic pregnant group, but other IR markers showed no statistical differences (Table 2).

III. Serum iron, copper and zinc statuses: Significantly, lower mean value for Fe in GDM compared to both non-pregnant and normoglycemic pregnant groups were noted in the current study. Opposite trend was obtained for TIBC mean value, where elevated TIBC was detected in pregnancy complicated with GDM compared to other studied groups. No significant change in ferritin mean values were noted between the studied groups. The present study indicated pronounced elevation in Cu and ceruloplasmin in pregnant groups; either normal pregnancy or GDM; compared to non-pregnant women. In relation to normal pregnancy, pregnancy complicated with GDM had higher serum copper and lower ceruloplasmin mean values. Furthermore, the current work indicated decreased serum Zn in pregnancy compared to non-pregnant, although it was not significant with GDM group (Table 3).

IV. Pearson correlations: correlations studies between all markers in non-pregnant, normal pregnancy and GDM are listed in Table 4.

V.

Table 1. Subject characteristics in non- pregnant, normal pregnancy and GDM groups ($\bar{x}$± SE).

Parameters \ Groups	Non -pregnant n=44	Normal pregnancy n=47	GDM n=42
MA (years) P* P**	27.75 ± 0.71 —	29.57 ± 0.78 N.S —	33.48 ± 0.83 0.001 0.001
GA (weeks) P* P**	—	26.98 ± 0.95 --- —	28.45 ± 1.03 --- N.S
BMI (kg/m²) P* P**	.2358 ± 0.65 —	28.42 ± 0.62 — —	.2953 ± 0.76 — N.S

MA: maternal age, GA: gestational age and BMI: body mass index.
P*: P value vs. non pregnant group, P**: P value vs. normal pregnancy group.

Table 2. Fasting blood glucose and markers of insulin resistance in non-pregnant, normal pregnancy and GDM groups ($\bar{x}$± SE).

Parameters \ Groups	Non-pregnant n=44	Normal pregnancy n=47	GDM n=42
FBG (mmol/L) P* P**	4.69 ± 0.08 —	4.55 ± 0.10 N.S —	5.53±0.28 0.001 0.001
FI (µU/ml) P* P**	8.74 ± 0.62 —	17.40 ± 2.92 N.S —	20.29 ± 3.88 0.001 N.S
G/I P* P**	0.62 ± 0.03 —	0.49 ± 0.04 0.05 —	0.53 ± 0.05 N.S N.S
FIRI P* P**	1.69 ± 0.12 —	2.97 ± 0.48 N.S —	4.73 ± 0.91 0.001 N.S
HOMA–IR P* P**	1.88 ± 0.13 —	3.29 ± 0.53 N.S —	5.26 ± 1.01 0.001 N.S
Log HOMA-IR P* P**	0.21 ± 0.02 —	0.36 ± 0.04 N.S —	0.48 ± 0.07 0.001 N.S
HOMA1- %B P* P**	178.25 ± 24.02 —	201.73 ± 95.46 N.S —	256.88 ± 53.01 N.S N.S

FBG: fasting blood glucose, FI: fasting insulin, G/I: glucose/insulin ratio, FIRI: fasting insulin resistance index, HOMA-IR: homeostasis model assessment-insulin resistance. P*: P value vs. non-pregnant group, P**: P value vs. normal pregnancy group.

Table 3: Iron and copper statuses and serum zinc in non-pregnant, normal pregnancy and GDM groups ($\bar{x}$± SE).

	Parameters \ Groups	Non - pregnant n=44	Normal pregnancy n=47	GDM n=42
Iron Status	Serum iron (mg/l) P* P**	2.32 ± 0.22 —	1.64 ± 0.16 0.01 —	0.90 ± 0.08 0.001 0.01
	Ferritin (ng/ml) P* P**	21.75 ± 2.44 —	19.68 ± 2.61 N.S —	32.61 ± 15.04 N.S N.S
	TIBC (ug/dl) P* P**	414.64 ±11.20 —	472.53 ± 12.19 0.001 —	507.67 ± 14.82 0.001 N.S
Copper Status	Serum copper (mg/l) P* P**	1.02 ± 0.04 —	1.69 ± 0.05 0.001 —	1.93 ± 0.07 0.001 0.001
	Ceruloplasmin (mg/dl) P* P**	32.30 ± 1.05 —	57.21 ± 1.43 0.001 —	49.43 ± 1.41 0.001 0.001
Zinc	Serum zinc (mg/l) P* P**	0.74 ± 0.04 —	0.59 ± 0.03 0.01 —	0.69 ± 0.03 N.S N.S

TIBC: total iron binding capacity.

