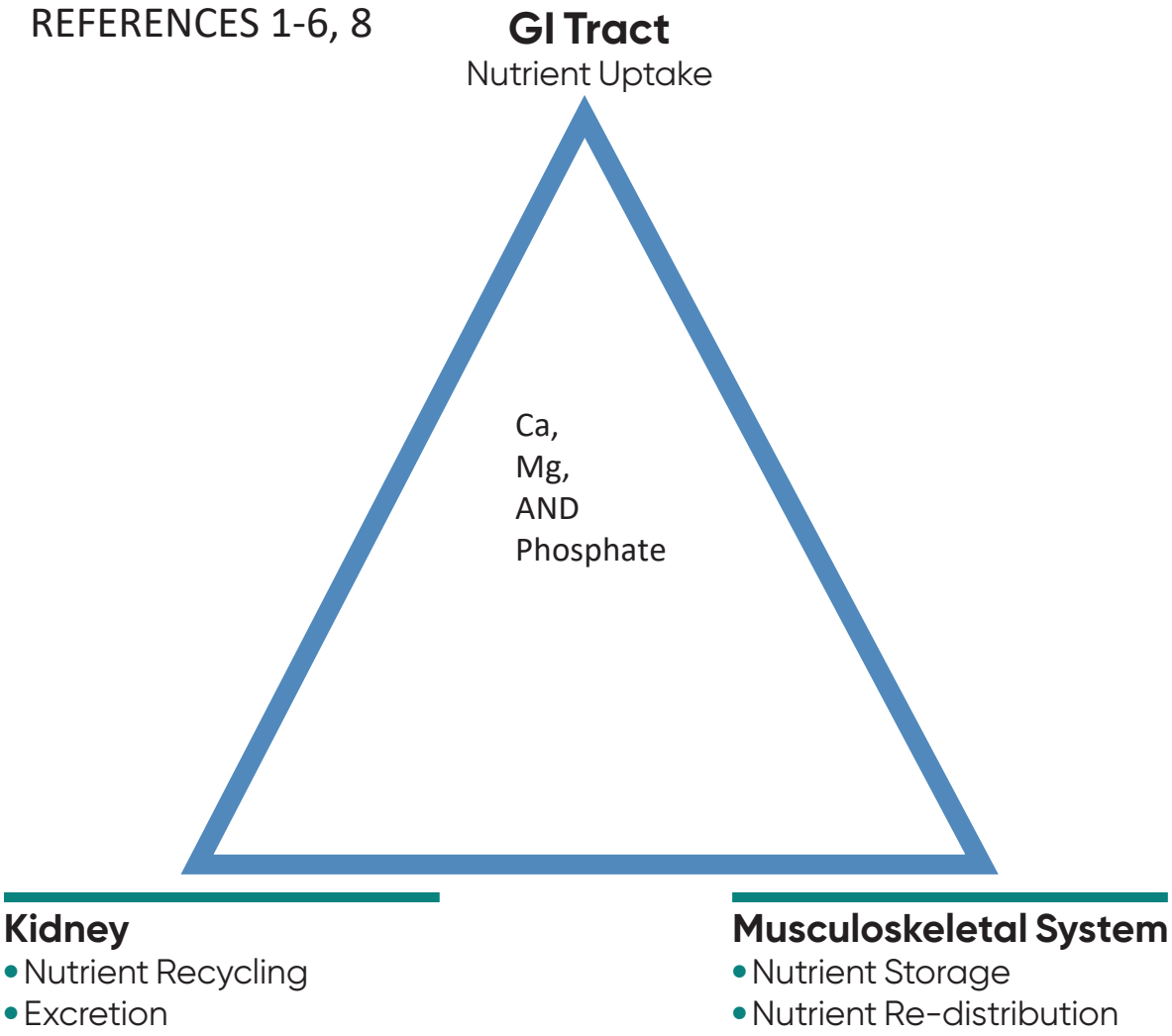
