Cidália Pereira, Rosário Monteiro, Maria João Martins*

2.3 Understanding the Metabolic Syndrome Using a Biomedical Chemistry Profile

2.3.1 Introduction

For quite some time, it has been identified that high blood pressure, dyslipidemia [increased triglycerides and reduced high-density lipoprotein (HDL) cholesterol levels], impaired glucose homeostasis and abdominal obesity take place concurrently more than by random, supporting the existence of the *metabolic syndrome* (MetSyn). Additionally, hyperuricemia, a prothrombotic state, oxidative stress, chronic low-grade inflammation, increased levels of apolipoprotein-B and small dense low-density lipoprotein (LDL) cholesterol (contributing to atherogenic dyslipidemia), non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis, obstructive sleep apnea and/or polycystic ovarian disease (Fulop, 2006; Alberti, 2009; Roberts, 2009; Ma, 2012; Matsuda, 2013; Mule, 2014; Carson, 2015) are quite often present on the MetSyn, although not yet included in its current/actual definition. Taking this into consideration, it is not surprising that the MetSyn associates with an increased risk of type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (Fulop, 2006; Qiao, 2007; Carson, 2015).

Epidemiological and experimental evidence has demonstrated beneficial effects of dietary magnesium, calcium, potassium and bicarbonate on the MetSyn or some of its individual components (Luft, 1990; Van Leer, 1995; Schorr, 1996; Whelton, 1997; Franch, 2004; Rylander, 2004; Schoppen, 2004; Franzoni, 2005; Karppanen, 2005; Schoppen, 2005; He, 2006; Feldeisen, 2007; Schoppen, 2007; Champagne, 2008; Rylander, 2008; Volpe, 2008; Perez-Granados, 2010; Adeva, 2011; Rice, 2011; Lee, 2013).

Natural mineral-rich waters are good sources of highly absorbable and bioavailable minerals (such as calcium, magnesium and potassium) and bicarbonate (Heaney, 1989; Bohmer, 2000; Kessler, 2000; Sabatier, 2002; Bacciottini, 2004; Kiss, 2004; Heaney, 2006; Karagulle, 2006; Petraccia, 2006; Karagulle, 2007; Sabatier, 2011). So, the particular composition of natural mineral-rich waters would be responsible for their favorable effects. In fact, the World Health Organization has recognized that

Cidália Pereira: Department of Biochemistry, Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319, Porto, Portugal; Escola Superior de Saúde, Instituto Politécnico de Leiria, Campus 2 – Morro de Lena - Alto do Vieiro, Apartado 4137, 2411-901, Leiria, Portugal.
Rosário Monteiro, Maria João Martins: Department of Biochemistry, Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319, Porto, Portugal ; Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Rua Alfredo Allen 208, 4200-135 Porto, Portugal.
*Email: mmartins@med.up.pt.

mineral-rich drinking-waters may provide substantial contributions to total intakes of calcium and magnesium in some populations or population subgroups (Cotruvo, 2009). In line, two recent and exhaustive studies revealed that consumption of public drinking waters and bottled natural mineral waters is a relevant complementary source of calcium and magnesium in Spain (Vitoria, 2014; Maraver, 2015).

Beneficial effects of natural mineral-rich waters ingestion on MetSyn features, included or not in its definition, and MetSyn complications (Luft, 1990; Simunic, 1990; Schorr, 1996; Polushina, 1998; Polushina, 2002; Rylander, 2004; Schoppen, 2004; Schoppen, 2005; Schoppen, 2007; Benedetti, 2009; Botvineva, 2010; Perez-Granados, 2010; Santos, 2010; El-Seweidy, 2011) as well as on the MetSyn itself (Pereira, 2012a; Pereira, 2013; Pereira, 2014a; Pereira, 2014b; Pereira, 2014c; Pereira, 2015) have been published.

2.3.2 Natural Mineral-rich Waters and MetSyn

The consumption of sodium bicarbonate containing/mineral-rich waters decreased systolic blood pressure in mildly hypertensive men (3 L day^{-1}, 7 days) (Luft, 1990) and mean arterial blood pressure in elderly normotensive individuals (1.5 L day^{-1}, 4 weeks) (Schorr, 1996). The ingestion of sulfate, calcium, magnesium and bicarbonate-rich natural mineral water (at least 1 L day^{-1}, 4 weeks) reduced systolic and diastolic blood pressure in adults with borderline hypertension and low urinary magnesium and calcium excretion levels (effect perceived after 2 weeks of consumption and sustained until the end of the dietary protocol) (Rylander, 2004). Vaquero *et al.* showed that, in moderately hypercholesterolemic young adults, the ingestion of bicarbonated natural mineral water, rich in sodium, chloride and potassium, and with a high bicarbonate to sodium ratio (1 L day^{-1}, 8 weeks), reduced systolic blood pressure (an effect already seen after 4 weeks), apolipoprotein-B, total-cholesterol and LDL-cholesterol fasting serum levels as well as total-cholesterol and LDL-cholesterol to HDL-cholesterol ratios (Perez-Granados, 2010). The same group showed, in healthy postmenopausal women, that a) the ingestion of the previous water (1 L day^{-1}, 2 months) increased HDL-cholesterol and decreased endothelial dysfunction markers, glucose, total-cholesterol and LDL-cholesterol fasting serum levels as well as total-cholesterol and LDL-cholesterol to HDL-cholesterol ratios (Schoppen, 2004), and b) the consumption of sodium-rich bicarbonated mineral waters (0.5 L each) with a standard fat-rich meal increased insulin sensitivity [more distinctly in the women with higher homeostasis model assessment (HOMA) index values] and decreased lipemia (Schoppen, 2005; Schoppen, 2007). Both a decrease in lipid and protein oxidation products and an increment of total antioxidant capacity and total thiol plasma levels were observed in healthy individuals drinking a sulfurous mineral water (0.5 L day^{-1}, 2 weeks) (Benedetti, 2009).

Our group evaluated the effects of the ingestion of a Portuguese natural mineral-rich water, and some of the possible mechanisms involved, on metabolic function in

a well-validated MetSyn animal model (Polizio, 2006; Rayssiguier, 2006; Oron-Herman, 2008): male Sprague-Dawley rats treated with 10% fructose in drinking water, for 8 weeks. Animals were randomly assigned into three groups with free access to food and a) tap water, b) 10% fructose in tap water or c) 10% fructose in Portuguese natural mineral-rich water. As expected, 10% fructose in tap water induced metabolic features characteristic of the MetSyn, such as increased plasma levels of triglycerides, insulin and leptin [with a strong tendency toward decreased insulin sensitivity index (Cacho, 2008)] and decreased plasma levels of magnesium as well as increased systolic blood pressure and heart rate. Fructose-induced effects in the redox state (liver), endoplasmic reticulum homeostasis (liver), glucocorticoid and insulin signalling pathways (liver and visceral and/or subcutaneous adipose tissue) and endothelial dysfunction markers expression (cavernous tissue) may have contributed to explain the induction of MetSyn; some compensatory mechanisms against fructose-ingestion were also revealed. Importantly, the co-ingestion of the Portuguese natural mineral-rich water reduced and/or prevented most of the changes induced by fructose and, additionally, strengthened the compensatory mechanisms and induced *per se* protective pathways in response to stress (Pereira, 2012a; Pereira, 2013; Pereira, 2014a; Pereira, 2014b; Pereira, 2014c; Pereira, 2015). This Portuguese natural mineral-rich water also increased hepatic catechol-O-methyltransferase activity in healthy Wistar Han rats (Bastos, 2014). Its high-content of protective minerals, such as magnesium, calcium and potassium, as well as bicarbonate, and low chloride content may explain the favourable results obtained (Pereira, 2012a; Pereira, 2013; Pereira, 2014a; Pereira, 2014b; Pereira, 2014c; Pereira, 2015).

