Nutrition and Health
Series Editor: Adrianne Bendich

Ronald Ross Watson
Victor R. Preedy
Sherma Zibadi *Editors*

Magnesium in Human Health and Disease

Humana Press

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Adrianne Bendich, PhD, FACN, Series Editor

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ISBN 978-1-62703-043-4 ISBN 978-1-62703-044-1 (eBook)
DOI 10.1007/978-1-62703-044-1
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2012945418

Printed on acid-free paper

Humana Press is a brand of Springer
Springer is part of Springer Science+Business Media (www.springer.com)

Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes: 1) a synthesis of the state of the science, 2) timely, in-depth reviews by the leading researchers in their respective fields, 3) extensive, up-to-date fully annotated reference lists, 4) a detailed index, 5) relevant tables and figures, 6) identification of paradigm shifts and the consequences, 7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, 8) suggestions of areas for future research and 9) balanced, data-driven answers to patient as well as health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The Series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The editor(s), whose training(s) is (are) both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"Magnesium and Health", edited by Professor Ronald Ross Watson PhD and Professor Victor R. Preedy PhD DSc FRIPH, is a welcome addition to the Nutrition and Health Series. Magnesium, as an essential mineral and the 4th most abundant mineral in the body and 2nd most abundant mineral within cells, is critical to the formation of energy within each cell of the body and is also involved in muscle contraction, neurological and cardiovascular functions and bone metabolism as examples. Over the past decade, there has been an increased interest in the importance of magnesium in the area of cellular biology as well as clinical nutrition. Thus, it is timely that the first volume solely dedicated to objective reviews of the latest research on magnesium and human health and disease be developed. This is the first volume on magnesium for the health professional which is neither the result of a scientific conference nor a single chapter that attempts to review an entire field of research.

The 20 chapters in this comprehensive volume examine the biological as well as clinical consequences of magnesium deficiency and review the data related to the beneficial effects of optimal magnesium status. The book is logically organized into five sections and begins with an overview section that includes informative chapters on the assessment of magnesium status, dietary sources of this essential nutrient, and reviews the essential functions of magnesium in inflammation, endothelial function and cytokine regulation using the clinically relevant data on the role of magnesium in cardiovascular disease as well as placental and neonatal neurological function. The extensively referenced first chapter includes over 500 citations as well as excellent tables of clinical importance.

The second section contains four chapters that describe the importance of magnesium status in certain clinical conditions and chronic diseases. The first chapter examines the negative effects of

magnesium deficiency that has been seen in asthmatics. Evidence suggests that magnesium can directly influence lung function by regulating smooth muscle contractility and neuromuscular excitability, immune function, inflammation and oxidative stress. Research indicates that adults with mild to moderate asthma may have inadequate magnesium intakes and may benefit from taking magnesium supplements. Another critical role of magnesium is electrolyte homeostasis. The chapter on magnesium and kidney function examines the importance of magnesium-dependent enzymes in controlling the electrolyte pumps in the glomerulus. This chapter clearly demonstrates the importance of the kidney to optimal cardiovascular function and their interactions during renal disease. Since the kidney controls magnesium blood levels, any alteration in kidney function will affect systemic magnesium levels. Adequate magnesium intake is also important in maintaining glucose and insulin homeostasis. Magnesium is an essential mineral needed for activation of over 300 enzymes, glucose transportation between membranes, glucose oxidation, all reactions involving phosphorylation, energy exchange, and for the proper activity of insulin. The next two chapters examine the association of magnesium status, genetic factors involved with magnesium metabolism and the risk of development of type 2 diabetes. The chapter by Song et al. includes informative tables and figures that include prospective studies linking magnesium status and type 2 diabetes and an extensive list of potential candidate genes involved in magnesium metabolism.

The third section contains unique chapters that examine the potential for magnesium supplementation to beneficially affect certain disease conditions. Type 2 diabetes is reviewed in two unique chapters; the first examines the potential for supplementation to affect insulin actions in the metabolic syndrome, hypertension and type 2 diabetes. The second chapter looks at the data from Asian versus non-Asian populations with regard to magnesium intake and risk of type 2 diabetes and considers the potential role of ethnically-specific genetic factors in differences in epidemiological findings linking magnesium to type 2 diabetes. As mentioned above, magnesium is important in bone formation and is a major component of the outer surface of bone. Magnesium also is involved in the regulation of parathyroid secretion as well as its actions and also affects vitamin D metabolism. The data on magnesium status and osteoporosis as well as magnesium supplementation and bone density are reviewed in detail. The last chapter in this section describes the adverse effects of certain cancer chemotherapy drugs including cisplatin, 5- fluorouracil and leucovorin. Due to the loss of absorptive surface of the gastrointestinal tract following chemotherapy, magnesium levels may be significantly reduced and some of the serious adverse effects associated with these drugs, including significant neuropathy, may be due in part to lowered magnesium status. Tables included in this chapter outline the clinical studies where magnesium supplementation has been provided to cancer patients treated with the above-mentioned drugs and the resultant reduction in adverse effects.