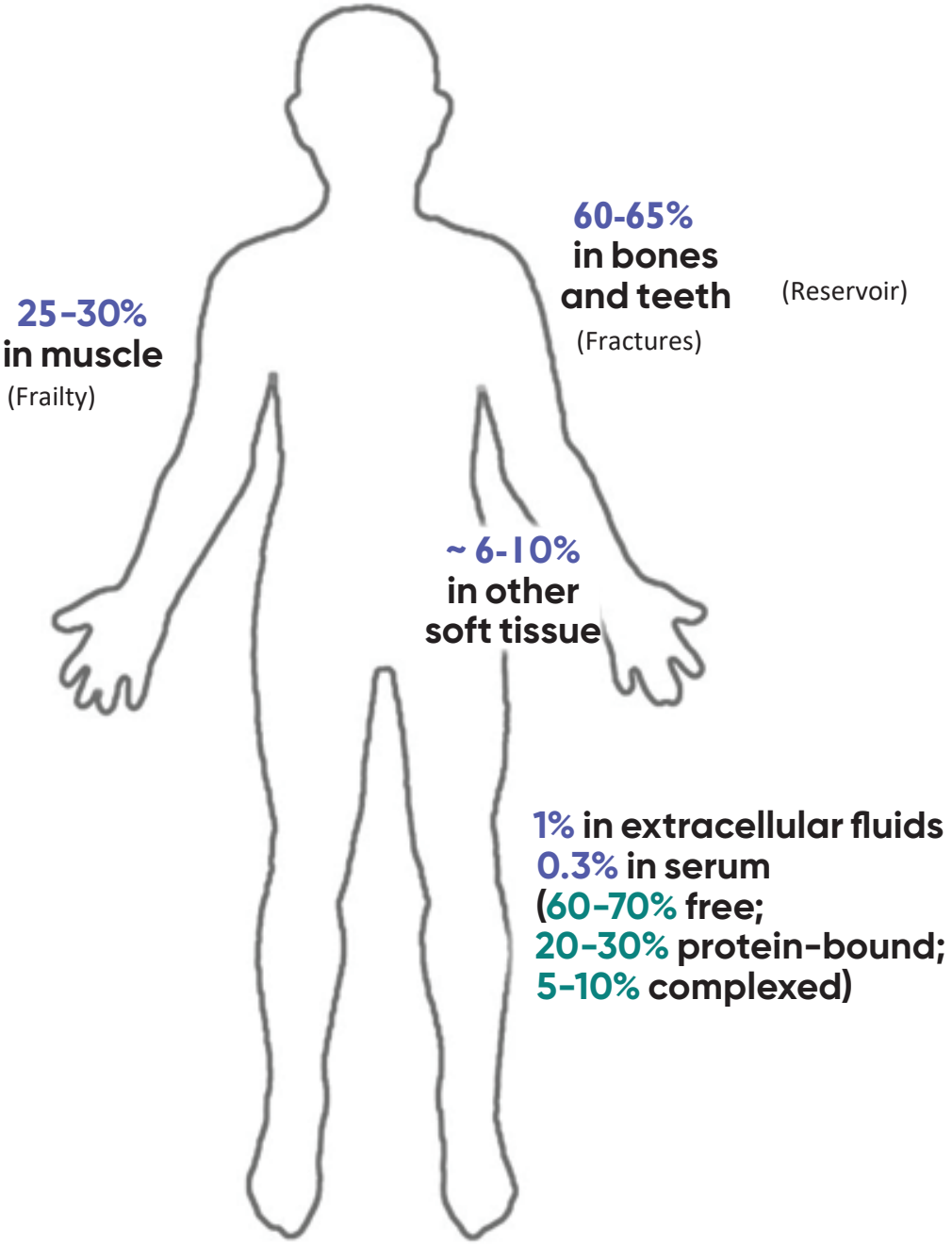
REFERENCES 1-6, 8