2.3.3 Magnesium and MetSyn/MetSyn Features – Associated Mechanisms

Chronic deficiency of magnesium (in animal models with low magnesium intake) is associated with hypertension and increased heart rate (and somewhat higher plasma corticosterone levels) as well as dyslipidemia, insulin resistance and oxidative stress (Caddell, 1991; Balon 1994; Laurant, 1999; Busserolles, 2003; Takaya, 2012).

Clinical and experimental studies point to magnesium intake/status being inversely associated with the risk of hypertension, T2DM and coronary heart disease. Additionally, magnesium intake may decrease triglycerides and increased HDL-cholesterol circulating levels (Balon, 1994; Touyz, 2003; Takaya, 2004; Barbagallo, 2007; Belin, 2007; Abete, 2011; Heer, 2015).

Individuals with MetSyn (or with some of its individual components) frequently show reduced magnesium status and reduced magnesium intake as compared with non-MetSyn (or healthy) subjects (Barbagallo, 2007; Belin, 2007; Evangelopoulos, 2008; Abete, 2011; Heer, 2015). Interestingly, hypomagnesaemia has been associated with metabolic abnormalities characteristic of MetSyn in the absence of obesity and,

conversely, normal circulating levels of magnesium seem to be protective against the development of metabolic complications in obese individuals (Guerrero-Romero, 2013). Often, circulating and/or intracellular magnesium levels are reduced under insulin resistance/T2DM in (obese) children, adolescents and adults (Takaya, 2004; Huerta, 2005; Belin, 2007; Wells, 2008; Celik, 2011). Lecube *et al.* provided evidence that T2DM was the main factor accounting for the hypomagnesemia found in morbidly obese individuals. They observed that the percentage of morbidly obese individuals with serum magnesium concentration lower than 0.75 mmol L^{-1} was three fold higher in T2DM patients than in non-T2DM subjects. They also found that not only the degree of blood glucose control (when considering fasting plasma glucose and HbA1c levels) and serum magnesium concentration were significantly and negatively correlated but also fasting plasma glucose and HbA1c levels were, in multiple linear regression analysis, independently associated with serum magnesium concentration. Additionally, in the morbidly obese patient subgroup that went through bariatric surgery, serum magnesium levels increased in T2DM subjects in whom diabetes resolved; serum magnesium levels lasted unchanged in whom T2DM did not resolve (the same happened in non-T2DM obese subjects) (Lecube, 2012).

The mechanisms by which T2DM could lead to low serum magnesium levels remain to be fully understood. However, insulin resistance, hyperinsulinemia, hyperglycemia and/or glycosuria may negatively interfere with renal reabsorption of magnesium, contributing to hypomagnesemia (McNair, 1982; Djurhuus, 1995; Barbagallo, 2007; Belin, 2007; Lecube, 2012; Takaya, 2012). Insulin has a prime role in magnesium metabolism regulation and insulin resistance/inhibition of insulin-stimulated glucose uptake may decrease magnesium uptake by tissues and increase magnesium efflux from tissues (Takaya, 2004; Barbagallo, 2007; Belin, 2007).

Magnesium is a cofactor of several enzymes involved in insulin and glucose metabolism, among other processes (Takaya, 2004; Barbagallo, 2007; Belin, 2007; Guerrera, 2009; Takaya, 2012). Briefly, insulin binds to its receptor (IR) inducing its autophosphorylation on tyrosine residues and, subsequently, tyrosine residues phosphorylation of its substrates (IRS) and Src homology 2 domain containing transforming protein 1 (Shc). Phosphorylated IRS, particularly IRS1 and 2, activate phosphatidylinositol 3-kinase (PI3K), which converts phosphatidylinositol (4,5)-bisphosphate into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) on the plasma membrane. PIP3 recruits, binds and activates phosphatidylinositol-dependent protein kinase-1 (PDK1), which phosphorylates protein kinase B (Akt) contributing to its activation. Akt activation mediates insulin-induced glycogen and protein synthesis, gluconeogenesis inhibition and glucose transporter 4 (GLUT4) translocation to the plasma membrane (what increases glucose uptake by insulin sensitive tissues). Instead, phosphorylation of Shc by IR promotes a parallel signaling pathway, leading to the activation of serine/threonine kinases, such as MAPK-kinase (MEK-1/2) and extracellular receptor kinase (ERK), responsible for insulin-induced cell growth and differentiation (Cohen, 2006; Tsatsoulis, 2013). Interestingly, magnesium has a positive

impact on tyrosine kinase activity at the IR level as well as on the translocation of the GLUT4 to the cellular membrane (Takaya, 2004; Barbagallo, 2007; Belin, 2007; Guerrera, 2009; Takaya, 2012). Moreover, magnesium deprivation, in a renal epithelial cell line (Madin-Darby canine kidney cells), inhibited cell proliferation and decreased ERK1/2 phosphorylation; re-addition of magnesium increased phosphorylated ERK1/2 levels. The use of a specific inhibitor of the MEK-ERK cascade inhibited this last effect, indicating that magnesium is involved in the regulation of the MEK-ERK cascade and cell proliferation, at least in this cell line (Ikari, 2010).

Magnesium deprivation may also increase glucocorticoid exposure, even during fetal development (Caddell, 1991; Laurant, 1999; Takaya, 2011a; Takaya, 2012), which is involved in insulin resistance/T2DM and dyslipidemia (Pereira, 2011; Pereira, 2012b; Pereira, 2012c; Paredes, 2014; van Raalte, 2014). Takaya *et al.* investigated the effects of feeding pregnant rats a very-low magnesium diet (0.003% magnesium) upon cytosine-guanine dinucleotides methylation in hepatic glucocorticoid genes of neonatal offspring *versus* controls (0.082% magnesium). Mean methylation of the 11β-hydroxysteroid dehydrogenase type 2 gene (Hsd11b2) promoter (11β-hydroxysteroid dehydrogenase type 2 inactivates tissue's glucocorticoids) in the magnesium-deficient offspring was three times higher than in controls, predicting higher hepatic intracellular glucocorticoid exposure (Takaya, 2011a). Additionally, in female weanling Wistar/NIN rats, maternal and postnatal Mg deficiency played important (and different) roles in the programming of increased body adiposity, insulin resistance and impaired glucose tolerance and insulin secretion in rat offspring (Venu, 2005; Venu, 2008).

Magnesium deficiency is associated with vascular smooth muscle cells (SMC) proliferation, intimal thickening, thinning and fragmentation of elastic membranes, collagen accumulation and calcification as well as inflammation [increased interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and C-reactive protein (PCR) circulating levels], high rate of free-radical formation (which leads to an increased NO degradation by superoxide anions), increased susceptibility of lipoproteins to peroxidation and increased tissue lipid peroxidation. All these effects contribute to/have been associated with hypertriglyceridemia, pro-atherogenic alterations in lipoprotein metabolism, cardiovascular lipid deposition and/or the pathogenesis of vascular lesions following magnesium deficiency (Bussière, 1995; Gueux, 1995; Laurant, 1999; Busserolles, 2003; Rayssiguier, 2006; Rayssiguier, 2010).