P*: P value vs. non-pregnant, P**: P value vs. normal pregnancy.

Table 4. Pearson's correlations between all markers in non-pregnant, normal pregnancy and GDM groups.

Correlations \ Groups		Non-pregnant n=44	Normal pregnancy n=47	GDM n=42
Fe	ferritin	0.32 (0.03)	-0.01 (NS)	0.16 (NS)
	TIBC	-0.45 (0.001)	-0.07 (NS)	-0.18 (NS)
Cu	ceruloplasmin	0.72 (0.001)	0.35 (0.01)	0.01 (NS)
IR markers : FBG	Fe	-0.09 (NS)	-0.09 (NS)	0.13 (NS)
	ferritin	0.073 (NS)	0.01 (NS)	-0.02 (NS)
	Cu	0.11 (NS)	0.15 (NS)	0.22 (NS)
	ceruloplasmin	0.15 (NS)	-0.24 (NS)	-0.08 (NS)
	Zn	0.17 (NS)	0.001 (NS)	0.01 (NS)
FI	Fe	-0.22 (NS)	-0.01 (NS)	-0.04 (NS)
	ferritin	0.01 (NS)	0.013	0.20
	Cu	0.08 (NS)	-0.16 (NS)	0.18 (NS)
	ceruloplasmin	0.13	0.18	0.22
	Zn	0.01 (NS)	-0.14 (NS)	-0.01 (NS)
G/I	Fe	0.13 (NS)	0.16 (NS)	-0.17 (NS)
	ferritin	0.010 (NS)	-0.08 (NS)	-0.02 (NS)
	Cu	-0.06 (NS)	0.19 (NS)	-0.09 (NS)
	ceruloplasmin	-0.09 (NS)	-0.04 (NS)	0.03 (NS)
	Zn	0.09 (NS)	0.25 (NS)	-0.24 (NS)
FIRI	Fe	-0.21 (NS)	-0.04 (NS)	-0.02 (NS)
	ferritin	-0.059 (NS)	-0.02 (NS)	-0.08 (NS)
	Cu	0.09 (NS)	-0.01 (NS)	0.26 (NS)
	ceruloplasmin	0.13 (NS)	-0.07 (NS)	0.03 (NS)
	Zn	0.03 (NS)	-0.18 (NS)	-0.02 (NS)
HOMA-IR	Fe	-0.21 (NS)	-0.04 (NS)	-0.02 (NS)
	ferritin	-0.058 (NS)	-0.02 (NS)	-0.08 (NS)
	Cu	0.09 (NS)	-0.10 (NS)	0.26 (NS)
	ceruloplasmin	0.13 (NS)	-0.07 (NS)	0.03 (NS)
	Zn	0.03 (NS)	-0.18 (NS)	-0.02 (NS)
LogHOMA-IR	Fe	-0.21 (NS)	-0.11 (NS)	0.12 (NS)
	ferritin	0.022 (NS)	0.02 (NS)	-0.03 (NS)
	Cu	0.09 (NS)	-0.12 (NS)	0.22 (NS)
	ceruloplasmin	0.14 (NS)	-0.10 (NS)	0.03 (NS)
	Zn	0.04 (NS)	-0.25 (NS)	0.10 (NS)
HOMA1-%B	Fe	0.10 (NS)	-0.08 (NS)	-.18 (NS)
	ferritin	0.114 (NS)	-0.30	-0.09 (NS)
	Cu	-0.10 (NS)	-0.03 (NS)	0.04 (NS)
	ceruloplasmin	-0.04 (NS)	-0.02 (NS)	0.05 (S)
	Zn	-0.20 (NS)	-0.04 (NS)	0.07 (NS)

FBG: fasting blood glucose, FI: fasting insulin, G/I: glucose/insulin, FIRI: fasting insulin resistance index, HOMA-IR: homeostasis model assessment-insulin resistance, Fe: iron, Cu: copper and TIBC: total iron binding capacity.

