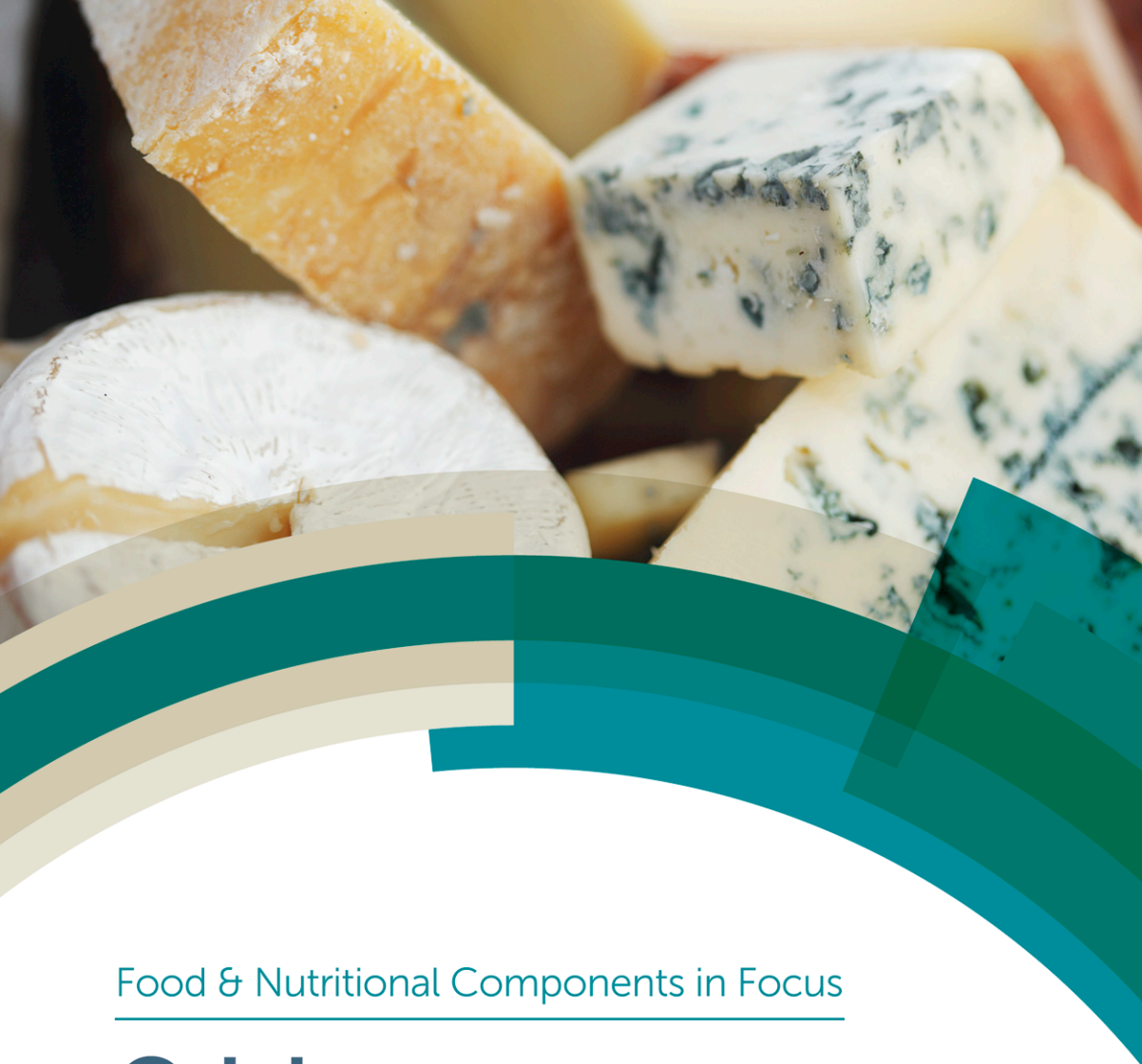




Food & Nutritional Components in Focus

Calcium

Chemistry, Analysis, Function and Effects

Edited by Victor R Preedy



Calcium

Chemistry, Analysis, Function and Effects

Food and Nutritional Components in Focus

Series Editor:

Professor Victor R. Preedy, *School of Medicine, King's College London, UK*

Titles in the Series:

- 1: Vitamin A and Carotenoids: Chemistry, Analysis, Function and Effects
- 2: Caffeine: Chemistry, Analysis, Function and Effects
- 3: Dietary Sugars: Chemistry, Analysis, Function and Effects
- 4: B Vitamins and Folate: Chemistry, Analysis, Function and Effects
- 5: Isoflavones: Chemistry, Analysis, Function and Effects
- 6: Fluorine: Chemistry, Analysis, Function and Effects
- 7: Betaine: Chemistry, Analysis, Function and Effects
- 8: Imidazole Dipeptides: Chemistry, Analysis, Function and Effects
- 9: Selenium: Chemistry, Analysis, Function and Effects
- 10: Calcium: Chemistry, Analysis, Function and Effects

How to obtain future titles on publication:

A standing order plan is available for this series. A standing order will bring delivery of each new volume immediately on publication.

For further information please contact:

Book Sales Department, Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge, CB4 0WF, UK

Telephone: +44 (0)1223 420066, Fax: +44 (0)1223 420247

Email: booksales@rsc.org

Visit our website at www.rsc.org/books

Calcium

Chemistry, Analysis, Function and Effects

Edited by

Victor R. Preedy

School of Medicine, King's College London, UK

Email: editor@publicationeditor.org.uk



Food and Nutritional Components in Focus No. 10

Print ISBN: 978-1-84973-887-3

PDF eISBN: 978-1-78262-213-0

ISSN: 2045-1695

A catalogue record for this book is available from the British Library

© The Royal Society of Chemistry 2016

All rights reserved

Apart from fair dealing for the purposes of research for non-commercial purposes or for private study, criticism or review, as permitted under the Copyright, Designs and Patents Act 1988 and the Copyright and Related Rights Regulations 2003, this publication may not be reproduced, stored or transmitted, in any form or by any means, without the prior permission in writing of The Royal Society of Chemistry or the copyright owner, or in the case of reproduction in accordance with the terms of licences issued by the Copyright Licensing Agency in the UK, or in accordance with the terms of the licences issued by the appropriate Reproduction Rights Organization outside the UK. Enquiries concerning reproduction outside the terms stated here should be sent to The Royal Society of Chemistry at the address printed on this page.

The RSC is not responsible for individual opinions expressed in this work.

The authors have sought to locate owners of all reproduced material not in their own possession and trust that no copyrights have been inadvertently infringed.

Published by The Royal Society of Chemistry,
Thomas Graham House, Science Park, Milton Road,
Cambridge CB4 0WF, UK

Registered Charity Number 207890

For further information see our web site at www.rsc.org

Preface

Recently, there have been major advances in our understanding of the chemistry and function of nutritional components. This has been enhanced by rapid developments in analytical techniques and instrumentation. Chemists, food scientists and nutritionists are, however, separated by divergent skills, and professional disciplines. Hitherto this transdisciplinary divide has been difficult to bridge.

The series *Food and Nutritional Components in Focus* aims to cover in a single volume the chemistry, analysis, function and effects of single components in the diet or its food matrix. Its aim is to link scientific disciplines so that information becomes more meaningful and applicable to health in general.

The series *Food and Nutritional Components in Focus* covers the latest knowledge base and has a structured format with major subsections covering

- Compounds in Context
- Chemistry
- Analysis
- Function and Effects

In some books the section on Chemistry is also linked with Biochemistry. Each chapter has a novel cohort of features namely by containing:

- *Summary Points*
- *Key Facts* (areas of focus explained for the lay person)
- *Definitions of Words and Terms*

The series covers numerous classes of dietary components including, for example, minerals, vitamins, food additives, and so on. The chapters are written by national or international experts, specialists and leaders in the field.

Calcium has the following material: Section 1 Calcium in Context has material on dietary sources and metabolism, ethnicity and geography, availability, milk and dairy products, legumes, vegetables, cereals, baked goods and meals. Section 2 Chemistry and Biochemistry has chapters covering chemistry, biological roles, analysis and vitamin D. Section 3 Analysis has material on ultrasonic-dialysis capillary electrophoresis, fluorescent polyanions, osteoclastic calcium resorption, X-ray diffraction patterns, nanocalcium, milk, food frequency questionnaires, calcium digestibility, *in vivo*, *in vitro* and *ex vivo* techniques, bioavailability and CaCo-2 cells. Section 4 Function and Effects has extensive coverage on calcium in relation to adolescents, dietary calcium, protein intake, bioaccessibility, legumes, rice calcium and phytic acid, acrylamide, gluten, breadmaking, soymilk, prebiotics, drinking water, saliva, intestinal absorption, calcium-sensing receptors, taste cells, calcium signalling, gene expression, mitochondria, pregnancy, lactation, bone health, hypertension, transporters, cholesterol metabolism, vitamin D, exercise, osteoprotegerin body fat, critical care, and hypercalcemia.