Through calcium antagonism, magnesium promotes vascular relaxation and thus plays an important role on blood pressure control (Laurant, 1999; Rice, 2011). Conversely, magnesium deprivation activates the sympathetic nervous system which contributes to increased blood pressure and heart rate (Laurant, 1999; Rayssiguier, 2010). Aldosterone, due to both genomic and non-genomic effects, also controls systemic vascular resistance, blood pressure and heart rate (MacFadyen, 1997; Freel, 2004). In line, magnesium deficiency has been described to stimulate the synthesis and secretion of aldosterone, possibly by decreasing the antagonism to calcium influx in the zona glomerulosa of the adrenal glands (Laurant, 1999).

Magnesium supplementation during 4 weeks not only decreased fasting circulating C-peptide and insulin concentrations in healthy overweight/obese individuals but also altered whole blood gene expression [with negative regulation of 36 genes (including some involved in metabolic and inflammatory signaling pathways) and with positive regulation of 24 genes (some of them involved in magnesium homeostasis)] (Chacko, 2011). Additionally, magnesium supplementation reduced liver damage induced by ethanol ingestion both in humans (Poikolainen, 2008) and in rats (Markiewicz-Gorka, 2011). Although magnesium deprivation alone may induce metabolic abnormalities similar to those observed in rodents under chronic high-fructose feeding (model of diet-induced MetSyn), upon magnesium deficiency high-fructose feeding metabolic actions are potentiated (Busserolles, 2003; Rayssiguier, 2006). In this context, magnesium supplementation of rats submitted to high-fructose feeding prevented and/or improved the alterations induced by fructose. In particular, it ameliorated insulin sensitivity [evaluated as homeostasis model assessment insulin resistance (HOMA-IR) and muscle glucose utilization] and fasting circulating lipid profile, and decreased blood pressure as well as fasting circulating glucose, insulin and lipid peroxidation marker levels (Balon, 1994; Olatunji, 2007).

In this regard, we have described that the Portuguese natural mineral-rich water mentioned above partially prevented the decrease of the hepatic magnesium content of fructose-fed Sprague-Dawley rats (Pereira, 2014a).

2.3.4 Calcium and MetSyn/MetSyn Features – Associated Mechanisms

Serum calcium levels are increased in individuals with MetSyn and positively correlated with serum triglycerides and blood pressure values (Park, 2012; Cho, 2011). Calcium and/or dairy products ingestion has been associated with decreased adipose tissue mass, lower blood pressure, better circulating lipid profile (increased HDL-cholesterol and decreased total-cholesterol and LDL-cholesterol levels as well as decreased total-cholesterol to HDL-cholesterol ratio and increased HDL-cholesterol to LDL-cholesterol ratio) and prevention/reduced incidence of insulin resistance, T2DM and MetSyn (Teegarden, 2006; van Meijl, 2008; Tremblay, 2009; Abete, 2011; Rice, 2011). The inconsistency between serum calcium levels and dietary calcium intake values with MetSyn still needs to be clarified (Park, 2012; Cho, 2011).

The increase of fecal excretion of fat and inhibition of intestinal bile salts absorption (with the consequent increase of cholesterol conversion into bile acids in the liver) as well as the stimulation of lipolysis and inhibition of lipogenesis improve plasma lipid profile and decrease adipose tissue mass as a consequence of calcium intake (Abete, 2011; Rice, 2011). Regulation of parathyroid hormone and 1,25-dihydroxycholecalciferol levels by dietary calcium mediates its effects on fat mass and insulin signaling/action (Teegarden, 2006). There is also evidence that adequate

calcium intake, by decreasing the concentration of 1,25-dihydroxycholecalciferol, decreased the uptake of calcium by vascular SMC and, so, impaired contraction and reduced peripheral resistance and blood pressure (Rice, 2011). Additionally, lowering of 1,25-dihydroxycholecalciferol associated with a calcium-induced decrease of reactive oxygen species, oxidative stress markers and pro-inflammatory markers (such as TNF-α, IL-6 and PCR) and increase of anti-inflammatory markers (such as adiponectin), in adipose tissue and/or blood in obese humans and/or obese mice (Zemel, 2008). Dietary calcium supplementation (started 120 days after birth and lasting for 2 months) in adult offspring rats programmed during lactation by maternal nicotine exposure restored insulin sensitivity, reversed the concentration of serum leptin as well as the percentage of both total body fat content and visceral fat mass, and decreased the mRNA expression of leptin in visceral adipose tissue *versus* the nicotine exposed/conditioned rat group. Dietary calcium supplementation of the programmed rats also increased the hepatic expression of sirtuin 1 (Sirt1) *versus* the control rat group (without nicotine exposure or calcium supplementation) (Nobre, 2011). Regarding Sirt1, growing evidence suggests that its deacetylase activity regulates glucose-lipid metabolism, glucose production, inflammation, oxidative stress, autophagy and mitochondrial function and biogenesis as well as adiponectin and insulin secretion. Positive effects of Sirt1 overexpression and Sirt1 activators have been described (Kitada, 2013a; Kitada, 2013b; Xu, 2013; Li, 2014).

With an opposite approach, female Wistar rats subjected to a very-low-calcium diet [(0.008% calcium) *versus* regular-calcium control diet-fed rats (0,9% calcium)], for 2 weeks, showed lower fasting serum levels of adiponectin and higher HOMA-IR. Moreover, the mRNA expression of 11β-hydroxysteroid dehydrogenase type 1 (activates tissue's glucocorticoids) in the liver was up-regulated (with the same tendency for the hepatic glucocorticoid receptor), before the animals developed obesity or other evident features of MetSyn (Takaya, 2011b), amplifying the glucocorticoid exposure in this tissue.

2.3.5 Potassium and MetSyn/MetSyn Features – Associated Mechanisms

Dietary potassium is inversely associated with hypertension and potassium supplementation may improve and/or prevent hypertension (Whelton, 1997; Franzoni, 2005; Rice, 2011). Inhibition of pro-inflammatory events in vascular SMC, reduction of platelet aggregation and reduction of renal vascular resistance seem to mediate potassium favorable effects on blood pressure (Rice, 2011).

Potassium intake and serum potassium levels have also been negatively associated with MetSyn prevalence (Lee, 2013; Sun, 2014). Lower serum potassium levels, and to a minor degree lower dietary potassium intake levels, have been associated with an increased risk of diabetes (Chatterjee, 2011; Lee, 2013). Even a moderate depletion of serum potassium (without frank hypokalemia) is associated with glucose intolerance/insulin resistance and, hence, with an increased risk of T2DM, by reducing insulin

secretion (Norbiato, 1984; Lee, 2013). Serum potassium levels are closely regulated by homeostatic mechanisms and depend on dietary potassium intake and potassium excretion (and its regulators) as well as on partitioning between intracellular and extracellular spaces (modulated by insulin, catecholamines and thyroid hormone) (Chatterjee, 2011). Renal potassium excretion is primarily controlled by sodium delivery to the distal nephron and urine flow, vasopressin levels, acid-base status (also hormone regulated, as above) and the renin-angiotensin-aldosterone system (Chatterjee, 2011). As a consequence of the strict control of serum potassium levels, dietary and serum potassium levels are not inevitably associated (Chatterjee, 2011).

