Refeeding syndrome describes the metabolic and clinical changes attributed to aggressive rehabilitation of malnourished subjects. The metabolic changes of refeeding are related to hypophosphatemia, hypokalemia, hypomagnesemia, sodium retention and hyperglycemia, and these are believed to be mainly the result of increased insulin secretion following high carbohydrate intake. In the past few decades, increased consumption of processed food (refined cereals, oils, sugar and sweeteners, and so on) lowered the intake of several macrominerals (mainly phosphorus, potassium and magnesium). This seems to have compromised the postprandial status of these macrominerals, in a manner that mimics low grade refeeding syndrome status. At the pathophysiological level, this condition favored the development of the different components of the metabolic syndrome. Thus, it is reasonable to postulate that metabolic syndrome is the result of long term exposure to a mild refeeding syndrome.

MINI REVIEW

Refeeding and metabolic syndromes: two sides of the same coin

OA Obeid, DH Hachem and JJ Ayoub

Refeeding syndrome represents a group of metabolic and clinical changes that occur in severely malnourished patients undergoing aggressive nutritional support. Metabolic changes include: hypophosphatemia, hypokalemia, hypomagnesemia, sodium retention and hyperglycemia. Although clinical changes cover most organ systems, including cardiovascular, gastrointestinal, musculoskeletal, respiratory, neurological and hematological abnormalities, these changes are the outcome of the metabolic changes in a scale that is synergistically related to the degree of the metabolic changes, in which under severe conditions multiple organ failure may occur leading to death. On the other hand, metabolic syndrome is a name for a group of risk factors that occur together, increasing the risk for coronary artery disease, stroke and type 2 diabetes. These factors are: central obesity, high triglycerides, low high-density lipoprotein cholesterol, elevated blood pressure and raised blood glucose. Classification according to the US National Cholesterol Education Program Adult Treatment Panel III requires the presence of at least three of the above factors.

The pathophysiology of refeeding syndrome is related to the fact that under conditions of starvation, the body shifts from carbohydrate to fat and protein utilization (state of catabolism) to produce glucose and energy. Therefore malnutrition, which usually exists in different disease states including cancer, Marasmus/Kwashiorcor, neurological problems, respiratory diseases, gastrointestinal and liver diseases, and so on, is the major risk factor for refeeding syndrome. Upon refeeding, especially with carbohydrate, the body shifts back instantaneously to carbohydrate metabolism (state of anabolism). Concomitantly, insulin secretion is increased leading to an increase in the cellular uptake of glucose and macrominerals (in particular phosphorus, potassium and magnesium) mainly occurring in the liver and muscles, and thus resulting in hypophosphatemia, hypomagnesaemia and hypokalemia. Simultaneously, insulin resistance prevails as indicated by the coexistence of hyperglycemia and hyperinsulinemia which reduces sodium clearance leading to sodium retention and thus resulting in fluid retention and expansion of the extracellular fluid volume. Thus, the clinical manifestations of these macromineral abnormalities have serious deleterious effects, some of which are hypotension, bradycardia, weakness, heart failure and arrhythmias. In brief, refeeding syndrome is the consequence of the ingestion of a high carbohydrate–low macrominers diet following prolonged fasting.

In normal subjects and under normal conditions, energy metabolism is known to fluctuate diurnally, as meal ingestion causes a shift to carbohydrate metabolism and an increase in both energy expenditure and carbohydrate oxidation. Meal ingestion ensues an increase in cellular uptake and utilization of glucose and macrominerals (predominantly phosphorus, potassium and magnesium), as a result of increased insulin secretion and demand for metabolic processes (for example, phosphorylation and so on). Therefore, plasma status of these macrominerals depends on insulin secretion (that is highly dependent on carbohydrate intake) and their meal content of macrominerals. Ingestion of pure glucose is known to be associated with a reduction in plasma concentration of these macrominerals and their inclusion in a meal was reported to improve their status. Thus, it is reasonable to postulate that under normal conditions the postprandial metabolic changes following the ingestion of high carbohydrate–low macrominerals diet resemble those of the refeeding syndrome but to a lower extent. Hence, what remains to be elucidated is whether the dietary changes that have occurred in the past few decades favored the consumption of high carbohydrate–low macrominerals diets and thus have exacerbated these metabolic changes.