MAGNESIUM DISTRIBUTION IN THE BODY



SLOW RELEASE MAGNESIUM COMPOSITION AND USES THEREOF

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/222,420, filed Jul. 1, 2009, which is incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

Magnesium is the fourth most abundant mineral in the human body and plays multiple roles in maintaining good health. At the molecular level, magnesium is a cofactor for over 300 enzymes responsible for some of the most important biological activities in mammals, including humans. In living cells, magnesium is involved in the homeostasis of other minerals, such as sodium, potassium and calcium, and the formation, transfer, storage and utilization of adenosine triphosphate (ATP), a principal source of energy in living cells. In the human body, magnesium is involved in the maintenance of normal muscle and nerve function, heart rhythm, bone strength, and immune system health. Magnesium is also involved in the regulation of blood sugar levels and the promotion of normal blood pressure.

Magnesium deficit has been associated with several diseases, including hypertension, atherosclerosis, arrhythmia, diabetes, and metabolic syndromes. In addition, magnesium deficit accelerates cell-aging processes (Killilea D W, Ames B N. Magnesium deficiency accelerates cellular senescence in cultured human fibroblasts. Proc Natl Acad Sci USA. 2008 Apr. 15; 105:5768-73). Magnesium is also important for brain function. For example, magnesium deficit is implicated in attention deficit hyperactivity disorder (Kozielec T, Starobrat-Hermelin B. Magnes Res. 1997 June; 10:143-8; Mousain-Bosc M, Roche M, Polge A, Pradal-Prat D, Rapin J, Bali J P. Magnes Res. 2006 March; 19:46-52), affective disorders (Murck H. Nutritional neuroscience. 2002 December; 5:375-89), Alzheimer's disease (Andrasi E, Pali N, Molnar Z, Kosel S. J Alzheimers Dis. 2005 August; 7:273-84; Cilliler A E, Ozturk S, Ozbakir S. Gerontology. 2007 Nov. 8; 53:419-22; Lemke M R. Biol Psychiatry. 1995 Mar. 1; 37:341-3), migraine (Ramadan N M, Halvorson H, Vande-Linde A, Levine S R, Helpern J A, Welch K M. Headache. 1989 October; 29:590-3; Facchinetti F, Sances G, Borella P, Genazzani A R, Nappi G. Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. Headache. 1991 May; 31:298-301), and Autism (Martineau J, Barthelemy C, Garreau B, Lelord G. Biol Psychiatry. 1985 May; 20:467-78; Pfeiffer S I, Norton J, Nelson L, Shott S. J Autism Dev Disord. 1995 October; 25:481-93; Strambi M, Longini M, Hayek J, Berni S, Macucci F, Scalacci E, Vezzosi P., Biol Trace Elem Res. 2006 February; 109:97-104).

Recently, it has been found that elevation of extracellular magnesium leads to a significant enhancement of synaptic plasticity and synaptic density in cultured hippocampal neurons (Slutsky I, Sadeghpour S, Li B, Liu G. Neuron. 2004 Dec. 2; 44:835-49). The synaptic network is believed to be involved in organization of neural circuits during early development and in learning and memory processes. Indeed, in patients with Alzheimer's disease, there is a strong inverse correlation between the number of synapses and the degree of cognitive impairment (Terry R D, Masliah E, Salmon D P, Butters N, DeTeresa R, Hill R, Hansen L A, Katzman R. Ann Neurol. 1991 October; 30:572-80; Selkoe D J. Science. 2002 Oct. 25; 298:789-91). During normal aging, memory decline also correlates with synaptic loss (Terry R D, Masliah E, Salmon D P, Butters N, DeTeresa R, Hill R, Hansen L A, Katzman R.Ann Neurol. 1991 October; 30:572-80). Interestingly, brain magnesium contents in AD patients (Andrasi E, Pali N, Molnar Z, Kosel S. J Alzheimers Dis. 2005 August; 7:273-84; Cilliler A E, Ozturk S, Ozbakir S. Gerontology. 2007 Nov. 8; 53:419-22) are lower than normal subjects. Elevation of brain magnesium might be beneficial for prevention of synapse loss and amelioration of memory decline during aging and the pathological processes of AD.

Despite the important physiological role of magnesium, people may not consume enough magnesium in their diets. In a national sample of the United States, the mean value of daily magnesium between the ages of 20-30 is ~300 mg for white and ~250 mg for black males. This daily intake declines, at ages above 70 years, to ~200 mg as a result of reduced food consumption. On the other hand, the recommended daily allowance (RDA) for males is 420 mg/day. Therefore, it is likely that the majority of the American male population has magnesium deficit, particularly during aging. A similar degree of deficit also occurs in American female population (Ford E S, Mokdad A H. J. Nutr. 2003 September; 133:2879-82). Based on this study, most of the American population needs to supplement their diet with an additional ~200 mg/day of magnesium. Interestingly, magnesium contained in food provides relatively high absorption rate magnesium (~50%), which may suggest that ~100 mg/day magnesium remains needed to be absorbed into the body. In general, most commercially available magnesium preparations have a magnesium absorption rate ≤~40%. For example, magnesium oxide, which is perhaps the most widely used magnesium supplement, has a magnesium absorption rate of only about 4% (Firoz M, Graber M. Bioavailability of US commercial magnesium preparations. Magnes Res. 2001 December; 14:257-62)). The present invention provides controlled release magnesium compositions for use as a magnesium dietary supplement.