2.3.6 Bicarbonate and MetSyn/MetSyn Features – Associated Mechanisms

In fact, besides calcium, magnesium and potassium content on natural mineral-rich waters, hydrogen carbonate concentration also deserves attention. Hydrogen carbonate-rich mineral waters may decrease calcium and magnesium renal excretion (by increasing their renal reabsorption) and, so, contribute to minerals´ homeostasis in the body (Brandolini, 2005; Rylander, 2008). Water pH and water hydrogen carbonate content are particularly relevant when considering the increased acid load of the Western diet, mainly related to the: a) high-ingestion of proteins (especially from animal origin), since sulfur ions are formed during amino acids metabolism, as well as high-sodium chloride consumption, and b) low-ingestion of fresh fruit, vegetables, tubers, roots and nuts, that are net base producers. As a result, the consumption of a Western diet induces a chronic, low-grade metabolic acidosis that worsens with the decline of kidney function, for example with aging (Cordain, 2005; Rylander, 2008; Zhang, 2009; Adeva, 2011). In line, it was observed that renal sulfate excretion negatively correlates with urine pH and is higher in insulin resistance *versus* normal insulin sensitivity, highlighting an association among (animal) protein ingestion, endogenous acid production and insulin resistance. Furthermore, insulin resistance has been linked with metabolic acidosis markers (such as low urine pH and low serum bicarbonate levels) (Adeva, 2011).

Metabolic acidosis may induce insulin resistance by impairing the insulin signaling pathway through inhibition of PI3K activity and, consequently, of its downstream effectors, in the skeletal muscle (Franch, 2004; Adeva, 2011). This gives dietary acid load a solid role in anticipating the metabolic dysfunction and the cardiovascular risk of the healthy, overweight and obese individuals as well as diabetic, hypertensive and chronic kidney failure patients (Zhang, 2009; Adeva, 2011; Odermatt, 2011). Moreover, acidosis-induced inhibition of PI3K activity blocked the antiproteolytic effect of insulin, which could be related to decreased lean body mass in chronic kidney failure patients (Franch, 2004). Metabolic acidosis increases both glucocorticoid secretion and plasma cortisol levels, which definitely contribute to insulin resistance, T2DM, MetSyn, blood pressure and inflammation. Contemporary acidogenic diet associates

with cortisol excess, the latter being prevented by bicarbonate administration (Zhang, 2009; Adeva, 2011; Pereira, 2011; Pereira, 2012b; Pereira, 2012c).

In this context, once more, natural mineral-rich water consumption would be extremely beneficial.

2.3.7 Magnesium, Calcium, Potassium and Bicarbonate *versus* Sodium

As highlighted above, an adequate intake of magnesium, calcium or potassium has a favorable effect on metabolic regulation and/or blood pressure (Whelton, 1997; Geleijnse, 2005; Karppanen, 2005; Teegarden, 2006; Feldeisen, 2007; Olatunji, 2007; van Meijl, 2008; Cho, 2009; Tremblay, 2009; Chaudhary, 2010; Abete, 2011; Rice, 2011). However, their association, as occurs in the dietary approaches to stop hypertension (DASH diet), which includes, among others, magnesium, calcium and potassium-rich foods, seems more effective, particularly in blood pressure control (Vaskonen, 2003; Al-Solaiman, 2010). Furthermore, magnesium, calcium and potassium reduce sodium retention, which may contribute to their positive effects on blood pressure (Vaskonen, 2003; Rice, 2011). In some studies, sodium chloride is clearly associated with hypertension (Ziomber, 2008; Santos, 2010). This association depends on sodium being accompanied by chloride, as sodium *per se* (in the drinking solution) does not increase blood pressure (Ziomber, 2008; Santos, 2010). Possibly through sodium potassium ATPase inhibition (Blaustein, 2006), only sodium chloride seems to increase plasma volume and blood pressure (Kunes, 2004; Santos, 2010), although sodium salts, with chloride or other anions (with equimolar amounts of sodium), produce similar suppression of the renin-angiotensin axis (Luft, 1990; Santos, 2010).

In line with these findings, natural mineral-rich waters intake, with a high content of both sodium and bicarbonate, decrease blood pressure (Schorr, 1996; Perez-Granados, 2010) or has no effect on it (Schoppen, 2004; Santos, 2010).

2.3.8 Conclusion

As shown above, an adequate body homeostasis of magnesium, calcium, potassium and bicarbonate has a prime role in preventing and/or improving MetSyn, or some of its features. The ingestion of natural mineral-rich waters could contribute to an adequate supply of those dietary micronutrients, being most relevant in the context of the Western diet.

Acknowledgements: This work has been supported by FCT (*Fundação para a Ciência e Tecnologia*, PEst-OE/SAU/UI0038/2014) and *Instituto de Investigação e Inovação em Saúde*, University of Porto, Porto, Portugal. We thank Unicer Bebidas, S.A. (Leça do Balio, Matosinhos, Portugal) the supply of the Portuguese natural mineral-rich water tested.

References

Abete, I., Goyenechea, E., Zulet, M. A., & Martinez, J. A. (2011). Obesity and metabolic syndrome: potential benefit from specific nutritional components. *Nutrition, Metabolism & Cardiovascular Diseases, 21*(S2), B1-15.

Adeva, M. M., & Souto, G. (2011). Diet-induced metabolic acidosis. Clin Nutr 30(4): 416-421.

Al-Solaiman, Y., Jesri, A., Mountford, W. K., Lackland, D. T., Zhao, Y., & Egan, B. M. (2010). DASH lowers blood pressure in obese hypertensives beyond potassium, magnesium and fibre. *Journal of Human Hypertension, 24*(4), 237-246.

Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., Fruchart, J. C., James, W. P., Loria, C. M., & Smith, S. C. Jr. (2009). Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*, *120*(16), 1640-1645.

Bacciottini, L., Tanini, A., Falchetti, A., Masi, L., Franceschelli, F., Pampaloni, B., Giorgi, G., & Brandi, M. L. (2004). Calcium bioavailability from a calcium-rich mineral water, with some observations on method. *Journal of Clinical Gastroenterology, 38*(9), 761-766.

Balon, T. W., Jasman, A., Scott, S., Meehan, W. P., Rude, R. K., & Nadler, J. L. (1994). Dietary magnesium prevents fructose-induced insulin insensitivity in rats. *Hypertension, 23*(6 Pt 2), 1036-1039.

Barbagallo, M., & Dominguez, L. J. (2007). Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. *Archives of Biochemistry and Biophysics, 458*(1), 40-47.

Bastos, P., Araújo, J. R., Azevedo, I., Martins, M. J., & Ribeiro, L. (2014). Effect of a natural mineral-rich water on catechol-O-methyltransferase function. *Magnesium research, 27*(3),131-141.

Belin, R. J., & He, K. (2007). Magnesium physiology and pathogenic mechanisms that contribute to the development of the metabolic syndrome. Magnes Res 20(2): 107-129.

Benedetti, S., Benvenuti, F., Nappi, G., Fortunati, N. A., Marino, L., Aureli, T., De Luca S., Pagliarani, S., & Canestrari, F. (2009). Antioxidative effects of sulfurous mineral water: protection against lipid and protein oxidation. *European Journal of Clinical Nutrition, 63*(1), 106-112.

Blaustein, M. P., Zhang, J., Chen, L., & Hamilton, B. P. (2006). How does salt retention raise blood pressure? *American Journal of Regulatory, Integrative, and Comparative Physiology, 290*(3), R514-523.

Bohmer, H., Muller, H., & Resch, K. L. (2000). Calcium supplementation with calcium-rich mineral waters: a systematic review and meta-analysis of its bioavailability. *Osteoporosis International, 11*(11), 938-943.