Evidence from epidemiological studies reveal that the increased prevalence of the ‘Western diet’ is implicated in the increased prevalence of obesity, diabetes and hypertension, observed in Africa, Asia, South America, Australia/New Zealand and Oceania. Western diet is characterized by the consumption of refined (cereals) carbohydrates, sugars, sweeteners (especially high fructose corn syrup), oils and fats. The implication of the
Western diet has further been proposed to promote the incidence of insulin resistance,11 and metabolic syndrome.12 Furthermore, the increased intake of fructose-based sweeteners has been also reported to be associated with the development of metabolic syndrome and obesity.13 This association was proposed to be related to its capacity to “sequester phosphate”,14 stimulate triglyceride synthesis,13,15,16 and promote insulin resistance.13,17

During the past few decades, the major changes in dietary habits, as have been discussed earlier in this paper, are mainly related to a dramatic increase in the intake of: (1) macronominal (P, K and Mg)-free commodities, such as oils, sugar and sweeteners, which contains negligible amounts of the above macrominerals) and (2) refined cereals commodities, where refinement is known to reduce the content of these macrominerals by about 70%. Cereals are known to contribute to more than 50% of the total energy intake in most countries,18 therefore, the shift from whole grain cereals (whole wheat, brown rice) to refined cereals would be expected to result in substantial reduction in the intake of these macrominerals. A further reduction would be expected from the increased consumption of macrominerals-free commodities. In developed and transitional countries, the consumption of these (above) commodities is known to be inversely related to socioeconomic status, mainly because of their high energy density (kcal g⁻¹ food) and low energy cost (US$per 1000 kcal). This has also been proposed to be an important factor behind the high prevalence of obesity and metabolic syndrome among urban people of low socioeconomic status.19

It is well known that in the past few decades, urbanization has increased in most countries. The changes in the consumption of the different food groups based on the change in gross national product per capita of the country and change in urbanization was studied by Popkin and Gordon-Larsen9 and Drewnowski and Popkin.20 Increased urbanization worldwide was found to be associated with increased consumption of vegetable fats and sugars. At the same time, a direct relationship was reported to be present between urbanization and gross national product per capita and the increase in the consumption of fats and sweeteners. High gross national product per capita was associated with higher consumption of vegetable, animal fats and sugars with a sharp decrease in the consumption of complex carbohydrates.20 Rapid urbanization worldwide has a major influence on accelerating the nutrition transition. It was also reported that an increased production and consumption of sweeteners derived from starch has been observed in the last several decades.21 For example, in the year 2000, the caloric consumption of sweeteners increased by one-third more than in the year 1962. Similarly, in the United States, the daily caloric intake was reported to increase, mainly from energy-dense and nutritiously poor food choices,8,22–27 such as fast food, salty snacks8,22–24 and added caloric sweeteners.8,27,28 In addition to fast food choices lacking essential nutrients,8,25,30 fruit and vegetable consumption was observed to be far lower than the recommended levels.8,21,22

It can therefore be deduced that the high intake of refined carbohydrates, fats and sweeteners accompanied with the low intake of fruits and vegetables, leads to a diet that is deficient or suboptimal in vitamins and minerals (including potassium, phosphorus and magnesium). Thus, the increased prevalence of metabolic syndrome among people consuming high quantities of commodities containing low levels of these macrominerals may implicate these macrominerals in the development of metabolic syndrome, as is the case in its implication in refeeding syndrome. Thus, decreased intake of these macrominerals would be expected to undermine their postprandial concentration, and it is yet to be determined whether such undermining would have any health implications. Such a question can be clarified by looking at the relationship between these macrominerals and the different components of the metabolic syndrome.