Calcium is specifically designed for chemists, analytical scientists, forensic scientists, food scientists, dieticians, nutritionists, food scientists, health professionals and research academics. The series is suitable for lecturers and teachers in food and nutritional sciences. Importantly, the series will be a valuable resource for college or university libraries as a reference guide.

Professor Victor R. Preedy
King's College London

Contents

Calcium in Context

Chapter 1	Calcium in the Context of Dietary Sources and Metabolism	3
	<i>Maciej S. Buchowski</i>	
1.1	Overview of Calcium and Its Physiological Functions	3
1.1.1	Sources of Calcium in the Diet	4
1.1.2	Calcium Absorption and Excretion	8
1.1.3	Calcium Homeostasis and Systemic Balance	9
1.1.4	Calcium Bioavailability and Dietary Factors Affecting Calcium Absorption	11
	Summary Points	13
	Key Facts	14
	Definitions of Words and Terms	16
	References	17
Chapter 2	The Biological Roles of Calcium: Nutrition, Diseases and Analysis	21
	<i>Leonardo M. Moreira, Raphael P. Araujo, Fernando P. Leonel, Henrique V. N. Machado, Alexandre O. Teixeira, Fabio V. Santos, Vanessa J. S. V. Santos, and Juliana P. Lyon</i>	
2.1	Introduction	21
2.1.1	Calcium in the Biological Medium	23
2.1.2	Calcium in the Diet	24
2.1.3	The Calcium Metabolism	25
2.1.4	The Calcium Action in Several Cardiovascular Diseases	25
2.1.5	Calcium and Osteoporosis	26

2.1.6	Methods of Analysis and Evaluation of Calcium in Feeds and Biological Tissues	26
2.1.7	Conclusions	27
	Summary Points	27
	Key Facts of Calcium in the Human Body	27
	Definitions of Words and Terms	27
	List of Abbreviations	28
	References	28
Chapter 3	Food Sources of Calcium Vary by Ethnicity and Geography	30
	<i>Noreen Willows</i>	
3.1	Introduction	30
3.2	Milk and Dairy Foods Consumed Worldwide	30
3.2.1	Europe	31
3.2.2	Middle East	32
3.2.3	Canada, United States of America, and Australia	33
3.2.4	South Asia	33
3.2.5	East and Southeast Asia	34
3.2.6	Africa	36
3.3	Nondairy Sources of Calcium Consumed Worldwide	36
3.3.1	Asia	36
3.3.2	Africa	38
3.3.3	Mexico and Central America	39
	Summary Points	39
	Key Facts	39
	Definitions of Words and Terms	40
	List of Abbreviations	41
	References	41
Chapter 4	Calcium Availability in Specific Foods: Milk and Dairy Products, Legumes, Vegetables, Cereals, Baked Goods and Cooked Meals	46
	<i>M^a Victorina Aguilar Vilas</i>	
4.1	Introduction	46
4.2	Bioavailability: Influencing Factors	47
4.2.1	Calcium Intake and Speciation	47
4.2.2	Vitamin D	47
4.2.3	Proteins or Specific Amino Acids	49
4.2.4	Carbohydrates	49
4.2.5	Fat	50
4.2.6	Minerals	50
4.2.7	Oxalic Acid	50
4.2.8	Phytic Acid	50

4.2.9 Fiber	50
4.2.10 Other Dietary Factors	51
4.3 Calcium Availability in Specific Foods	51
4.3.1 Milk and Dairy Products	51
4.3.2 Legumes	56
4.3.3 Vegetables	57
4.3.4 Cereals and their Derivatives	58
4.3.5 Baked Goods	59
4.3.6 Beverages	59
4.3.7 Cooked Meals	60
Summary Points	60
Key Facts of Availability	60
Definition of Words and Terms	61
List of Abbreviations	61
References	62