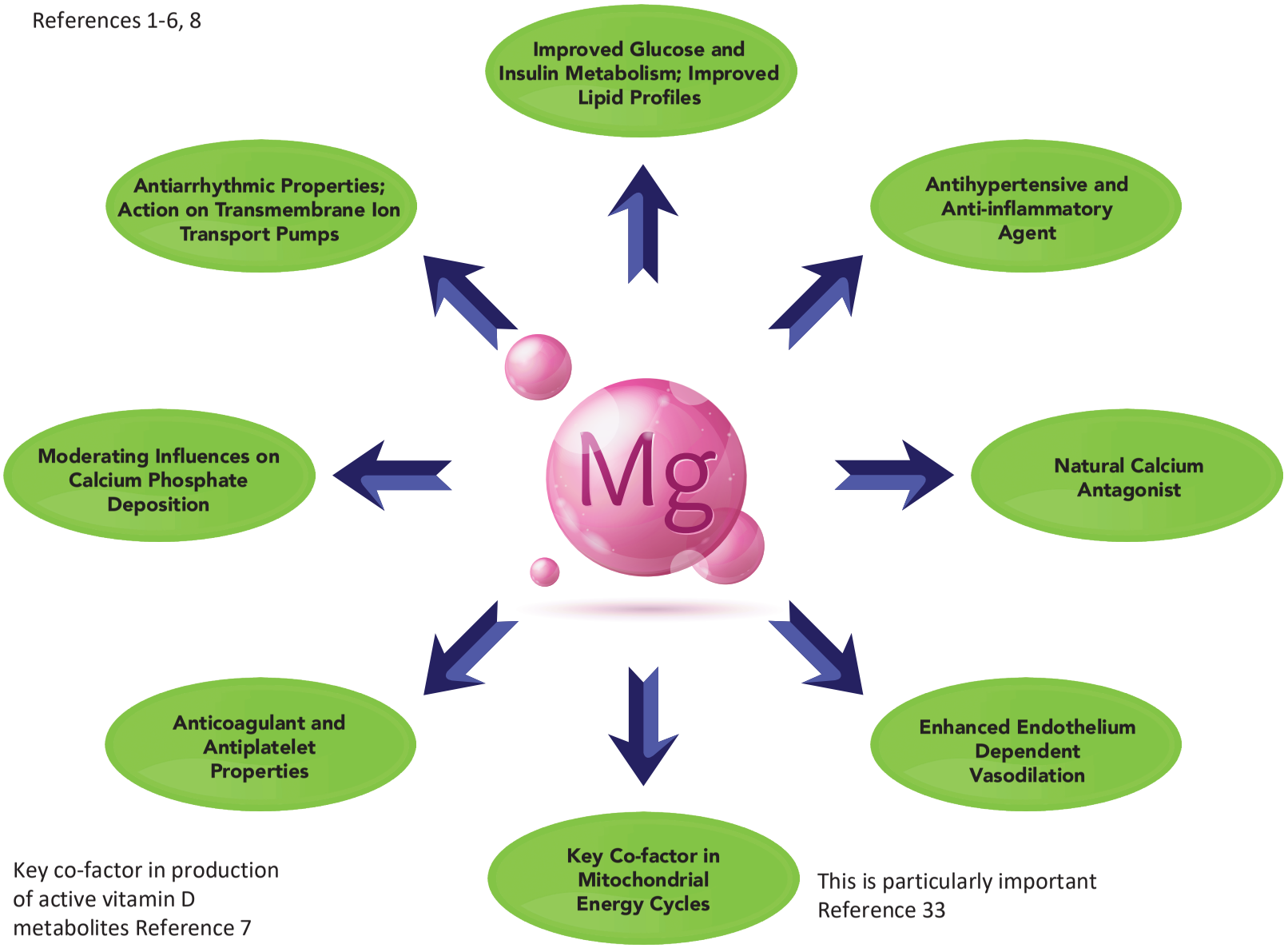
SUMMARY OF THE INVENTION

To supply the population with sufficient magnesium, a very high dose of magnesium supplement is required to reach the recommended daily allowance (RDA). For example, 4 grams of magnesium oxide would be required as an oral supplement. A slow release magnesium composition offers several advantages. Slow release avoids high concentration of magnesium in the gastrointestinal (GI) tract. Unabsorbed magnesium in the GI tract often leads to diarrhea. Slow release can avoid accumulation of unabsorbed magnesium and reduce such adverse effects. The present invention discloses such dosage forms and methods of use thereof.