The fourth section contains four chapters that specifically examine the critical role of magnesium in hypertension and cardiovascular disease. Magnesium's role as a natural calcium channel blocker theoretically should affect blood pressure. The chapter objectively examines the epidemiological data as well as mechanisms of action of magnesium and posits that higher than recommended intakes of magnesium may lower blood pressure especially if combined with reduced sodium intake. Magnesium addition in vitro to heart cells prevents intracellular depletion of magnesium, potassium and high-energy phosphates. Laboratory animal studies report that magnesium supplementation improves myocardial metabolism, prevents intra-mitochondrial calcium accumulation and reduces vulnerability to oxygen-derived free radicals. Magnesium affects vascular tone, platelet aggregation, endothelial function, infarct size, lipid metabolism, cardiac arrhythmias, myocardial infarction and heart failure. The next three chapters provide detailed review of the studies that show the beneficial impact of magnesium on cardiovascular tissues and resultant data linking low magnesium status with increased risk of cardiovascular diseases and their consequences. Data on the use of intravenous magnesium in patients with arrhythmias are also reviewed objectively. Although intravenous magnesium has been used for a variety of ventricular arrhythmias, the evidence to support its anti-arrhythmic effects is

strongest in the prevention of atrial fibrillation after cardiac surgery, reduction of ventricular rate in acute-onset atrial fibrillation, and prevention and treatment of certain types of tachycardia.

The final section on magnesium and neurological function contains five comprehensive, clinically relevant chapters. The chapters include investigations that span the entire lifetime from prenatal development to loss of neurological function associated with aging. The chapters include chronic diseases as well as in-depth discussions of the mechanisms by which acute injuries such as thermal or electrical burns, head or musculoskeletal trauma, subarachnoid hemorrhage and/or intracerebral bleeds can result in loss of magnesium or increased requirement. Acute stressor states involve systemic inflammatory responses accompanied by neurohormonal activation. The adrenergic nervous and renin-angiotensin-aldosterone systems and effector hormones are integral to stressor responses that require optimal levels of magnesium for reduction of adverse effects. Intravenous magnesium is also used in the treatment of acute brain injuries and the clinical studies are tabulated for the reader. The final chapter reviews the multitude of effects of acute and chronic alcohol exposure. Two effects are to decrease total diet quality including magnesium intake and at the same time, increase magnesium excretion. Low magnesium status has been implicated in the neurological dysfunctions seen with excess alcohol intake.

The logical sequences of the Sections as well as the chapters within each Section enhance the understanding of the latest information on the current standards of practice with regard to the physiological and pharmacological uses of magnesium. The volume is of value to clinicians, related health professionals including dieticians, nurses, pharmacists, physical therapists, and others involved in the successful treatment of hypomagnesemia. This comprehensive volume also has great value for academicians involved in the education of graduate students and post-doctoral fellows, medical students and allied health professionals who plan to interact with patients with relevant disorders.

The volume contains over 55 detailed tables and figures that assist the reader in comprehending the complexities of the metabolism as well as the potential benefits and risks of magnesium on human health. The over-riding goal of this volume is to provide the health professional with balanced documentation and awareness of the newest research and therapeutic approaches including an appreciation of the complexity of the effects magnesium can have on virtually every organ system within the body. Hallmarks of the 20 chapters include key words and bulleted key points at the beginning of each chapter, complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. There are over 2,400 up-to-date references; all chapters include a conclusion to highlight major findings. The volume also contains a highly annotated index.

This unique text provides practical, data-driven resources based upon the totality of the evidence to help the reader understand the basics, treatments and preventive strategies that are involved in the understanding of how magnesium may affect healthy individuals as well as those with acute injuries and/or chronic diseases. Of equal importance, critical issues that involve patient concerns, such as malnourishment, potential effects on mental, cardiovascular and immune functions are included in well-referenced, informative chapters. The overarching goal of the editors is to provide fully referenced information to health professionals so they may have a balanced perspective on the value of various preventive and treatment options that are available today as well as in the foreseeable future.

In conclusion, “Magnesium and Health”, edited by Ronald Ross Watson, PhD and Victor R. Preedy, PhD DSc FRIPH FRSH FIBiol FRCPath provides health professionals in many areas of research and practice with the most up-to-date, well referenced and comprehensive volume on the current state of the science concerning magnesium. This volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., FACN, FASN

Preface

Magnesium is an essential mineral which is required for growth and survival of humans. Since magnesium is a mineral and not synthesizable, it must be obtained through dietary foods and/or supplements. Magnesium is found in many sources, primarily whole grains, green leafy vegetables, nuts, and legumes. Even with many dietary sources, only about one-third of Americans maintain the appropriate dietary intake of magnesium. A very small number of people have drug-induced severe magnesium deficiency. So major issues reviewed are the benefits of magnesium supplementation to reach (a) recommended intakes or (b) *above*-recommended intakes to promote health or treat various diseases and risk factors.

While two-thirds of people have intakes of magnesium below recommended amounts, only a small group is frankly deficient. Symptoms of magnesium deficiency include excitability, weak muscles, and fatigue. Deficiency of magnesium can cause low serum potassium and calcium levels, retention of sodium, and low circulating levels of regulatory hormones. These changes in nutrients cause neurological and muscular symptoms, such as tremor and muscle spasms. Further, magnesium deficiency may cause loss of appetite, nausea, vomiting, personality changes, and death from heart failure. Just as high magnesium intakes improve insulin resistance and diabetics' health, low serum levels play an important role in carbohydrate metabolism and worsen insulin resistance. Causes of magnesium deficiency include alcohol abuse, poorly controlled diabetes, excessive or chronic vomiting, and/or diarrhea. Thus, the effects of inadequate or deficient intakes of magnesium are critical to health and are be reviewed by experts in this book.