Botvineva, L. A., Nikitin, E. N., Mel'nikova, L. N., & Akaeva, E. A. (2010). The use of drinking mineral waters and the fiber-enriched diet for the treatment of patients with type 2 diabetes mellitus. *Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury, Mar-Apr*(2), 13-16 (In Russian).

Brandolini, M., Gueguen, L., Boirie, Y., Rousset, P., Bertiere, M. C., & Beaufrere, B. (2005). Higher calcium urinary loss induced by a calcium sulphate-rich mineral water intake than by milk in young women. *British Journal of Nutrition*, *93*(2), 225-231.

Busserolles, J., Gueux, E., Rock, E., Mazur, A., & Rayssiguier, Y. (2003). High fructose feeding of magnesium deficient rats is associated with increased plasma triglyceride concentration and increased oxidative stress. *Magnesium research*, *16*(1), 7-12.

Bussière, L., Mazur, A., Gueux, E., Nowacki, W., & Rayssiguier, Y. (1995). Triglyceride-rich lipoproteins from magnesium-deficient rats are more susceptible to oxidation by cells and promote proliferation of cultured vascular smooth muscle cells. *Magnesium research, 8*(2), 151-157.

Cacho, J., Sevillano, J,. de Castro, J., Herrera, E., & Ramos, M.P. (2008). Validation of simple indexes to assess insulin sensitivity during pregnancy in Wistar and Sprague-Dawley rats. *American Journal of Physiology Endocrinology and Metabolism, 295*(5), E1269-E1276.

Caddell, J. L., & Dunn, J. D. (1991-1992). Plasma corticosterone in stressed magnesium-deficient weanling rats. *Magnesium and trace elements, 10*(1), 40-46.

Carson, M. P. (2015). Society for maternal and fetal medicine workshop on pregnancy as a window to future health: Clinical utility of classifying women with metabolic syndrome. *Semin Perinatol, 39*(4), 284-289.

Celik, N., Andiran, N., & Yilmaz, A. E. (2011). The relationship between serum magnesium levels with childhood obesity and insulin resistance: a review of the literature. *Journal of Pediatric Endocrinology and Metabolism, 24*(9-10), 675-678.

Chacko, S. A., Sul, J., Song, Y., Li, X., LeBlanc, J., You, Y., Butch, A., & Liu, S. (2011). Magnesium supplementation, metabolic and inflammatory markers, and global genomic and proteomic profiling: a randomized, double-blind, controlled, crossover trial in overweight individuals. *American Journal of Clinical Nutrition, 93*(2), 463-473.

Champagne, C. M. (2008). Magnesium in hypertension, cardiovascular disease, metabolic syndrome, and other conditions: a review. Nutrition in Clinical Practice, *23*(2), 142-151.

Chatterjee, R., Yeh, H. C., Edelman, D., & Brancati, F. (2011). Potassium and risk of Type 2 diabetes. *Expert Review of Endocrinology and Metabolism, 6*(5), 665-672.

Chaudhary, D. P., Sharma, R., & Bansal, D. D. (2010). Implications of magnesium deficiency in type 2 diabetes: a review. *Biological Trace Element Research, 134*(2), 119-129.

Cho, G. J., Park, H. T., Shin, J. H., Hur, J. Y., Kim, Y. T., Kim, S. H., Lee, K. W., & Kim, T. (2009). Calcium intake is inversely associated with metabolic syndrome in postmenopausal women: Korea National Health and Nutrition Survey, 2001 and 2005. *Menopause*, *16*(5), 992-997.

Cho, G. J., Shin, J. H., Yi, K. W., Park, H. T., Kim, T., Hur, J. Y., & Kim, S. H. (2011). Serum calcium level is associated with metabolic syndrome in elderly women. *Maturitas, 68*(4), 382-386.

Cohen, P. (2006). The twentieth century struggle to decipher insulin signalling. *Nature Reviews Molecular Cell Biology, 7*(11), 867-873.

Cordain, L., Eaton, S. B., Sebastian, A., Mann, N., Lindeberg, S., Watkins, B. A., O'Keefe, J. H., & Brand-Miller, J. (2005). Origins and evolution of the Western diet: health implications for the 21st century. *American Journal of Clinical Nutrition, 81*(2), 341-354.

Cotruvo, J., & Bartram, J., eds (2009). Calcium and magnesium in drinking-water: public health significance. Geneva, World Health Organization.

Djurhuus, M. S., Skott, P., Hother-Nielson, O., Klitgaard, N. A., & Beck-Nielsen, H. (1995). Insulin increases renal magnesium excretion: a possible cause of magnesium depletion in hyperinsulinaemic states. *Diabetic Medicine, 12*(8), 664-669.

El-Seweidy, M. M., Sadik, N. A., & Shaker, O. G. (2011). Role of sulfurous mineral water and sodium hydrosulfide as potent inhibitors of fibrosis in the heart of diabetic rats. *Archives of Biochemistry and Biophysics, 506*(1), 48-57.

Evangelopoulos, A. A., Vallianou, N. G., Panagiotakos, D. B., Georgiou, A., Zacharias, G. A., Alevra, A. N., Zalokosta, G. J., Vogiatzakis, E. D., & Avgerinos, P. C. (2008). An inverse relationship between cumulating components of the metabolic syndrome and serum magnesium levels. Nutr Res, 28(10), 659-663.

Feldeisen, S. E., & Tucker, K. L. (2007). Nutritional strategies in the prevention and treatment of metabolic syndrome. *Applied Physiology, Nutrition, and Metabolism, 32*(1), 46-60.

Franch, H. A., Raissi, S., Wang, X., Zheng, B., Bailey, J. L., & Price, S. R. (2004). Acidosis impairs insulin receptor substrate-1-associated phosphoinositide 3-kinase signaling in muscle cells: consequences on proteolysis. *American Journal of Physiology Renal Physiology, 287*(4), F700-706.

Franzoni, F., Santoro, G., Carpi, A., Da Prato, F., Bartolomucci, F., Femia, F. R., Prattichizzo, F., & Galetta, F. (2005). Antihypertensive effect of oral potassium aspartate supplementation in mild to moderate arterial hypertension. *Biomedicine & Pharmacotherapy, 59*(1-2), 25-29.

Freel, E. M., & Connell, J. M. (2004). Mechanisms of hypertension: the expanding role of aldosterone. *Journal of the American Society of Nephrology, 15*(8), 1993-2001.

Fulop, T., Tessier, D., & Carpentier, A. (2006). The metabolic syndrome. *Pathologie Biologie (Paris) 54*(7), 375-386.

Geleijnse, J. M., Grobbee, D. E., & Kok, F. J. (2005). Impact of dietary and lifestyle factors on the prevalence of hypertension in Western populations. *Journal of Human Hypertension, 19* (S3), S1-4.

Guerrera, M. P., Volpe, S. L., & Mao, J. J. (2009). Therapeutic uses of magnesium. *American Family Physician,* 80(2): 157-162.

Guerrero-Romero, F., & Rodriguez-Moran, M. (2013). Serum magnesium in the metabolically-obese normal-weight and healthy-obese subjects. *European Journal of Internal Medicin, 24*(7), 639-643.

Gueux, E., Azais-Braesco, V., Bussière, L., Grolier, P., Mazur, A., & Rayssiguier, Y. (1995). Effect of magnesium deficiency on triacylglycerol-rich lipoprotein and tissue susceptibility to peroxidation in relation to vitamin E content. *British Journal of Nutrition 74*(6), 849-856.

He, K., Song, Y., Belin, R. J., & Chen, Y. (2006). Magnesium intake and the metabolic syndrome: epidemiologic evidence to date. *Journal of the cardiometabolic syndrome, 1*(5), 351-355.