PHOSPHORUS AND METABOLIC SYNDROME

Phosphorus is an essential mineral and is known to be involved in several metabolic reactions especially that of glucose and energy metabolism. Hypophosphatemia is known to be associated with insulin resistance and impaired glucose tolerance, and plasma phosphate level was reported to be synergistically related to glucose tolerance and insulin sensitivity.51–33 In the postprandial status, low serum phosphate levels were reported to be associated with elevated blood glucose levels and reduced insulin sensitivity.54 We have recently found that the inclusion of phosphorus in oral glucose load was able to improve insulin sensitivity4 and this may probably relate to its capacity to trap glucose intracellularly as a result of its phosphorylation. In addition, phosphorus seems to be involved in the control of both energy intake and expenditure.35–39 Food intake control is believed to be partially governed by signals related to hepatic postprandial ATP production, which is dependent on adequate sources of phosphorus.35 In line with that, human studies reported an inverse relation between hepatic ATP status and body mass index.36 We have previously reported that the addition of 500 mg phosphorus to different preloads resulted in a substantial reduction in subsequent energy intake.37 The relationship between phosphorus and obesity has been reviewed recently by Obeid,40 and low phosphorus status was hypothesized to be involved in the development of obesity. Moreover, ingestion of phosphorus was reported to increase resting metabolic rate38 and postprandial thermogenesis.39 Thus, it is of no surprise that several authors have found an inverse relation between plasma phosphorus status and the different components of the metabolic syndrome.31–33 Table 1 summarizes the relationship between phosphorus status and the different components of metabolic syndrome as reported by several studies. In brief, the majority of the studies showed an inverse relationship between phosphorus status and adiposity,31,41–49 glycemia,31,32,44–48,50,51 lipid profile,32,47,51 and blood pressure.43,45–49,51–59

MAGNESIUM AND METABOLIC SYNDROME

The role of serum or dietary magnesium, the resultant altered magnesium status and the effect on the development of metabolic syndrome has been reviewed by Belin and He.39 Low magnesium status was found to be associated with the development of hypertension, insulin resistance, impaired glucose tolerance, dyslipidemia and central obesity. A meta-analysis conducted by Kass et al.60 concluded that despite the need for further large randomized trials to support such an association, magnesium supplementation was found to significantly reduce blood pressure. Another clinical review by Gums61 states that hypertension, congestive heart failure, arrhythmias, myocardial infarction and diabetes mellitus are all conditions that might be associated with magnesium deficiency; thus concluding that clinical studies found benefits when magnesium was supplemented in these cases. Similarly, magnesium was reported in another review by Guerrera et al.62 to be possibly effective in lowering the risk of metabolic syndrome and improving the metabolism of both glucose and insulin. In a prospective study by He et al.,63 an inverse association was determined between magnesium intake and the risk of metabolic syndrome and its components in healthy young adults. In a large cohort study on middle-aged and older US female women from the Women’s Health Study,64 a significant inverse association was found between magnesium intake and the prevalence of metabolic syndrome and its components. Similarly, in a nationally representative sample of US adults, the dietary intake of magnesium was found to be inversely related to the prevalence of metabolic syndrome concluding that a diet rich in magnesium may be essential in maintaining a good cardiometabolic health.65 Lima et al.66 reported that serum and intracellular magnesium
| Authors                  | Country             | Study design                  | Biomarkers for phosphorus | Outcomes                          |
|-------------------------|---------------------|-------------------------------|--------------------------|-----------------------------------|
| Çelik and Andiran, 2011  | Turkey              | Cross-sectional (n = 298). Age: 6-12 and 12-16 years | Serum                    | (j) Obese in 6-12 age group (j) Obese in 12-16 age group |
| Farhangi et al., 2011    | Iran                | Cross-sectional (n = 82). 100% F Age: 17-50 years | Serum                    | (j) BMI ND ND (j) IR in 6-12-year-old obese children |
| Holecck et al., 2011     | Poland              | Cross-sectional (n = 77). 100% F Age: 46-57 years | Serum                    | (j) BMI ND ND ND ND |
| Alonso et al, 2010       | United States       | Cohort (n = 13444). Age: 45-64 and 45-84 years | Dietary P from dairy products | (j) BMI (j) SBP and DBP (j) risk for HTN |
| Vyssoulis et al, 2010    | Greece              | Cohort (n = 2600). 100% M Age: 55 ± 11 years | Serum                    | (j) BMI ND ND ND ND |
| Foley et al, 2009        | United Kingdom      | Cohort (n = 3015). Age: 18-30 years. 42.7% M and 57.3% F | Serum                    | (j) BMI (j) SBP (j) DBP (j) TG |
| Lippi et al, 2009        | Italy               | Retrospective study (n = 11228). Age: > 20 years. 42.7% M and 57.3% F | Serum                    | (j) BMI (j) WC (j) SBP and DBP |
| Park et al, 2009         | South Korea         | Cross-sectional (n = 46798). 64.6% M, 35.4% F. Age: above 20 years | Serum                    | (j) BM (j) WC (j) SBP and DBP (j) FBG |
| Elliott et al, 2008      | Japan, China, UK and US Norway | Cross-sectional (n = 4680). Age: 40-59 years. 50.4% M and 49.6% F | Dietary                  | (j) BP ND ND ND ND |
| Gudmundsdottir et al, 2008 | Norway          | Cohort (n = 56). Age: ≈ 42 years. 100% M | Serum                    | (j) BMI (j) BP (j) HDL (j) T |
| Dhingra et al, 2007      | United States; Framingham Study | Prospective study (n = 3368). Age: 44 years. 51% F and 49% M | Serum                    | (j) BMI (j) BP (j) HDL (j) T |
| Haap et al, 2006         | Germany             | Cross-sectional (n = 881). 61% F; 39% M Age: 19-73 years | Serum                    | (j) BMI (j) BP (j) HDL (j) T |
| Kalaitzidis et al, 2005  | Greece              | Cross-sectional (n = 255). 54.5% M, 45.5% F. Age: 48.8 ± 10.5 years | Serum                    | (j) WC (j) SBP and DBP (j) HDL (j) T |
| Hajjar et al, 2003       | United States       | Analysis of data obtained from NHANES-III (n = 17752). Age: ≧ 18 years. 47% M and 53% F | Dietary                  | (j) BP ND ND ND ND |
| Haglín et al, 2001       | Sweden              | Cross-sectional (n = 27252). 43.8% M, 56.2% F. Age: 50.1 ± 10 years | Serum                    | (j) BMI in F (j) SBP and DBP in M (j) TC in F |
| Paula et al, 1998        | Brazil              | Case-control (n = 19). 47% M, 53% F. Age: 25-80 years | Serum                    | (j) SBP in M and F (j) FBG in M |
| Kesteloot et al, 1988    | Belgium             | Cross-sectional (n = 8058). Age: 49 ± 13 years. 51.7% M and 48.3% F | Serum                    | (j) SBP in M and F (j) FBG |

