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MINI REVIEW

Refeeding and metabolic syndromes: two sides of the same coin

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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.

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Refeeding syndrome represents a group of metabolic and clinical changes that occur in severely malnourished patients undergoing aggressive nutritional support.[1] Metabolic changes include: hypophosphatemia, hypokalemia, hypomagnesemia, sodium retention and hyperglycemia.[2] 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.[1] 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.[3] Classification according to the US National Cholesterol Education Program Adult Treatment Panel III requires the presence of at least three of the above factors.[3]

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.[2] Therefore malnutrition, which usually exists in different disease states including cancer, Marasmus/Kwashiorkor, neurological problems, respiratory diseases, gastrointestinal and liver diseases, and so on,[2,4] is the major risk factor for refeeding syndrome.[2,4] Upon refeeding, especially with carbohydrate, the body shifts back instantaneously to carbohydrate metabolism (state of anabolism).[2] 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.[2] Simultaneously, insulin resistance prevails as indicated by the coexistence of hyperglycemiam and hyperinsulinemia,[1,2,4] which reduces sodium clearance leading to sodium retention and thus resulting in fluid retention and expansion of the extracellular fluid volume.[1,2] Thus, the clinical manifestations of these macromineral abnormalities have serious deleterious effects, some of which are hypotension, bradycardia, weakness, heart failure and arrhythmias.[4] In brief, refeeding syndrome is the consequence of the ingestion of a high carbodydrate–low macrominerals 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.[5] 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 marominerals. 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.[6] 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.[7–10] Western diet is characterized by the consumption of refined (cereals) carbohydrates, sugars, sweeteners (especially high fructose corn syrup), oils and fats.[7,8] The implication of the

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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) macromineral (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–Larsen[9] 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 snacks[8,22–24] and added caloric sweeteners.[8,21,28] In addition to fast food choices lacking essential nutrients,[8,29,30] 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.[31–33] In the postprandial status, low serum phosphate levels were reported to be associated with elevated blood glucose levels and reduced insulin sensitivity.[34] We have recently found that the inclusion of phosphorus in oral glucose load was able to improve insulin sensitivity[6] 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 relation 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 rate[38] 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 Gums[61] 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