P value < 0.05 is significant, P value > 0.05 is non-significant (NS).
Numbers outside parenthesis indicated r value. Numbers inside parenthesis indicated P value.

DISCUSSION

In the present investigation, changes in iron status was noted in normal pregnancy and in GDM compared to non-pregnant control group. Serum iron was significantly lower in normal pregnancy. Further reduction in serum iron was developed in GDM subjects compared to other two groups. Decreased serum iron in pregnancy was associated with significantly elevated TIBC, indicating iron deficiency. The current results are in line with [17]. On the contrary, some authors reported higher serum iron in GDM [18,19], however, others reported no change in GDM compared to normal pregnancy [20]. In pregnancy, increased iron utilization by the developing fetus and placenta, as well as blood volume expansion significantly increases the iron requirement during pregnancy [21]. Inadequate intake of iron related to diets poor in bioavailable iron is thought to be responsible for the majority of deficiency both before and during pregnancy [22].

In this study, ferritin mean values did not show significant variations between the three studied groups, although it was higher in GDM group compared to non-pregnant (~50%) and normal pregnant (65.5%) groups. Higher serum ferritin among GDM subjects was indicated by many authors [18,20,23,24]. Chen et al. [25] reported elevated maternal serum ferritin concentrations associated with a twofold increased GDM risk. Inconsistency between this study and others regarding ferritin could be due to differences in the severity of the enrolled GDM cases in each study. Although serum ferritin is a good indicator of body iron stores under most circumstances [26], however, ferritin is an acute phase reactant protein and its serum concentrations can be elevated; regardless the change in iron stores; by infection or inflammation [26,27]. Therefore, it might be difficult to interpret the concentration of ferritin where infectious diseases are common [28].

In the present study, significant associations between serum iron and each of serum ferritin and TIBC in non-pregnant group were noted. These associations were not detected in normal pregnancy and in GDM, indicating the existence of other factors that might musk or disturb these correlations. It has been reported that the inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-1 induce ferritin synthesis in the experimental models [29]. Thus, serum ferritin may be an unreliable indicator of iron stores when there is infection or inflammation [30,31]. Different studies have shown that pregnancy is a pro-anti-inflammatory state

depending on GA [32], and increased IR is associated with high levels of TNF-α [33,34]. Increased TNF-α in GDM has been reported earlier by many studies [35-37]. The observed higher mean value for maternal serum ferritin in GDM (although it was not significant) compared to other two groups, might be due to the existence of increased inflammation and decreased insulin sensitivity which are known to be associated with pregnancies complicated with GDM.

In the current investigation, maternal iron, ferritin or TIBC showed no associations with FBG or IR markers in GDM. These results might indicate that the changes in iron status might be a consequence of GDM rather than a cause of impending IR. This result was partially supported by Swaminathan et al. [7] who reported that the modest elevation in ferritin levels was not a cause of disturbed IR in type II diabetes.

Our study indicated a tendency towards elevation in serum copper during pregnancy (either normal or complicated with GDM) compared to non-pregnant group, where rise in serum copper by 65.7% and 89.2% in normal pregnancy and in GDM respectively were noted. Elevated serum copper in pregnancy was associated with significantly elevated maternal ceruloplasmin mean values. Alvarez et al. [38] previously reported increased serum copper in early pregnancy which continues to raise reaching levels at full term, approximately twice those found in non-pregnant women. The study carried out by Al-Sarrag et al. [39] revealed that the levels of copper and ceruloplasmin rises from the 6th week onwards, reaching high levels during the third trimester and then it returns to normal, 6 weeks following delivery. Mcardle et al. [40] indicated that maternal age does not influence serum copper levels and the increase in serum copper was parallel with the increased serum ceruloplasmin.

In our study, higher serum copper was detected in GDM compared to normoglycemic control, however, ceruloplasmin was lower in GDM. These results were supported by Wang et al. [41]. The authors reported increased copper level in GDM compared to normoglycemic pregnant women. On the contrary, Loven et al. [42] reported no significant differences in maternal serum copper and ceruloplasmin level between healthy pregnant women and women with GDM, however, the activity of ceruloplasmin in GDM was slightly higher. Moreover, the authors observed significantly increased Cu-Zn supper oxide dismutase activity in GDM. In the current study, strong positive correlation exists between serum copper and ceruloplasmin in non-pregnant and normal pregnancy. This correlation was not detected in pregnancy complicated with GDM.