**Table 1.** Results of human studies that investigated the association between serum/dietary phosphorous and components of the metabolic syndrome.
| Authors                  | Country         | Study design          | Biomarkers for phosphorus | Metabolic syndrome | Outcomes                      | Lipid profile | Blood glucose |
|-------------------------|-----------------|-----------------------|--------------------------|--------------------|-------------------------------|----------------|---------------|
| Kjeldsen et al.          | Oslo            | Cross sectional       | Serum, ND                | ND                 | ND                            | ND             | ND            |
| Harlan et al.            | United States   | Longitudinal data     | Serum, ND                | ND                 | ND                            | ND             | ND            |
| Daniels et al.           | Albany          | Retrospective         | Serum, ND                | ND                 | ND                            | ND             | ND            |
| Ljunghall et al.         | Sweden          | Cross sectional       | Serum, ND                | ND                 | ND                            | ND             | ND            |

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC/HDL-C, total cholesterol to HDL cholesterol ratio; WC, waist circumference. Positive relation; inverse relation; no relation.

Table 1. (Continued)

Deficiency is common in obese patients with metabolic syndrome and is common in non-white patients suffering from insulin resistance. Similarly, Corica et al. found that hypomagnesemia is highly prevalent in a sample of diabetic patients from Italy. Serum magnesium levels were also found to be low in patients with low high-density lipoprotein-C, high triglyceride values, elevated blood pressure and elevated waist circumference in this study population. Serum magnesium levels have been also reported to be inversely related to glycated hemoglobin levels and be directly related to glucose disposal in diabetic subjects upon glucose injection. Another study by Zofkova et al. reports further that acute hypermagnesemia reduces glucose tolerance during oral glucose tolerance test. Magnesium supplementation of a meal was also reported to increase postprandial magnesium levels and to improve hyperlipidemia in healthy subjects. Table 2 summarizes the relationship between magnesium status and the different components of metabolic syndrome as reported by several studies. In brief, the majority of the studies showed an inverse relationship between magnesium status and adiposity, glycemia, lipid profile and blood pressure.