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*	*Outcomes*				
				Obesity	*BP*	*Lipid profile*	*Blood glucose*	*Metabolic syndrome*
Çelik and Andiran, 2011[41]	Turkey	Cross-sectional ($n=298$). Age: 6–12 and 12–16 years	Serum	(↓) Obese in 6–12 age group (∼) Obese in 12–16 age group	ND	ND	(↓) IR in 6–12-year old obese children	ND
Farhangi *et al.*, 2011[50]	Iran	Cross-sectional ($n=82$). 100% F Age: 17–50 years	Serum	(∼) BMI	ND	(∼) TC (∼) TG (∼) LDL (∼) HDL	(↓) FBG	ND
Holecki *et al.*, 2011[42]	Poland	Cross-sectional ($n=77$). 100% F. Age: 46–57 years	Serum	(↓) BMI	ND	ND	ND	ND
Alonso *et al.*, 2010[43]	United States	Cohort ($n=13\,444$). Age: 45–64 and 45–84 years	Dietary (P from dairy products)	(↓) BMI	(↓) SBP and DBP (↓) risk for HTN	ND	ND	ND
Vyssoulis *et al.*, 2010[52]	Greece	Cohort ($n=2600$). 100% M. Age: 55 ± 11 years	Serum	ND	(↓) HTN	ND	ND	(↓) MS
Foley *et al.*, 2009[44]	United Kingdom	Cohort ($n=3015$). Age: 18–30 years. 42.7% M and 57.3% F	Serum	(↓) BMI	(↓) SBP (↑) DBP	(↑) TG (↑) HDL (↓) LDL	(↓) FBG	ND
Lippi *et al.*, 2009[32]	Italy	Retrospective study ($n=11\,228$). Age: >20 years. 42.7% M and 57.3% F	Serum	ND	ND	(↓)TG (↓) TC (↓) LDL (↑) HDL (↓) TC/HDL-C	(↓) FBG	ND
Park *et al.*, 2009[45]	South Korea	Cross-sectional ($n=46\,798$). 64.6% M, 35.4% F. Age: above 20 years	Serum	(↓) BMI(↓) WC	(↓) SBP and DBP	(↑) TC (↑) LDL (↑) HDL (↑) Lp a (↓) TG	(↓) FBG (↓) Insulin (↓) HOMA-IR	(↓) MS
Elliott *et al.*, 2008[53]	Japan, China, UK and US	Cross-sectional ($n=4680$). Age: 40–59 years. 50.4% M and 49.6% F	Dietary	ND	(↓) BP	ND	ND	ND
Gudmundsdottir *et al.*, 2008[51]	Norway	Cohort ($n=56$). Age: ≈42 years. 100% M	Serum	(∼) BMI (∼) WC	(↓) BP (↓) HTN	(↑) HDL (↓) TG	(↓) HOMA-IR in men (↓) Insulin in men (↓) BG in men	(↓) MS
Dhingra *et al.*, 2007[46]	United States; Framingham Study	Prospective study ($n=3368$). Age: 44 years. 51% F and 49% M	Serum	(↓) BMI	(↓) SBP (↓) DBP (↓) HTN	(∼) TC/HDL-C ratio (∼) TG	(↓) Diabetes	ND
Haap *et al.*, 2006[33]	Germany	Cross-sectional ($n=881$) 61% F, 39% M Age: 19–73 years	Serum	(↓) BMI	ND	ND	(↓) 2-h blood glucose (↑) IS	ND
Kalaitzidis *et al.*, 2005[47]	Greece	Cross-sectional ($n=255$). 54.5% M, 45.5% F. Age: 48.8 ± 10.5 years	Serum	(↓) WC	(↓) SBP and DBP	(↑) HDL (↓) TG	(↓) FBG (↓) HOMA and Insulin	(↓) MS (dietary and serum phosphorus)
Hajjar *et al.*, 2003[54]	United States	Analysis of data obtained from NHANES-III ($n=17\,752$). Age: ⩾18 years. 47% M and 53% F	Dietary	ND	(↓) BP	ND	ND	ND
Haglin *et al.*, 2001[48]	Sweden	Cross-sectional ($n=2752$). 43.8% M, 56.2% F. Age: 50.1 ± 10 years	Serum	(↓) BMI in F (∼) BMI in M	(↓) SBP and DBP in M (∼) SBP and DBP iin F	(↑) TC in F (∼) TC in M (∼) HDL (∼) TG	(↓) FBG in M (∼) FBG in F	ND
Paula *et al.*, 1998[86]	Brazil	Case–control ($n=19$). 47% M, 53% F. Age: 25–50 years	Serum	ND	ND	ND	(↓) hyperinsulinemia (↑) IS	ND
Kesteloot *et al.*, 1988[55]	Belgium	Cross-sectional ($n=8058$). Age: 49 ± 13 years. 51.7% M and 48.3% F	Serum	ND	(↓) SBP in M and F (∼) DBP	ND	ND	ND

Table 1. (Continued)

Authors	Country	Study design	Biomarkers for phosphorus	Outcomes				
				Obesity	*BP*	*Lipid profile*	*Blood glucose*	*Metabolic syndrome*
Kjeldsen *et al.*, 1988[56]	Oslo	Cross sectional ($n = 79$). Age: 40 years. 100% M	Serum	ND	(↓) BP	ND	ND	ND
Harlan *et al.*, 1984[57]	United States	Longitudinal data obtained from NHANES-I ($n = 20\,749$). Age: 1–74 years	Dietary and Serum	ND	(↓) BP	ND	ND	ND
Daniels *et al.*, 1983[58]	Albany	Retrospective ($n = 120$). Age: 55 ± 2 years. 30% M and 70% F	Serum	ND	(↓) BP	ND	ND	ND
Havlik *et al.*, 1980[59]	United States; Framingham	Cohort ($n = 5430$) Age: 20–56 years. 53% F and 47% M	Serum	ND	(↓) BP	ND	ND	ND
Ljunghall *et al.*, 1976[49]	Sweden	Cross sectional ($n = 1768$). Age: 49–50 years. 100% M	Serum	(↓) Body weight	(↓) BP	ND	ND	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; IS, insulin sensitivity; LDL, low-density lipoprotein; Lp a, lipoprotein a; M, male; ND, not determined; SBP, systolic blood pressure; TG, triglycerides; TC/HDL-C, total cholesterol to HDL cholesterol ratio; WC, waist circumference; (↑) positive relation; (↓) inverse relation; (∼) no relation.