Ceruloplasmin acts as a ferrioxidase which is able to convert Fe^{+2} to Fe^{+3} and stimulate iron efflux from the liver [43]. During pregnancy, the metabolism of copper and iron are correlated and the deficiency of one has marked effects on the metabolism of the other metal. In the mother, iron deficiency resulted in increased liver copper levels, which is associated with increased both serum copper and ceruloplasmin activity in maternal serum [44,45]. Therefore, the significant increase in serum copper in this study might be due to the imbalance in iron status during pregnancy that alters copper levels; as a result of enhanced gene expression; leading to elevated serum copper in pregnant women [46]. In the current study, although no significant correlations were detected between serum iron and each of serum copper and ceruloplasmin in pregnancy, the present finding of decreased serum iron and increased serum copper and ceruloplasmin in normal pregnancy and in GDM are consistent with previous reports [44,45].

In the present investigation, no significant associations were found between copper status (either serum copper or ceruloplasmin) and each of FBG or markers of IR, indicating that elevated serum copper does not play a role in decreased insulin sensitivity in normal pregnancy or in GDM. Other study detected positive association between serum copper and fasting blood glucose in GDM [47]. The authors concluded that the increased copper in GDM was directly linked to decreased sensitivity. However, the authors did not assess FI levels and they did not examine the association between serum copper and fasting insulin and markers of IR which is more accurate in examining the correlations with IR.

The current study demonstrated decreased maternal serum zinc, both in normal pregnancy and in GDM compared to non-pregnant women group, although the changes were only significant in case of normal pregnancy. Significantly lower serum zinc levels in pregnancy have been reported in different studies [48-50]. Other researches [49,51,52], reported decreased plasma zinc level as pregnancy progresses, which was further supported by Ejezie and Nwagha [50] who established that the plasma zinc level decreased as gestation progressed, with the lowest concentration of serum zinc obtained during the third trimester. Brito et al. [53] reported that during pregnancy, plasma zinc decreased by 20% to 30% from the third month, with decreasing related to the progress of pregnancy. Parallel to the current study [54] did not find a significant difference in plasma zinc

between normal pregnant women and those with GDM, although they obtained decreased plasma zinc in normal pregnancy compared to non-pregnant groups. Inconsistence to our study, they obtained significantly reduced maternal serum zinc in GDM compared to non-pregnant group. In the current study, one possible explanation for the non-significant difference in serum zinc between GDM and normal pregnancy groups might be the degree of severity of GDM cases. Most of the included GDM subjects were under well nutritional control and their FBG, FI and IR markers showed no variation between the two groups.

Goldenberg et al. [55] reported an association between decreased plasma zinc and reduced plasma levels of albumin during pregnancy, therefore, reduced plasma zinc concentrations during pregnancy may be due to the expansion of plasma volume seen in nearly all pregnant women which in turn resulted in low albumin concentration [56]. Reduction of this mineral may be also due to increased urinary excretion [57], or estrogen levels during pregnancy [58]. High levels of corticosteroids are also related to this common reduction especially at the end of a normal pregnancy [59,60]. Altered rate of intestinal absorption, changed dietary habits might also be a reasonable explanation for decreased maternal zinc during this physiological state [61]. Determining red blood cell zinc concentration was recommended by Leung et al. [62] since it is more accurate index to detect cellular deficiency than plasma zinc.

CONCLUSION

Levels of trace elements namely iron, copper and zinc are affected during pregnancy, especial pregnancy complicated with GDM compared to non-pregnant women. Iron status showed trend towards decrease, while copper was increased. On the other hand, maternal serum zinc showed significant reduction in pregnancy although it was not statistically different in GDM. No significant correlations were detected between each of serum iron, ferritin, TIBC, copper, ceruloplasmin and zinc with markers of insulin resistance were detected in all studied groups, indicating that the imbalance in the status of these elements has no effect on the pathogenesis of GDM.

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