In one aspect, the present invention provides an oral dosage form comprising magnesium (Mg) and threonate (T), wherein said threonate comprises one or more of a threonate salt or a threonate precursor, wherein said oral dosage form has an in vitro dissolution profile in a dissolution medium, and wherein said dissolution profile ranges between less than or equal to 5% in about 2 hours, less than 10% in about 4 hours, less than 40% in about 6 hours, greater than or equal to 60% in about 10 hours, and greater than or equal to 80% in about 12 hours as measured using a USP type II (paddle) dissolution system at 75 rpm, at a temperature of 37° C.

In some embodiments, the magnesium and threonate in said oral dose form is encapsulated in a tablet. In some embodiments, at least a portion of said magnesium (Mg) and threonate (T) is complexed in a salt form of MgT_2. In some embodiments, at least a portion of said magnesium (Mg) and threonate (T) is complexed in a salt form of MgT_2 present in

References 1-6, 8



Key co-factor in production of active vitamin D metabolites Reference 7

This is particularly important Reference 33

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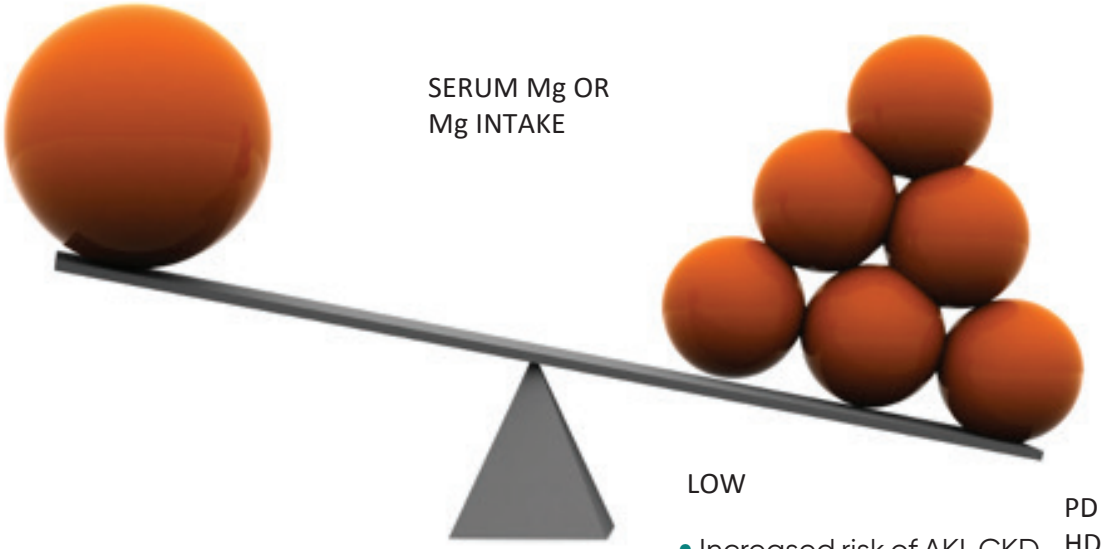
HIGH

- Improved cellular energy metabolism — References 11, 36, 61; post-transplant 51, 52
- Reduced incidence and progression of CKD — References 45, 66
- Higher levels of survival in CKD and ESRD patients — References 42, 63
- Lower prevalence of vascular calcification — Reference 66 and see below
- Stimulation of bone maintenance — References 54 and 57



SERUM Mg OR
Mg INTAKE

LOW

- Increased risk of AKI, CKD, or progression to ESRD — References 45, 53 — PD Ref 19, 62; HD Ref 31
- Decreased production of active vitamin D metabolites — Reference 7
- Increased risk of manifestation of low grade chronic inflammation — References 55,56,65
- Increased risk of vascular calcification and mortality — Refs 21, 27, 32, 40, 43 — PD Ref 12; HD Ref 29,30
- Increased risk of carotid atherosclerosis and stroke — Refs 13, 67
- Increased risk of peripheral thromboses — Ref 5
- Decreased RBC stability and circulating lifetime — Refs 58, 59
- Inadequate support of musculoskeletal health — Reference 41
- Increased risk of new-onset diabetes in ren al transplant recipients — Refs 25, 26

Sudden Death References 18, 38, 50

Coronary Artery Disease Reference 41

Anemia Reference 64