deficiency is common in obese patients with metabolic syndrome and is common in non-white patients suffering from insulin resistance. Similarly, Corica *et al.*[67] 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.[67] 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.[68] Another study by Zofkova *et al.*[69] 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.[70] 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,[64–67] glycemia,[63–68] lipid profile[63,65,67,70] and blood pressure.[63,64,66,67,71]

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.[72] 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.[73] Similarly, another study by Dluhy *et al.*[74] found that the potassium ion is involved in regulating or augmenting the secretion of insulin in humans. Resnick *et al.*[75] 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.[76] Potassium supplementation was found to attenuate salt-induced high blood pressure[77,78] and to improve salt-induced insulin resistance[79] in hypertensive patients and animals.[80] 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[80,81] related to the diet's composition of fruits and vegetables, which are rich sources of potassium.[80] On the basis of these findings, Fujita[80] 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.*[82] 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,[82] glycemia,[73,75,82] lipid profile[82] and blood pressure.[75,76,82]

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

Table 2. Results of human studies that investigated the association between serum/dietary magnesium and components of the metabolic syndrome

Authors	*Country*	*Study design*	*Biomarkers for magnesium*	*Outcomes*				
				Obesity	*BP*	*Lipid profile*	*Blood glucose*	*MS*
Lima *et al.*, 2009[66]	Brazil	Cross-sectional ($n=72$). Age: 18–54 years	Serum	(↓) BMI (↓) WC in F	(↓) SBP	(↑) HDL (∼) TG	(↓) HOMA-IR	(↓) MS
Kishimoto *et al.*, 2010[70]	Tokyo	Case–control ($n=16$) 100% M. Age: 41.7 ± 2.6 years	Dietary, Supplementation	ND	ND	(↓) TG (↓) Postprandial lipidemia	ND	ND
Corica *et al.*, 2006[67]	Italy	Cross-sectional ($n=290$). 51.7% M and 48.3% F. Age: 63.1 ± 10.4 years	Serum	(↓) WC	(↓) BP	(↑) HDL (↓) TG	(↓) HbA1C (↓) Diabetes	ND
Ford *et al.*, 2007[65]	United States	Cross-sectional (NHANES-III) ($n=7669$). Age: ⩾20 years	Dietary	(↓) BMI(↓) WC	(∼) BP	(↓) LDL (∼) TG	(↓) Insulin (↓) BG	(↓) MS
He *et al.*, 2006[63]	United States	Prospective ($n=4637$). 46.2% M and 53.8% F. Age: 18–30 years	Dietary	(↓) WC in White M&F (∼) WC in Black M&F (∼) BMI in Blacks and Whites	(↓) SBP and DBP in White M&F (∼) SBP and DBP in Black M&F	(↓) HDL in Blacks and Whites (↓) TG in White M&F (∼) TG in Black M&F	(↓) FBG in Black M&F (∼) FBG in White M&F	(↓) MS
Song *et al.*, 2005[64]	Boston	Cross-sectional ($n=11\,686$)100% F. Age: above 45 years	Dietary	(↓) WC (↓) BMI	(↓) BP	(↓) HDL (∼) TG	(↓) BG	(↓) MS
Witteman *et al.*, 1994[71]	Belgium	Case–control ($n=91$)100% F. Age: ≈57 years	Magnesium supplementation	(∼) Body weight	(↓) SBP(↓) DBP	(∼) TC (∼) HDL	ND	ND
Yajnik, *et al.*, 1984[68]	Britain	Cross-sectional ($n=117$). 78% M and 22% F. Age≈50 years	Serum	ND	ND	ND	(↓) HbA1c (↑) Glucose disposal	ND
Zofkova *et al.*, 1980[69]	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.