Hypermagnesemia is a *rare* electrolyte disturbance caused due to very high serum levels of magnesium. Normally, the kidney is very effective in excreting excess magnesium. Hypermagnesemia occurs due to excessive intakes of antacids or laxatives which contain magnesium salts. Often, very high serum potassium and low calcium are also major causes. These may result in muscle weakness, cardiac arrhythmia, or sudden death. Certain drugs can also deplete magnesium levels, such as osmotic diuretics, some anticancer drugs, cyclosporine, amphetamines, and proton pump inhibitors. Magnesium is absorbed orally at about 30 % bioavailability from any water-soluble salt. Magnesium citrate is a common oral magnesium salt available in 100- and 200-mg magnesium supplements typically per capsule. Some multinutrient supplements sold in developed countries contain magnesium. Insoluble magnesium salts, such as milk of magnesia (magnesium hydroxide) and magnesium oxide, are released by the stomach acid for neutralization before they can be absorbed and, thus, offer poor oral magnesium sources. Severe low serum magnesium levels are treated medically with intravenous or intramuscular magnesium sulfate solutions which are bioavailable and effective. As magnesium excess occurs rarely and usually due to drug use, it will be reviewed but not as a major focus of the book.

Since magnesium is a mineral and not synthesizable, it must be obtained through the dietary foods and/or supplements. Magnesium is found in many sources primarily whole grains, green leafy vegetables, nuts, and legumes. Even with many dietary sources, only about one-third of Americans maintain the appropriate dietary intake of magnesium. Interestingly, higher intakes of magnesium positively

affect insulin resistance in type 2 diabetics, suggesting that the optimum intake for people with this disease may be higher than the recommended daily intake. In addition, hypertension, cholesterol levels, and cardiovascular disease are all modified positively for health promotion by high intakes of magnesium. Recent research found that magnesium supplementation in overweight individuals decreased insulin markers and led to changes in genes related to metabolism and inflammation. The benefits of dietary supplements to produce *high* levels and/or treat deficiency are be reviewed by several authors. New research is suggesting more roles of magnesium supplementation as a therapy to reach intakes above the recommended ones. For example, magnesium supplementation are reviewed as a modifier of diseases of old age and for treatment of preeclampsia, asthma, ocular health, etc. Thus, the *primary goal* of this book are to get expert reviews of the potential benefits, or lack thereof, of normal and high magnesium supplementation. Animal model research and early human trials are reviewed to document other disease states that would benefit from increased magnesium intake.

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Acknowledgments

The work of our editorial assistant, Bethany L. Stevens, and Kevin M. Wright of Humana Press in communicating with authors and working with the manuscripts and the publisher was critical to the successful completion of the book and is much appreciated. Their daily responses to queries and collection of manuscripts and documents were extremely helpful. Support for Ms. Stevens' work was graciously provided by the Natural Health Research Institute, as part of its mission to communicate to scientists about bioactive foods and dietary supplements was vital (http://www.naturalhealthresearch.org). This was part of its efforts to educate scientists and the lay public on the health and economic benefits of nutrients in the diet as well as supplements. Mari Stoddard of the Arizona Health Sciences Library was instrumental in finding the authors and their addresses in the early stages of the book's preparation. The support of Humana Press staff as well as the input by the series editor, Adrianne Bendich, is greatly appreciated for the improved organization of this book.

Biography

Ronald R. Watson, Ph.D. attended the University of Idaho but graduated from Brigham Young University in Provo, Utah, with a degree in chemistry in 1966. He earned his Ph.D. in biochemistry from Michigan State University in 1971. His postdoctoral schooling in nutrition and microbiology was completed at the Harvard School of Public Health, where he gained 2 years of postdoctoral research experience in immunology and nutrition. From 1973 to 1974 Dr. Watson was assistant professor of immunology and performed research at the University of Mississippi Medical Center in Jackson. He was assistant professor of microbiology and immunology at the Indiana University Medical School from 1974 to 1978 and associate professor at Purdue University in the Department of Food and Nutrition from 1978 to 1982. In 1982 Dr. Watson joined the faculty at the University of Arizona Health Sciences Center in the Department of Family and Community Medicine of the School of Medicine. He is currently professor of health promotion sciences in the Mel and Enid Zuckerman Arizona College of Public Health. Dr. Watson is a member of several national and international nutrition, immunology, cancer, and alcoholism research societies. Among his patents he has one on a dietary supplement; passion fruit peel extract with more pending. He had done DHEA research on its effects on mouse AIDS and immune function for 20 years. He edited a previous book on melatonin (Watson RR. *Health Promotion and Aging: The Role of Dehydroepiandrosterone (DHEA).* Harwood Academic Publishers, 1999, 164 pages). For 30 years he was funded by Wallace Research Foundation to study dietary supplements in health promotion. Dr. Watson has edited more than 100 books on nutrition, dietary supplements and over-the-counter agents, and drugs of abuse as scientific reference books. He has published more than 500 research and review articles.