Heaney, R. P. (2006). Absorbability and utility of calcium in mineral waters. *American Journal of Clinical Nutrition, 84*(2), 371-374.

Heaney, R. P., Smith, K. T., Recker, R. R., & Hinders, S. M. (1989). Meal effects on calcium absorption. *American Journal of Clinical Nutrition,* 49(2), 372-376.

Heer, M., & Egert, S. (2015). Nutrients other than carbohydrates: their effects on glucose homeostasis in humans. *Diabetes/Metabolism Research and Reviews*, *31*(1), 14-35.

Huerta, M. G., Roemmich, J. N., Kington, M. L., Bovbjerg, V. E., Weltman, A. L., Holmes, V. F., Patrie, J. T., Rogol, A. D., & Nadler, J. L. (2005). Magnesium deficiency is associated with insulin resistance in obese children. Diabetes Care, *28*(5), 1175-1181.

Ikari, A., Atomi, K., Kinjo, K., Sasaki, Y., & Sugatani, J. (2010). Magnesium deprivation inhibits a MEK-ERK cascade and cell proliferation in renal epithelial Madin-Darby canine kidney cells. *Life Sciences*, *86*(19-20), 766-773.

Karagulle, O., Kleczka, T., Vidal, C., Candir, F., Gundermann, G., Kulpmann, W. R., Gehrke, A., & Gutenbrunner, C. (2006). Magnesium absorption from mineral waters of different magnesium content in healthy subjects. *Forsch Komplementmed*, *13*(1), 9-14.

Karagulle, O., Smorag, U., Candir, F., Gundermann, G., Jonas, U., Becker, A. J., Gehrke, A., & Gutenbrunner, C. (2007). Clinical study on the effect of mineral waters containing bicarbonate on the risk of urinary stone formation in patients with multiple episodes of CaOx-urolithiasis. *World Journal of Urology, 25*(3), 315-323.

Karppanen, H., Karppanen, P., & Mervaala, E. (2005). Why and how to implement sodium, potassium, calcium, and magnesium changes in food items and diets? *Journal of Human Hypertension, 19*(Suppl 3), S10-19.

Kessler, T., & Hesse, A. (2000). Cross-over study of the influence of bicarbonate-rich mineral water on urinary composition in comparison with sodium potassium citrate in healthy male subjects. *British Journal of Nutrition, 84*(6), 865-871.

Kiss, S. A., Forster, T., & Dongo, A. (2004). Absorption and effect of the magnesium content of a mineral water in the human body. *Journal of the American College of Nutrition, 23*(6), 758s-762s.

Kitada, M., Kume, S., Kanasaki, K., Takeda-Watanabe, A., & Koya, D. (2013a). Sirtuins as possible drug targets in type 2 diabetes. *Current Cancer Drug Targets, 14*(6), 622-636.

Kitada, M., & Koya, D. (2013b). SIRT1 in Type 2 Diabetes: Mechanisms and Therapeutic Potential. *Diabetes and Metabolism Journal, 37*(5), 315-325.

Kunes, J., Zicha J., & Jelinek, J. (2004). The role of chloride in deoxycorticosterone hypertension: selective sodium loading by diet or drinking fluid. *Physiological Research, 53*(2), 149-154.

Laurant, P., Dalle, M., Berthelot, A., & Rayssiguier, Y. (1999). Time-course of the change in blood pressure level in magnesium-deficient Wistar rats. *British Journla of Nutrition, 82*(3), 243-251.

Lecube, A., Baena-Fustegueras, J. A., Fort, J. M., Pelegri, D., Hernandez, C., & Simo, R. (2012). Diabetes is the main factor accounting for hypomagnesemia in obese subjects. *PLoS One, 7*(1), e30599.

Lee, H., Lee, J., Hwang, S. S., Kim, S., Chin, H. J., Han, J. S., & Heo, N. J. (2013). Potassium intake and the prevalence of metabolic syndrome: the Korean National Health and Nutrition Examination Survey 2008-2010. *PLoS One, 8*(1), e55106.

Li, Y., Wong K., Giles, A., Jiang, J., Lee, J. W., Adams, A. C., Kharitonenkov, A., Yang, Q., Gao, B., Guarente, L., & Zang, M. (2014). Hepatic SIRT1 attenuates hepatic steatosis and controls energy balance in mice by inducing fibroblast growth factor 21. *Gastroenterology, 146*(2), 539-549.e537.

Luft, F. C., Zemel, M. B., Sowers, J. A., Fineberg, N. S., & Weinberger, M. H. (1990). Sodium bicarbonate and sodium chloride: effects on blood pressure and electrolyte homeostasis in normal and hypertensive man. *Journal of Hypertension, 8*(7), 663-670.

Ma, K., Jin, X., Liang, X., Zhao, Q., & Zhang X. (2012). Inflammatory mediators involved in the progression of the metabolic syndrome. *Diabetes/Metabolism Research and Reviews, 28*(5), 388-394.

MacFadyen, R. J., Barr, C. S., & Struthers, A. D. (1997). Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. *Cardiovascular Research, 35*(1), 30-34.

Maraver, Fi, Vitoria, I., Ferreira-Pêgo, C., Armijo, F., & Salas-Salvadó, J. (2015). Magnesium in tap and bottled mineral water in spain and its contribution to nutritional recommendations. *Nutr Hosp, 31*(n05), 2297-2312.

Markiewicz-Gorka, I., Zawadzki, M., Januszewska, L., Hombek-Urban, K., & Pawlas, K. (2011). Influence of selenium and/or magnesium on alleviation alcohol induced oxidative stress in rats, normalization function of liver and changes in serum lipid parameters. *Human & Experimental Toxicology, 30*(11), 1811-1827.

Matsuda, M., & Shimomura, I. (2013). Increased oxidative stress in obesity: implications for metabolic syndrome, diabetes, hypertension, dyslipidemia, atherosclerosis, and cancer. *Obesity Research & Clinical Practice, 7*(5), e330-341.

McNair, P., Christensen, M. S., Christiansen, C., Madsbad, S., & Transbol, I. (1982). Renal hypomagnesaemia in human diabetes mellitus: its relation to glucose homeostasis. *European Journal of Clinical Investigation, 12*(1), 81-85.

Mule, G., Calcaterra, I., Nardi, E., Cerasola, G., & Cottone, S. (2014). Metabolic syndrome in hypertensive patients: An unholy alliance. *World Journal of Cardiology, 6*(9), 890-907.

Nobre, J. L., Lisboa, P. C., Santos-Silva, A. P., Lima, N. S., Manhaes, A. C., Nogueira-Neto, J. F., Cabanelas, A., Pazos-Moura, C. C., Moura, E. G., & de Oliveira, E. (2011). Calcium supplementation reverts central adiposity, leptin, and insulin resistance in adult offspring programed by neonatal nicotine exposure. *Journal of Endocrinology, 210*(3), 349-359.

Norbiato, G., Bevilacqua, M., Meroni, R., Raggi, U., Dagani, R., Scorza, D., Frigeni, G., & Vago, T. (1984). Effects of potassium supplementation on insulin binding and insulin action in human obesity: protein-modified fast and refeeding. *European Journal of Clinical Investigation, 14*(6), 414-419.

Odermatt, A. (2011). The Western-style diet: a major risk factor for impaired kidney function and chronic kidney disease. *American Journal of Physiology Renal Physiology, 301*(5), F919-931.