**POTASSIUM AND METABOLIC SYNDROME**

One of the most pronounced effects of consuming increased potassium intake is its inverse relationship with blood pressure and cardiovascular diseases as reviewed by He and MacGregor. In line with that, a strong relationship was also determined between thiazide-induced hypokalemia and glucose intolerance in thiazide-treated subjects. One other effect is related to the involvement of potassium in glucose metabolism, in which potassium depletion resulting from a low potassium diet impairs insulin secretion, which in turn induces glucose intolerance. Similarly, another study by Dluhy et al. found that the potassium ion is involved in regulating or augmenting the secretion of insulin in humans. Resnick et al. further confirmed that potassium deficiency is a common feature involved in essential hypertension as well as in type 2 diabetes. Low potassium intake was also reported to be significantly associated with elevated systolic blood pressure and diastolic blood pressure in hypertensive Japanese patients and with the prevalence of metabolic syndrome in Japanese women. Potassium supplementation was found to attenuate salt-induced high blood pressure and to improve salt-induced insulin resistance in hypertensive patients and animals. In parallel with these findings, the DASH diet has been considered to lower lipid-induced oxidative stress in obese individuals and to decrease blood pressure and fasting blood glucose in hypertensive patients related to the diet’s composition of fruits and vegetables, which are rich sources of potassium. On the basis of these findings, Fujita concluded that salt restriction along with a diet rich in potassium food sources (fruits and vegetables) is the first-line therapy for treating patients with metabolic syndrome; when combined together with physical activity, further improvement in insulin resistance and salt-sensitive hypertension can be achieved. Lee et al. further explained that higher dietary potassium intake was found to be associated with a reduced risk of insulin resistance and metabolic syndrome among Korean women. Table 3 summarizes the relationship between potassium status and the different components of metabolic syndrome as reported by several studies. In brief, the majority of the studies showed an inverse relationship between phosphorus status and adiposity, glycemia, lipid profile and blood pressure. In summary, the above macrominerals have the metabolic and the mechanistic bases to be involved in the different components of metabolic syndrome, especially that of insulin sensitivity. Such metabolic bases are supported by evidence that show a link between the status of these macrominerals and the different
| Authors                         | Country   | Study design          | Biomarkers for magnesium | Outcomes                                                      |
|--------------------------------|-----------|-----------------------|--------------------------|---------------------------------------------------------------|
| Lima et al., 2009<sup>66</sup> | Brazil    | Cross-sectional (n = 72). Age: 18–54 years | Serum                    | (↑) BMI (↑) WC in F (↑) SBP (↑) HDL (↑) HOMA-IR (↑) MS |
| Kishimoto et al., 2010<sup>70</sup> | Tokyo     | Case-control (n = 16) 100% M. Age: 41.7 ± 2.6 years | Dietary, Supplementation | ND ND ND (↑) TG ND ND |
| Corica et al., 2006<sup>67</sup> | Italy     | Cross-sectional (n = 290). 51.7% M and 48.3% F. Age: 63.1 ± 10.4 years | Serum                    | (↑) WC (↑) BP (↑) HDL (↑) HbA1C ND |
| Ford et al., 2007<sup>65</sup>  | United States | Cross-sectional (NHANES-III) (n = 7669). Age: ≥ 20 years | Dietary                  | (↑) BMI (↑) WC (↑) BP (↑) HDL |
| He et al., 2006<sup>63</sup>    | United States | Prospective (n = 4637). 46.2% M and 53.8% F. Age: 18–30 years | Dietary                  | (↑) WC in White M&F (↑) SBP and DBP in White M&F (↑) HDL in Blacks and Whites (↑) TG in Black M&F (↑) FBG in White M&F (↑) MS |
| Song et al., 2005<sup>64</sup>  | Boston    | Cross-sectional (n = 11 686)100% F. Age: above 45 years | Dietary                  | (↑) WC (↑) BM (↑) BMI (↑) BP (↑) HDL |
| Witteman et al., 1994<sup>71</sup> | Belgium   | Case-control (n = 91)100% F. Age: ≥ 57 years | Magnesium supplementation Serum | (↑) WC (↑) BM (↑) BMI (↑) BP (↑) HDL |
| Yajnik et al., 1984<sup>68</sup> | Britain   | Cross-sectional (n = 117). 78% M and 22% F. Age: ≥ 50 years | Serum                    | ND ND ND (↑) HbA1c |
| Zofkova et al., 1980<sup>69</sup> | Prague    | Case-control (n = 14). 93% F and 7% M. Age: 20–38 years | Serum                    | ND ND ND (↑) Glucose tolerance ND |