Victor R. Preedy, BSc, DSc, FSB, FRCPath, FRSPH is currently Professor of Nutritional Biochemistry in the Department of Nutrition and Dietetics, King's College London, and Honorary Professor of Clinical Biochemistry in the Department of Clinical Biochemistry, King's College Hospital. He is also Director of the Genomics Centre, King's College London, and a member of the School of Medicine, King's College London. King's College London is one of the world's leading universities. Professor Preedy gained his Ph.D. in 1981, and in 1992, he received his Membership of the Royal College of Pathologists (MRCPath), based on his published works. He was elected a Fellow of the Royal College of Pathologists (FRCPath) in 2000. In 1993, he gained his second doctorial degree (D.Sc.) for his outstanding contribution to protein metabolism. In 2004, Professor Preedy was elected a Fellow to both the Royal Society for the Promotion of Health (FRSH) and the Royal Institute

of Public Health (FRIPHH). In 2009, he was elected a Fellow of the Royal Society for Public Health (RSPH). He is also a Fellow of the Society of Biology (FSB). Professor Preedy has written or edited over 550 articles, which include over 160 peer-reviewed manuscripts based on original research, 85 reviews, and 30 books. His interests pertain to matters concerning nutrition and health at the individual and societal levels.

Dr. Sherma Zibadi, MD, Ph.D., received her Ph.D. in nutrition from the University of Arizona and is a graduate of the Mashhad University of Medical Sciences, where she earned her M.D. She has recently completed her postdoctoral research fellowship awarded by the American Heart Association. Dr. Zibadi engages in the research field of cardiology and complementary medicine. Her main research interests include maladaptive cardiac remodeling and heart failure, studying the underlying mechanisms and potential mediators of the remodeling process, which helps to identify new targets for treatment of heart failure. Dr. Zibadi's research interest also extends into alternative medicine, exploring the preventive and therapeutic effects of natural dietary supplements on heart failure and their major risk factors in both basic animal and clinical studies, translating lab research findings into clinical practice. Dr. Zibadi is an author of multiple research papers published in peer-reviewed journals and books as well as coeditor of several books.

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Section A
Introduction and Mechanism of Action

Chapter 1
Clinical Assessment of Magnesium Status in the Adult: An Overview

Adel A.A. Ismail, Yasmin Ismail, and Abbas A. Ismail

Key Points

- Serum magnesium measurement is potentially flawed, can be normal despite deficiency.
- Magnesium deficiency is common but under diagnosed; assessment of the patient's lifestyle can help diagnosis.
- Hypermagnesaemia is easy to diagnose analytically in serum but not clinically.
- Treatment of magnesium deficiency and hypermagnesaemia is straightforward and beneficial.

Keywords Magnesium • Hypomagnesaemia • Hypermagnesaemia • Symptoms • Clinical and laboratory assessment • Diagnosis • Treatment

Introduction

The relationship between magnesium and health has been recognized some 400 years ago and well before magnesium was even identified as an element. The English summer in 1618 was exceptionally hot and dry. A farmer by the name of Henry Wicker in Epsom, Surrey, dug out a few wells in his farm to get water for his herd of cows. He noticed that his thirsty animals refused to drink this water because it had a tart and bitter taste. However, he noted that this water has the ability to rapidly heal scratches, sores and rashes both in animals and humans. Tried by others, the fame of this water spread by the word of mouth. Londoners flocked to Epsom which became a spa town, surpassing other more fashionable ones at the time such as Tunbridge wells in Kent for its water and salt. A physician (also a botanist) with extensive practice in London by the name of Nehemiah Grew (Fig. 1.1) noted that the salt in this water had a laxative effect. This "mind-boggling" discovery was patented as a purging salt, and a

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R.R. Watson et al. (eds.), *Magnesium in Human Health and Disease*, Nutrition and Health,
DOI 10.1007/978-1-62703-044-1_1,

Fig. 1.1 *Nehemiah Grew*, English physician and microscopist, 1641–1712 (Reprinted from Makers of British Botany, Cambridge University Press, 1913)

factory in London was established for worldwide marketing. In England this salt was (and still is) known as "Epsom salt" and in continental Europe as "salt anglicum".

Late in the seventeenth century and thereafter, Epsom salt was one of the most popular medicinal drugs. The people who used it did not know exactly why it was so beneficial, but they did understand that in some way, it was good for health and promoted longevity. Even now, it is surprising to know that there is an "Epsom Salt Council" in the UK whose members are wild about the goodness of "Epsom salt". Currently, 13 wonderful ways have been described for the use of "Epsom salt" by this council.

Epsom salt is hydrated magnesium sulphate ($MgSO_4.7H_2O$). In 1755, the Scottish chemist Joseph Black in Edinburgh identified magnesium as an element, and the English chemist Sir Humphry Davy was the first to isolate magnesium by electrolysis in 1808 and suggested the name "magnium" (using the suffix noun "ium" as in sodium, potassium, etc.). The name magnesium was subsequently used, derived from the Greek district of "Magnesio" in Thessaly in which magnesium carbonate (magnesio alba) was abundant. Permutation of that name is used worldwide apart from Slavic countries in which magnesium in Cyrillic is known as "horcik".

The nineteenth century was the age of chemistry of magnesium; its biology, however, became clearer during the twentieth century. Magnesium is the fourth most abundant mineral in the body after calcium, potassium and sodium. Approximately 40% of magnesium is intracellular and some 60% in bone and teeth with 1% or less present in the circulation [1].