Table 3. Results of human studies that investigated the association between serum/dietary potassium and components of the metabolic syndrome

Authors	*Country*	*Study design*	*Biomarkers for potassium*	*Outcomes*				
				Obesity	*BP*	*Lipid profile*	*Blood glucose*	*MS*
Lee *et al.*, 2013[82]	Korea	Data obtained from the Korean National health and Nutritional Examination ($n=16\,637$). 40.5% M and 59.5% F. Age: 44 ± 0.25 years	Dietary	(↓) BMI in F	(↓) HTN in F	(↓) TG in F (↓) HDL in F	(↓) IR in F (↓) glucose in F (↓) diabetes in F	(↓) MS in F
Teramoto *et al.*, 2011[76]	Japan	Prospective, large-scale observational study ($n=$ 9585). 48.6% M and 51.4% F. Age: 50–79 years	Dietary	ND	(↓) SBP (↓) DBP	ND	ND	(↓) MS in F (∼) MS in M
Resnick *et al.*, 2001[75]	New York	Cross-sectional ($n=42$). 38% M and 62% F. Age 54–68 years	Serum	ND	(↓) SBP and DBP (↓) HTN	ND	(↓) Diabetes	ND
Rowe *et al.*, 1980[73]	United States, Boston	Case–control ($n=7$) 100% M. Age 20–31 years	Dietary	ND	ND	ND	(↓) Glucose intolerance (↓) impaired insulin secretion	ND
Dluhy *et al.*, 1972[74]	United States, Boston	Case–control ($n=10$). 80% M and 20% F. Age	Dietary and serum	ND	ND	ND	(↓) Insulin secretion	ND

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; F, female; HDL, high-density lipoprtotein; HTN, hypertension; IR, insulin resistance; M, male; MS, metabolic syndrome; ND, not determined; SBP, systolic blood pressure; TG, triglycerides(↑) positive relation; (↓) inverse relation; (∼) no relation.

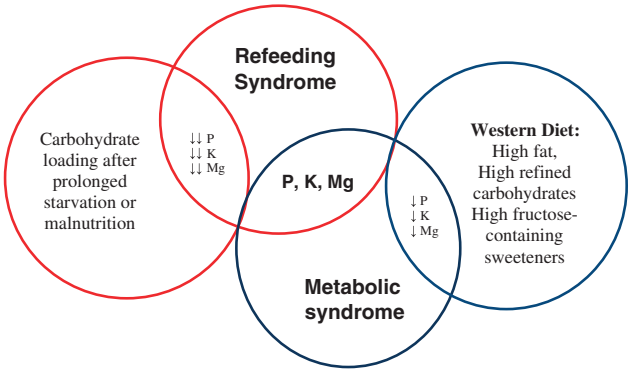

Figure 1. Common link between metabolic syndrome and refeeding syndrome.

metabolic abnormalities associated with metabolic syndrome. In addition, these associations may contribute to the understanding of several experimental observations. For example, their high content in dairy products may have contributed to the observed inverse association between dairy product intake and metabolic syndrome,[12] especially given that calcium failed to explain such association.[83] Moreover, the inverse relationship between increased intake of whole grains and the risk of the different components of metabolic syndrome[84] may be partially explained by their richness in these macrominerals, 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.[85] 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 of protein and dairy (rich in phosphorus)[12] and fruit and vegetable (rich in magnesium and potassium)[62,80] consumption on 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, appear to compromise 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 with the state of insulin resistance observed in both syndromes (Figure 1). The pathophysiology of these metabolic conditions appears to stem from an alteration in insulin status 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, especially stable food. This may perhaps be accomplished by the restoration or fortification of white flour and/or the establishment of a carbohydrate to macromineral ratio comparable to that of carbohydrate to thiamin. Therefore, the significance of this paper is its role in understanding the drawbacks of the global dietary changes on macromineral imbalances, and further explains the common link between refeeding syndrome and metabolic syndrome. This supports our hypothesis that metabolic syndrome seems to manifest from the sustenance of a mild refeeding syndrome status.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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