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; f, female; FBG, fasting blood glucose; HDL, high-density lipoprotein; HTN, hypertension; IR, insulin resistance; LDL, low-density lipoprotein; M, male; MS, metabolic syndrome; ND, not determined; SBP, systolic blood pressure; WC, waist circumference; TG, triglycerides; (↑) positive relation; (↓) inverse relation; (↔) no relation.
Moreover, the inverse relationship between dietary habits, favoring the Western diet, and the increasing epidemic of obesity and its health-related diseases has been studied extensively in the literature, through proposing and testing different dietary interventions that focused mainly on whole grains were highly ascribed to their contents of these macrominerals, as added cereal fiber by their richness in these macrominerals, as added cereal fiber, which highlight the importance of these minerals’ involvement in metabolic syndrome and its components. These macrominerals are essential for the metabolism of macronutrients (mainly carbohydrates) and thus call for research to further clarify the link or the role of these macrominerals in metabolic syndrome and its components, especially given evidence suggesting a protective effect on macrominerals in metabolic syndrome and its abnormalities. Moreover, evidence suggests that the global increase in intake of fats, processed food and sugars that are calorically dense and nutritiously poor, lacking phosphorus, potassium and magnesium, may explain the postprandial status of these macrominerals in blood. Knowing that macrominerals are essential for the metabolism of macronutrients (mainly carbohydrates) renders the importance of these minerals’ involvement in the development of metabolic syndrome. Metabolically, such a compromise seems to induce several metabolic conditions that favor the development of the different components of the metabolic syndrome, starting from the sustenance of a mild refeeding syndrome and thereby, resemble that of refeeding syndrome. The resemblance in the metabolic basis between metabolic and refeeding syndromes demands the use of a common approach for their management, necessitating boosting the status of these macrominerals in the diet, as added cereal fiber failed to induce such an effect and was proposed to be a marker of other components of whole grains that impart health advantages. Thus, it is plausible to assume that the benefits of whole grains were highly ascribed to their contents of these macrominerals (the other components) rather than to their fiber content.

In conclusion, the proper treatment or management for the increasing epidemic of obesity and its health-related diseases has been studied extensively in the literature, through proposing and testing different dietary interventions that focused mainly on macronutrients. However, these types of interventions seem to have a limited rate of success, especially with the global change in dietary habits, favoring the Western diet, and the increasing prevalence of obesity in developing as well as in developed countries. For this reason, attention should be given to the role of macrominerals that are involved in carbohydrate metabolism and thus call for research to further clarify the link or the role of these macrominerals in metabolic syndrome and its components, especially given evidence suggesting a protective effect on macrominerals in metabolic syndrome and its components. Moreover, evidence suggests that the global increase in intake of fats, processed food and sugars that are calorically dense and nutritiously poor, lacking phosphorus, potassium and magnesium, may explain the postprandial status of these macrominerals in blood. Knowing that macrominerals are essential for the metabolism of macronutrients (mainly carbohydrates) renders the importance of these minerals’ involvement in the development of metabolic syndrome. Metabolically, such a compromise seems to induce several metabolic conditions that favor the development of the different components of the metabolic syndrome, starting from the sustenance of a mild refeeding syndrome and thereby, resemble that of refeeding syndrome. The resemblance in the metabolic basis between metabolic and refeeding syndromes demands the use of a common approach for their management, necessitating boosting the status of these macrominerals in the diet, as added cereal fiber failed to induce such an effect and was proposed to be a marker of other components of whole grains that impart health advantages. Thus, it is plausible to assume that the benefits of whole grains were highly ascribed to their contents of these macrominerals (the other components) rather than to their fiber content.

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![Figure 1. Common link between metabolic syndrome and refeeding syndrome.](image-url)
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