Biochemically, magnesium is regarded with justification as a "chronic regulator" and physiologically as a "forgotten electrolyte". An adequate magnesium store is necessary for the function of hundreds of widely distributed kinases, a group of magnesium-dependent enzymes that catalyse the transfer of a phosphate group and attach it to the recipient molecule, i.e. phosphorylation. The underlying mechanism seems to be the same for all known kinases and necessitates the presence of magnesium. Kinases can

only bind "ATP-Mg" molecules, cleave the γ phosphate group which is subsequently transferred to the recipient molecule. Phosphorylation is an ion-radical, electron-spin selective process [2] which transforms (switches on) an inactive molecule into an active or "functional" one, which can then perform a specific biological/biochemical task (or vice versa). In addition to the phosphorylation of small organic molecules, up to 30% of functional body proteins are activated by magnesium-dependent kinases.

Magnesium-dependent kinases [3–10] are paramount in regulating the cell cycle and growth, as well as apoptosis. It has also a vital role in signal transduction and the production and actions of second messengers such as c-AMP, diacylglycerol, calmodulin and c-GMP. Central to all these intracellular functions is that each protein must be at the right place and work at the right time. Individual kinases regulate and control a particular subset of proteins in these highly complex systems within each cell.

Magnesium plays an important role in electrolyte homeostasis, being necessary for the activation of ATP/ATPase pumps such as Na^+/K^+ pump, Na^+/Ca^{++}, Na^+/Mg^{++} and Mg^{++}/Ca^{++} pumps which, if deficient, causes impairment and reduction in their efficacy and activities. Chronic magnesium deficiency with time may eventually lead to overt pathology and electrolyte disturbances such as "refractory" hypokalaemia and/or hypocalcaemia. Neither the former nor the latter can be corrected by potassium or calcium treatment alone, and magnesium replacement becomes essential for restitution. It is therefore paramount to note that magnesium itself is an electrolyte which plays a major role in the homeostasis of other major electrolytes, namely, Na^+, K^+ and Ca^{++}. Furthermore, magnesium plays an important role in bioenergetics, regulating oxidative energy metabolism of protein, carbohydrate and fat metabolism, energy transfer, storage and use. It is also necessary for bone mineral density. About 150 magnesium-dependent kinases are linked to a wide variety of diseases; it is not therefore surprising that magnesium deficiency can potentially cause/exacerbate a wide range of disorders [11–17].

Considering the many vital roles of magnesium, there was surprisingly a lack of information regarding its homeostasis. Only in the last decade, two ion channels have been suggested as magnesium transporters which appear to play a pivotal role in its homeostasis through the dual processes of its absorption from the gut and reabsorption by the kidneys. Ion channels conduct a particular ion after which it is named whilst excluding others, e.g. Na^+, K^+ and Ca^{++} channels. Ion hydration energy (water shell surrounding each ion) and the charges at the binding sites by the ligand make the internal milieu within each channel favourable for conducting only a specific ion. The two dedicated ion channels specifically aimed at transporting Mg^{++} belong to the transient receptor potential melastatin (TRPM), a subfamily of the transient receptor potential protein superfamily involved in transporting other cellular cations such as calcium by TPRM3. Recently, TRPM6 and TRPM7 have been suggested as unique transporters for Mg^{++} termed chanzymes because they possess a channel and a kinase domain. These two chanzymes may therefore represent molecular mechanism aimed at regulating magnesium homeostasis at cellular level [18–24]. They are differentially expressed, with TRPM6 being found primarily in colon and renal distal tubules. Up-regulation of TRPM6 occurs in response to reduction in intracellular magnesium; this in turn enhances magnesium absorption from the gut and its reabsorption by the kidneys and can therefore alter whole-body magnesium homeostasis. TRPM7 is ubiquitous, occurring in numerous organs (e.g. lung). These two chanzymes may therefore represent a molecular mechanism specifically aimed at regulating body magnesium balance [18–24].

Clinical Conditions Associated with Magnesium Deficiency in Adults

Magnesium deficiency is common in the general population as well as in hospitalized patients and can occur in individuals with an apparently healthy lifestyle. Latent magnesium deficiency may be present in >10% of population, more common in the elderly, probably exacerbated by oestrogen which decline in women and men with age. Oestrogen influences body magnesium balance through its effect on TRPM6 which may help in explaining the hypermagnesuria in the elderly in general and postmenopausal in particular. Magnesium deficiency is a clinically under-diagnosed condition yet surprisingly easy to treat [25–29].

Table 1.1 Conditions associated with magnesium deficiency (The numbers between brackets are additional references published from 1990 to April 2011 for each entity)

Electrolytes(1–24): Hypocalcaemia, Hypokalaemia
CVS (25–162): Ventricular arrhythmias esp. torsades de pointes
Cardiac conduction abnormalities: SVTs
Abnormal vascular tone, congestive cardiac failure
Ischaemic heart disease/myocardial infarction
Hypertension (163–215): Pre-eclampsia/eclampsia, primary hypertension
Endocrine (216–285): Type II diabetes mellitus
Metabolic (286–294): The metabolic syndrome
Bone (295–335): BMD and osteoporosis
Muscular (336–353): Muscle weakness, fatigue, numbness, tingling, spasms/cramps/tetany and fibromyalgia
Neurological (354–387): Irritability, depression, migraines and vertical and horizontal nystagmus
Cancer (388–398): Colorectal
Alcoholics (399–420): Exhibiting any of the above manifestations
Respiratory (421–472): Asthma

We have researched peer-reviewed articles on magnesium published in English between 1990 and April 2011 in MEDLINE and EMBASE using database keywords "magnesium, deficiency, diagnosis, treatment and hypomagnesaemia". Bibliographies of retrieved articles have been searched and followed. We have also carried out a manual search of each individual issue of major clinical and biochemical journals in which most of these reports have appeared.