Olatunji, L. A., & Soladoye, A. O. (2007). Increased magnesium intake prevents hyperlipidemia and insulin resistance and reduces lipid peroxidation in fructose-fed rats. *Pathophysiology, 14*(1), 11-15.

Oron-Herman, M., Kamari, Y., Grossman, E., Yeger, G., Peleg, E., Shabtay, Z., Shamiss, A., & Sharabi, Y. (2008). Metabolic syndrome: comparison of the two commonly used animal models. *American Journal of Hypertension, 21*(9), 1018-1022.

Paredes, S., & Ribeiro, L. (2014). Cortisol: the villain in Metabolic Syndrome? *Revista da Associação Médica Brasileira, 60*(1), 84-92.

Park, S. H., Kim, S. K., & Bae, Y. J. (2012). Relationship between serum calcium and magnesium concentrations and metabolic syndrome diagnostic components in middle-aged Korean men. *Biological Trace Element Research, 146*(1), 35-41.

Pereira, C., Monteiro, R., Constância, M., & Martins, M. J. (2012c). 11β-Hydroxysteroid Dehydrogenases in the Regulation of Tissue Glucocorticoid Availability. Steroids - From Physiology to Clinical Medicine. S. Ostojic, InTech: 83-106.

Pereira, C., Passos, E., Neves, D., Ascensão, A., Magalhães, J., Monteiro, R., & Martins, M. J. (2013). Modulation of stress pathways by a hypersaline sodium-rich carbonated natural mineral water seems to improve the hepatic insulin signalling in an animal model of metabolic syndrome. 5th International Symposium Nutrition, Oxygen Biology and Medicine - Société Française de Recherche sur les Radicaux Libres.

Pereira, C. D., Azevedo, I., Monteiro, R., & Martins, M. J. (2012b). 11beta-Hydroxysteroid dehydrogenase type 1: relevance of its modulation in the pathophysiology of obesity, the metabolic syndrome and type 2 diabetes mellitus. Diabetes, Obesity and Metabolism 14(10): 869-881.

Pereira, C. D., Collado, M. C., Passos, E., Azevedo, I., Monteiro, R., & Martins, M. J. (2014c). Comment to: Luo (2013) *International Journal of Cardiology*, *168*(4), 4454-6. *International Journal of Cardiology, 172*(2), 512-514.

Pereira, C. D., Martins, M. J., Azevedo, I., & Monteiro, R. (2011). 11β-Hydroxysteroid Dehydrogenase Type 1 and the Metabolic Syndrome. Steroids - Clinical Aspect. P. H. Abduljabbar, InTech: 25-50.

Pereira, C. D., Severo, M., Araújo, J. R., Guimarães, J. T., Pestana, D., Santos, A., Ferreira, R., Ascensão, A., Magalhães, J., Azevedo, I., Monteiro, R., & Martins, M. J. (2014a). Relevance of a hypersaline sodium-rich naturally sparkling mineral water to the protection against metabolic syndrome induction in fructose-fed sprague-dawley rats: a biochemical, metabolic, and redox approach. *International Journal of Endocrinology, 2014* (Article ID 384583).

Pereira, C. D., Severo, M., Neves, D., Ascensao, A., Magalhaes, J., Guimaraes, J. T., Monteiro, R., & Martins, M. J. (2015). Natural mineral-rich water ingestion improves hepatic and fat glucocorticoid-signaling and increases sirtuin 1 in an animal model of metabolic syndrome, *Hormone Molecular Biology and Clinical Investigation*, *21*(2), 149-157.

Pereira, C. D., Severo, M., Rafael, L., Martins, M. J., & Neves, D. (2014b). Effects of natural mineral-rich water consumption on the expression of Sirtuin 1, vascular endothelial growth factor, angiopoietins, and receptors in the erectile tissue of rats with fructose-induced Metabolic Syndrome. *Asian Journal of Andrology, 16*(4), 631-638.

Pereira, C. D., Silva, M. B., Monteiro, R., & Martins, M. J. (2012a). Modulation of 11ß-HSD1 by chronic ingestion of a hypersaline sodium-rich carbonated Portuguese natural mineral water in an animal model of the Metabolic Syndrome. Revista Portuguesa de Cirurgia Suplemento novembro: 33.

Perez-Granados, A. M., Navas-Carretero, S., Schoppen, S., & Vaquero, M. P. (2010). Reduction in cardiovascular risk by sodium-bicarbonated mineral water in moderately hypercholesterolemic young adults. *Journal of Nutritional Biochemistry, 21*(10), 948-953.

Petraccia, L., Liberati, G., Masciullo, S. G., Grassi, M., & Fraioli, A. (2006). Water, mineral waters and health. *Clinical Nutrition, 25*(3), 377-385.

Poikolainen, K., & Alho, H. (2008). Magnesium treatment in alcoholics: a randomized clinical trial. Subst Abuse Treat Prev Policy 3: 1.

Polizio, A.H., Gonzales, S., Muñoz, M.C., Peña, C., & Tomaro, M.L. (2006). Behaviour of the anti-oxidant defence system and heme oxygenase-1 protein expression in fructose-hypertensive rats. *Clinical and Experimental Pharmacology and Physiology, 33*(8), 734-739.

Polushina, N. D. (1998). [The effect of mineral water on serotonin and insulin production (an experimental study)]. *Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury, Jul-Aug* (4), 9-10.

Polushina, N. D., Vladimirov, V. I., & Frolkov, V. K. (2002). [Effect of drinking mineral water on hormonal regulation of glucose homeostasis after mastectomy for breast cancer]. *Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury,* Nov-Dec (6), 19-21.

Qiao, Q., Gao, W., Zhang, L., Nyamdorj, R., & Tuomilehto, J. (2007). Metabolic syndrome and cardiovascular disease. *Annals of Clinical Biochemistry, 44*(Pt 3), 232-263.

Rayssiguier, Y., Gueux, E., Nowacki, W., Rock, E., & Mazur, A. (2006). High fructose consumption combined with low dietary magnesium intake may increase the incidence of the metabolic syndrome by inducing inflammation. *Magnesium research, 19*(4), 237-243.

Rayssiguier, Y., Libako, P., Nowacki, W., & Rock, E. (2010). Magnesium deficiency and metabolic syndrome: stress and inflammation may reflect calcium activation. *Magnesium research, 23*(2), 73-80.

Rice, B. H., Cifelli, C. J., Pikosky, M. A., & Miller, G. D. (2011). Dairy components and risk factors for cardiometabolic syndrome: recent evidence and opportunities for future research. *Advances in Nutrition*, *2*(5), 396-407.

Roberts, C. K., & Sindhu, K. K. (2009). Oxidative stress and metabolic syndrome. *Life Sciences, 84*(21-22), 705-712.

Rylander, R. (2008). Drinking water constituents and disease. *Journal of Nutrition, 138*(2), 423s-425s.

Rylander, R., & Arnaud, M. J. (2004). Mineral water intake reduces blood pressure among subjects with low urinary magnesium and calcium levels. *BMC Public Health, 4*, 56.

Sabatier, M., Arnaud, M. J., Kastenmayer, P., Rytz, A., & Barclay, D. V. (2002). Meal effect on magnesium bioavailability from mineral water in healthy women. *The American Journal of Clinical Nutrition, 75*(1), 65-71.

Sabatier, M., Grandvuillemin, A., Kastenmayer, P., Aeschliman, J. M., Bouisset, F., Arnaud, M. J., Dumoulin, G., & A. Berthelot (2011). Influence of the consumption pattern of magnesium from magnesium-rich mineral water on magnesium bioavailability. *British Journal of Nutrition, 106*(3), 331-334.