Clinically, magnesium deficiency may present acutely or with chronic latent manifestations. Clinical presentation of chronic/latent magnesium deficiency may vary from vague and non-specific symptoms to causing and/or exacerbating the progression of a wide range of diseases such as cardiovascular pathology (CVS), primary hypertension and Type II Diabetes Mellitus.

Magnesium is a physiological calcium antagonist and natural calcium channel blocker in skeletal and smooth muscle, promoting relaxation, whilst calcium stimulates contraction. A high calcium/magnesium ratio caused by magnesium deficiency and/or high calcium intake may affect this finely regulated homeostatic balance and may be a factor in the increased risk of cardiovascular events in patients receiving calcium supplementation [30, 31]. Magnesium deficiency is implicated/present in almost all patients with hypokalaemia and those with magnesium-dependent hypocalcaemia [32–38].

A growing body of literature has demonstrated a wide pathological role for magnesium deficiency. In 201 peer-reviewed studies published from 1990 to April 2011, magnesium deficiency was associated with increased risk and prevalence in the 11 conditions listed in Table 1.1 (irrespective of the nature, design, parameters, size and statistical approach of these studies). Such an inverse relationship was also demonstrable irrespective of the wide range of methods used to assess magnesium body stores (see references in Table 1.1 for each of these conditions).

Similarly, in 72 studies over the same period, magnesium deficiency was found to predict adverse events, and a reduced risk of pathology was noted when supplementation/treatment was instituted. In a recent study [39], a direct aetiological link between magnesium deficiency, impaired glucose tolerance and CVS pathology was demonstrated. In this study, 13 postmenopausal American women (12 Caucasian and 1 African-American) volunteered to reduce their dietary magnesium intake to ~ one-third of the recommended daily requirement (average 101 mg/day). In less than 3 months, five subjects had cardiac rhythm abnormalities, and three exhibited atrial fibrillation/flutter that responded quickly to magnesium supplementation [39]. Impaired glucose homeostasis was found in ten volunteers who underwent intravenous glucose tolerance test (IV GTT). The clinical manifestation was reflected in reduced levels in red-cell membranes; however, serum levels remained within reference range. This study, though small, is consistent with epidemiological surveys, supplementation trials and animal studies [40, 41] (see Table 1.1 for more references).

"Modus Vivendi" and Potential Magnesium Deficiency

Potential causes of magnesium deficiency are outlined in Table 1.2. It may not be difficult to surmise potential magnesium deficiency from an individual's lifestyle as body stores are dependent on the balance between daily intake and renal loss [23, 42–44]. Approximately 30–70% of dietary magnesium intake is absorbed by a healthy gut with negative magnesium store and high gastric acidity enhancing absorption [23, 42–47]. The commonly recommended daily intake for adults is 320–400 mg/day (or 6 mg/kg/body weight for both genders) [48] and increases during pregnancy, lactation and regular strenuous exercise [49–51] which increases magnesium losses in urine and sweat. An average healthy daily diet supplies ~250 mg of magnesium (120 mg/1,000 calories), with green vegetables, cereals, fish and nuts being a rich source (see Table 1.3). Refined grains and white flour are generally low in magnesium. Unrefined sea salt is very rich in magnesium occurring at ~ 12% of sodium mass; however, because this makes raw sea salt bitter, magnesium (and calcium) is removed, making purified table salt essentially ~99% sodium chloride.

Another important source is water [52, 53], with some (but not all) hard tap water containing more magnesium than soft water. Local water supplier can provide information regarding magnesium concentration in tap water to each location (e.g. postcode area in the UK). The bioavailability of magnesium in water is generally good at ~ 60%; however, its absorption from water significantly declines with age [54, 55].

The magnesium content in tap and/or bottled water varies greatly. Hardness of water is caused by dissolved calcium and magnesium and is usually expressed as the equivalent quantity of calcium carbonate in mg/l (e.g. a hardness of 100 mg/l would contain 40 mg/l of elemental Ca and/or Mg and 60 mg as carbonate). Water containing > 200 mg/l equivalent calcium carbonate is considered hard; medium hardness is between 100 and 200 mg/l, moderately soft < 100 mg/l and soft < 50 mg/l calcium carbonate equivalent. Hardness above 200 mg/l results in scale deposition on heating if large amount of calcium carbonate is present because it is less soluble in hot water.

Table 1.2 Factors contributing to chronic/latent magnesium deficiency

Age: Elderly absorb less and lose more magnesium
Daily diet low in magnesium
Soft drinking water, bottled or hard water low in magnesium
Refined salt for cooking and in food
Pregnancy, lactation and regular strenuous exercise
Regular alcohol intake esp. spirits
Malabsorption (also short-bowel syndrome/intestinal surgery)
Drugs such as diuretics

Table 1.3 Magnesium content in food

Magnesium-rich food contains > 100 mg per measure. A measure is a cup of vegetables, grains, legumes or 2 oz (or 56 g) of nuts and seeds
Vegetables: Green and leafy, e.g. spinach, seaweed and artichoke
Fish: Halibut (4 oz)
Grains: Barley, wheat, oat and bran (whole grain bread)
Legumes: Soybean, *adzuki* and black bean
Nuts: Almond, Brazil, cashews, pine and peanuts (peanut butter)
Seeds: (Dried) pumpkin, sunflower and watermelon
Chocolate: Dark (2 oz)
Intermediate values of magnesium are present in other vegetables, fruits, meats, dairy products and fish

It may be important to point out that the ratio of calcium to magnesium in hard water varies. Hard water may, in some cases, have predominantly high concentration of calcium but low in magnesium or vice versa. Furthermore, the type of anion in the calcium salt is important. For example, hard water which is rich in calcium carbonate is usually regarded as "temporarily hard" because on heating, calcium carbonate precipitates. In other forms of hard waters, magnesium and/or calcium may combine with anions other than carbonate, such as sulphate, and in this case, water is referred to as "permanently hard" because these elements are not affected by heating. All naturally occurring magnesium salts unlike those of calcium are relatively more soluble in both cold and heated water, including $MgCO_3$. Although hard water is a general term which encompasses wide ratios of calcium to magnesium, the magnesium contents in most hard water (but not all) are 5–20 times more than in soft water and can potentially provide up to 30% of daily requirement.

The term soft water is straightforward because it is used to describe types of water that contain few calcium or magnesium ions. Soft water usually comes from peat or igneous rock (volcanic rocks which make 95% of the earth's crust after the cooling of magma); other sources are granite and sandstone. All such sedimentary rocks are usually low in calcium and magnesium. The magnesium content of soft drinking water is between 2 and 20 mg/l, average ~ 6 mg/l. The content of magnesium in bottled water varies from 0 to 126 mg/l [56], whilst carbonated tonic and soda water contain little or no magnesium. One gram of instant coffee granules releases ~ 5 mg of magnesium in hot water; the corresponding figure for tea is ~ 0.6 mg [57].

Significant magnesium deficiency has been reported in both elderly self-caring in the community and in hospitalized Norwegians [58]. In a consensus survey involving 37,000 Americans, 39% were found to ingest less than 70% of the recommended daily magnesium intake and 10% of women over the age of 70 years consume less than 42% of the recommended dietary requirement [59–61]. When dietary magnesium intake is poor, the kidney can compensate by increasing fractional reabsorption from the filtered load, mainly in the loop of Henle with further reabsorption in the distal tubule. Normally, plasma magnesium is filtered at the glomeruli apart from the fraction bound to albumin. Reabsorption of the filtered load can vary depending on the body store, being lowest when body stores are adequate to maximum in deficiencies. Prolonged periods of poor dietary intake, however, would eventually lead to a decline in intracellular magnesium concentration.

Excessive renal loss is, however, a common cause of negative magnesium stores. Alcohol is a known cause, being magnesium diuretic as even moderate amounts produce magnesiuresis. Alcohol increases urinary magnesium loss above baseline by an average of 167% (range 90–357%), and its effect is rapid [62–67] and occurs even in individuals with an already negative magnesium balance. Alcohol consumption has increased with availability and cheaper cost [66, 68] and in moderate amounts, is considered socially and culturally acceptable (taken as 2–4 units, i.e. 16–32 g of alcohol a day, though there is no standard definition). It may be of interest to point out that spirits such as gin, rum, brandy, cognac, vodka and whisky contain little or no magnesium; fermented apple ciders have 10–50 mg/l of magnesium whilst beer and wine have levels ranging from ~ 30–250 mg/l. Although drinks such as some ciders, beer and wine may be considered "magnesium-rich", they cannot be recommended as a reliable source. Furthermore, large consumption of magnesium-rich beer and wine can have a laxative or even diarrhoeic effect, potentially impeding bioavailability and absorption.

It appears reasonable therefore to suggest that a lifestyle associated with low dietary magnesium intake in food and drinking water, purified table salt for cooking and in food, and regular and strenuous exercise coupled with moderate and regular consumption of alcoholic drinks which cause a net renal magnesium loss can additively lead to negative balance over time. Magnesium deficiency can be further compounded with malabsorption and those receiving medications [69–73] such as diuretics (loop and thiazide); proton pump inhibitors (e.g. omeprazole); tacrolimus; chemotherapeutic agents such as cisplatin, cyclosporine and cetuximab; and some phosphate-based drugs.

In summary, modus vivendi when carefully examined can determine the potential of latent magnesium deficiency which may be associated with a wide range of major pathologies. It is, however, a common practice for clinicians to rely more on laboratory tests in the diagnosis of magnesium deficiency.

Laboratory Tests and Assessment of Magnesium Deficiency

Assessment of magnesium status is biochemical. Serum magnesium is the most commonly requested test and is informative when magnesium is reduced, indicating hypomagnesaemia. However, normal serum magnesium (commonly reported between ~0.75 and <1.2 mmol/l) remained problematical because in patients suspected with magnesium deficiency, serum concentration can be normal despite whole-body deficiency [74–77]. This is not surprising due to the fact that magnesium in the circulation does not represent total body magnesium, being only 1% or less of total body content. A fraction of bone magnesium appears to be on a surface-limited pool, present either within the hydration shell or else on the crystal lattice. Based largely on animal studies, it has been speculated that this form of bone surface magnesium may represent a limited buffering capacity [38].