Santos, A., Martins, M. J., Guimaraes, J. T., Severo, M., & Azevedo, I. (2010). Sodium-rich carbonated natural mineral water ingestion and blood pressure. *Revista Portuguesa de Cardiologia, 29*(2), 159-172.

Schoppen, S., Perez-Granados, A. M., Carbajal, A., Oubina, P., Sanchez-Muniz, F. J., Gomez-Gerique, J. A., & Vaquero, M. P. (2004). A sodium-rich carbonated mineral water reduces cardiovascular risk in postmenopausal women. *Journal of Nutrition, 134*(5), 1058-1063.

Schoppen, S., Perez-Granados, A. M., Carbajal, A., Sarria, B., Sanchez-Muniz, F. J., Gomez-Gerique, J. A., & Pilar Vaquero, M. (2005). Sodium bicarbonated mineral water decreases postprandial lipaemia in postmenopausal women compared to a low mineral water. *British Journal of Nutrition, 94*(4), 582-587.

Schoppen, S., Sanchez-Muniz, F. J., Perez-Granados, M., Gomez-Gerique, J. A., Sarria, B., Navas-Carretero, S., & Pilar Vaquero, M. (2007). Does bicarbonated mineral water rich in sodium change insulin sensitivity of postmenopausal women? *Nutricion Hospitalaria, 22*(5), 538-544.

Schorr, U., Distler, A., & Sharma, A. M. (1996). Effect of sodium chloride- and sodium bicarbonate-rich mineral water on blood pressure and metabolic parameters in elderly normotensive individuals: a randomized double-blind crossover trial. *Journal of Hypertension, 14*(1), 131-135.

Simunic, S., & Pintac, L. (1990). [Use of the Varazdinske Toplice mineral water in the treatment of diabetes mellitus]. *Reumatizm, 37*(1-6), 71-74.

Sun, K., Su, T., Li, M., Xu, B., Xu, M., Lu, J., Liu, J., Bi, Y. & Ning, G. (2014). Serum potassium level is associated with metabolic syndrome: A population-based study. Clin Nutr 33(3): 521-527.

Takaya, J., Higashino, H., & Kobayashi, Y. (2004). Intracellular magnesium and insulin resistance. *Magnesium Research, 17*(2), 126-136.

Takaya, J., Iharada, A., Okihana, H., & Kaneko, K. (2011a). Magnesium deficiency in pregnant rats alters methylation of specific cytosines in the hepatic hydroxysteroid dehydrogenase-2 promoter of the offspring. *Epigenetics, 6*(5), 573-578.

Takaya, J., Iharada, A., Okihana, H., & Kaneko, K. (2011b). Upregulation of hepatic 11beta-hydroxysteroid dehydrogenase-1 expression in calcium-deficient rats. *Annals of Nutrition and Metabolism, 59*(2-4), 73-78.

Takaya, J., Iharada, A., Okihana, H., & Kaneko, K. (2012). Down-regulation of hepatic phosphoenolpyruvate carboxykinase expression in magnesium-deficient rats. *Magnesium Research, 25*(3), 131-139.

Teegarden, D. (2006). Dietary Calcium and the Metabolic Syndrome. Calcium in Human Health. Nutrition and Health. C. Weaver and R. P. Heaney, Humana Press: 401-409.

Touyz, R. M. (2003). Role of magnesium in the pathogenesis of hypertension. *Molecular Aspects of Medicine, 24*(1-3), 107-136.

Tremblay, A., & Gilbert, J. A. (2009). Milk products, insulin resistance syndrome and type 2 diabetes. *Journal of the American College of Nutrition, 28*(S1), 91s-102s.

Tsatsoulis, A., Mantzaris, M. D., Bellou, S., & Andrikoula, M. (2013). Insulin resistance: an adaptive mechanism becomes maladaptive in the current environment - an evolutionary perspective. *Metabolism, 62*(5), 622-633.

Van Leer, E. M., Seidell, J. C., & Kromhout, D. (1995). Dietary calcium, potassium, magnesium and blood pressure in the Netherlands. *International Journal of Epidemiology, 24*(6), 1117-1123.

van Meijl, L. E., Vrolix, R., & Mensink, R. P. (2008). Dairy product consumption and the metabolic syndrome. *Nutrition Research Reviews, 21*(2), 148-157.

van Raalte, D. H., & Diamant, M. (2014). Steroid diabetes: from mechanism to treatment? *Netherlands Journal of Medicine, 72*(2), 62-72.

Vaskonen, T. (2003). Dietary minerals and modification of cardiovascular risk factors. *Journal of Nutritional Biochemistry, 14*(9), 492-506.

Venu, L., Kishore, Y. D., & Raghunath, M. (2005). Maternal and perinatal magnesium restriction predisposes rat pups to insulin resistance and glucose intolerance. *Journal of Nutrition, 135*(6), 1353-1358.

Venu, L., Padmavathi, I. J., Kishore, Y. D., Bhanu, N. V., Rao, K. R., Sainath, P. B., Ganeshan, M., & Raghunath, M. (2008). Long-term effects of maternal magnesium restriction on adiposity and insulin resistance in rat pups. *Obesity* (Silver Spring), *16*(6), 1270-1276.

Vitoria, I., Maraver, F., Ferreira-Pêgo, C., Armijo, F., Moreno Aznar, L., & Salas-Salvadó, J. (2014). The calcium concentration of public drinking waters and bottled mineral waters in Spain and its contribution to satisfying nutritional needs. *Nutrición Hospitalaria, 30*(1), 188-199.

Volpe, S. L. (2008). Magnesium, the metabolic syndrome, insulin resistance, and type 2 diabetes mellitus. *Critical Reviews in Food Science and Nutrition, 48*(3), 293-300.

Wells, I. C. (2008). Evidence that the etiology of the syndrome containing type 2 diabetes mellitus results from abnormal magnesium metabolism. *Canadian Journal of Physiology and Pharmacology, 86*(1-2), 16-24.

Whelton, P. K., He, J., Cutler, J. A., Brancati, F. L., Appel, L. J., Follmann, D., & Klag, M. J. (1997). Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA*, *277*(20), 1624-1632.

Xu, C., Bai, B., Fan, P., Cai, Y., Huang, B., Law, I. K., Liu, L., Xu, A., Tung, C., Li, X., Siu, F. M., Che, C. M., Vanhoutte, P. M., & Wang, Y. (2013). Selective overexpression of human SIRT1 in adipose tissue enhances energy homeostasis and prevents the deterioration of insulin sensitivity with ageing in mice. *American Journal of Translational Research, 5*(4), 412-426.

Zemel, M. B., & Sun, X. (2008). Dietary calcium and dairy products modulate oxidative and inflammatory stress in mice and humans. *Journal of Nutrition, 138*(6), 1047-1052.

Zhang, L., Curhan, G. C., & Forman, J. P. (2009). Diet-dependent net acid load and risk of incident hypertension in United States women. *Hypertension, 54*(4), 751-755.

Ziomber, A., Machnik, A., Dahlmann, A., Dietsch, P., Beck, F. X., Wagner, H., Hilgers, K. F., Luft, F. C., Eckardt, K. U. & Titze, J. (2008). Sodium-, potassium-, chloride-, and bicarbonate-related effects on blood pressure and electrolyte homeostasis in deoxycorticosterone acetate-treated rats. *American Journal of Physiology Renal Physiology, 295*(6), F1752-1763.