Magnesium in serum is subdivided into three heterogeneous fractions, namely, magnesium-bound to albumin (~ 30%), a fraction loosely complexed with anions such as phosphate, citrate and bicarbonate (~20%) and a free ionized fraction. Although serum ionized magnesium which represents ~ 50% of total serum magnesium correlates with total magnesium concentrations [78], it is mistakenly regarded by some to be the biologically active moiety, i.e. analogous to ionized calcium. Unlike calcium, however, the bulk of magnesium is intracellular, bound to numerous subcellular components, and these are the moieties which account for its biological role. In other words, it is the intracellular bound magnesium which expresses its primary biological role, and normal serum magnesium, total or ionized, must be interpreted with caution [77]. However, ionized magnesium measurement has an advantage because it can be made on whole blood thus avoiding the laborious and time-consuming step of separating serum from cells [78, 79].

Deficiency of other major minerals such as calcium, sodium and potassium are commonly reflected in their serum concentrations; similarly, low serum magnesium (with normal albumin) in a fasting or random sample also confirms significant deficiency warranting supplementation. However, some cases with latent magnesium deficiency may not be associated with low serum levels. For this reason, the practicable, inexpensive and commonly used serum magnesium must be regarded as potentially flawed test, capable of identifying magnesium deficiency in some but not all patients with deficiency and negative body stores.

To exclude with confidence latent/chronic magnesium deficiency in cases with high index of suspicion albeit normal serum magnesium, a dynamic study, namely, magnesium loading test, would be appropriate if renal function is normal. This procedure is probably the best physiological "gold standard test" within the capability of all routine hospital laboratories. It involves the administration of elemental magnesium load (as sulphate or chloride) intravenously followed by assessment of the amount of elemental magnesium excreted in the urine in the following 24 h [80–84]. A large fraction of the given magnesium load is retained, and a smaller amount of the given dose appears in the urine in patients with latent magnesium deficiency. Such a procedure in the experience of one of us was valuable, accurate and informative; however, it is time-consuming and (understandably) not commonly used in clinical practice. It is also contraindicated in individuals with renal impairment.

Magnesium Loading Test

The loading test measures the body's retention of magnesium and therefore reflects the degree of deficiency [80–84]. Attention to details is, however, paramount for valid interpretation of data. Patients should empty their bladder immediately before the test. The test involves intravenous administration of 30 mmol of elemental magnesium (1 mmol = 24 mg) in 500 ml 5% dextrose over a period of 8–12 h. A slow-rate infusion is important because plasma magnesium concentration affects the renal reabsorption threshold, and abrupt elevation of plasma concentration above the normal range would

reduce magnesium retention and increase urinary excretion with its potential misinterpretation. Urine collection begins with the onset of magnesium infusion and continues over the next 24-h period, including a last void at the end of this period.

Patients with adequate body magnesium stores retain less than 10% of the infused elemental magnesium load. Latent magnesium deficiency is considered present if less than 25 mmol of elemental magnesium is excreted in the 24-h collection. Repeat of magnesium loading test to check repletion can also be informative because average difference between repeats is ~ 2%. Magnesium body stores are considered repleted when >90% of the elemental magnesium load is excreted in the following 24-h urine.

Magnesium loading test is contraindicated in patients with renal impediment, salt-losing nephropathy, respiratory failure and medications which affect renal tubular function such as diuretics, cisplatin, cyclosporine… etc.

A number of studies attempted to simplify the magnesium loading test [85] by reducing the infused magnesium load to 0.1 mmol of elemental magnesium per kilogram body weight, reducing the infusion time to 1–2 h and collecting urine over a shorter period of 12 h. Oral magnesium loading test was also described. However, although these modifications are simpler, their usage was limited and the 8–12-h infusion of 30 mmol remained the standard test.

Cellular Magnesium Concentration In Vitro

Since ~99% of magnesium is intracellular, it would be reasonable to assess body magnesium status by measuring cellular magnesium concentration rather than serum magnesium levels. Fractionating cellular components in blood and tissues can be time-consuming, and its handling can be inaccurate. Cellular zone separation commonly relies on centrifugal force (sedimentation velocity) which in blood allows sample to separate into RBC-rich bottom layer, an intermediate "buffy-coat" layer of WBCs and an upper plasma portion.

Magnesium concentration in RBC's membrane has been used for assessing body magnesium status [39]. After isolating RBCs, they are lysed by suspension into a hypotonic medium. Their uptake of water by osmosis causes the cells to explode, leaving behind an empty membrane sack (commonly referred to as "ghost") which can be subsequently separated as a pellet after centrifugation at 12,000 g. However, extra care is necessary because pellet can still be contaminated by tangles of fibrin, white cells, platelets and unlysed RBCs. Intra-erythrocyte, mononuclear blood cells and granulocytes magnesium levels are also used; however, levels showed poor correlation with other clinical and biochemical parameters [86–88].

Methods for Assessing Intracellular Magnesium In Vivo

Non-invasive methods are research tools of limited pragmatic clinical applications [89–95]. Example is the use of nanorod potentiometric selective sensor electrodes to measure intracellular magnesium. ZnO nanorods were functionalized for selectivity of Mg^{++} by applying a coat of polymeric membrane with Mg^{++}-selective ionophores which exhibited an Mg^{++}-dependent electrochemical potential difference versus Ag/AgCl reference microelectrode [89]. Others used fluorescent probes or magnetic resonance spectroscopy to assess intracellular magnesium.

Another non-invasive technique for quantitating cellular magnesium uses sublingual cells and energy-dispersive X-ray microanalysis (EXA). Sublingual cells have advantages such as accessibility, turnover of < 3 days, non-cornified with long shelf-life exhibiting 99% viability. Excitation of cellular