Chemistry and Biochemistry

Chapter 5 The Chemistry of Calcium 67

Daniel Perrone and Mariana Monteiro

5.1 Chemical Properties of Calcium	67
5.2 Calcium Isotopes in Nutrition Research	70
Summary Points	71
Keys Facts of Alkaline-Earth Metals	72
Definitions and Explanation of Key Terms	72
List of Abbreviations	73
References	73

Chapter 6 Vitamin D and Impact on Total-Body Calcium 75

Howard A. Morris

6.1 Introduction	75
6.2 Calcium is an Essential Nutrient	76
6.2.1 Recommended Daily Intakes for Calcium	76
6.2.2 Oestrogen, the Calcium Economy and Influence on Recommended Daily Intake	77
6.3 Vitamin D is an Essential Nutrient	78
6.3.1 Vitamin D Requirement and Metabolism	79
6.3.2 Vitamin D and Metabolic Bone Disorders	80
6.3.3 Regulation of Plasma 1,25D Levels	83
6.4 Vitamin D Activities and Regulation of Bone-Mineral Homeostasis	84
6.4.1 The Basic Multicellular Unit of Bone Remodeling	84
6.4.2 Vitamin D Activities within Osteoblasts and Osteocytes	86
6.5 Conclusions	87

Summary Points	87
Key Facts	88
Definitions and Explanations	88
List of Abbreviations	89
References	89

Analysis

Chapter 7	Ultrasonic-Dialysis Capillary Electrophoresis Inductively Coupled Plasma Optical Emission Spectrometry Analysis of Calcium Speciation in Red Blood Cells	95
	<i>Biyang Deng, Shuangjiao Sun, and Yingzi Wang</i>	
7.1	Introduction	95
7.2	Methodological Considerations	97
7.3	Effects of Various Factors	99
7.3.1	Effect of Buffer Concentration	99
7.3.2	Effect of Applied Voltage	100
7.4	Lysis of HRBC	100
7.5	Electrophoresis Separation of Calcium Species in HRBC Cytoplasm	100
7.6	Electrophoresis Separations of Calcium Species in HRBC	101
7.7	Quantification of Calcium-Containing Species in HRBC	102
7.8	Identification of Other Calcium Species Using Ultrasonic Dialysis	102
7.9	Identification of Free Ca^{2+} in HRBC Cytoplasm	104
7.10	Quantification, Detection Limit and Recovery of Free Ca^{2+} in HRBC Cytoplasm	104
	Summary Points	104
	Key Facts	105
	Key Facts of Ultrasonic Dialysis	105
	Key Facts of Capillary Electrophoresis Inductively Coupled Plasma Mass Spectrometry/Atomic Emission Spectrometry	105
	Key Facts of Metallomics	106
	Key Facts of Requirements for Reliable Elemental Speciation Analysis	106
	Key Facts of Detection Systems for Elemental Speciation Analysis	106
	Definitions of Words and Terms	107
	List of Abbreviations	108
	Acknowledgments	108
	References	108

Chapter 8	Using Fluorescent Polyanions to Assay for Osteoclastic Calcium-Resorption Activity	111
	<i>Tatsuya Miyazaki and Osamu Suzuki</i>	
8.1	Introduction	111
8.2	Current Methods of Evaluating Osteoclast Function	112
8.3	Fluorescent Polyanions to Assay for Osteoclastic Calcium-Resorption Activity	113
8.3.1	CaP (Hydroxyapatite) Plate	114
8.3.2	Coating of Fluorescein-Labeled Polyanion to CaP Plate	115
8.3.3	Bone Resorption Assay	116
8.3.4	Evaluation of Drugs for Osteoporosis	119
8.4	Concluding Remarks	120
	Summary Points	120
	Key Facts about Fluorescent Polyanions and CaP Resorption	121
	Definitions of Words and Terms	122
	List of Abbreviations	123
	References	123
Chapter 9	Methods for the X-Ray Diffraction Patterns of Nanocalcium in Milk	126
	<i>Ching-Hsiang Chen, Liang-Yih Chen, and Hsiao-Chien Chen</i>	
9.1	Overview of Calcium in Food Nanotechnology	126
9.1.1	Function of Calcium in Human Body	126
9.1.2	Food Nanotechnology	128
9.1.3	Analysis of Calcium	129
9.2	X-Ray Diffraction Technology	130
9.2.1	X-Ray Generation	131
9.2.2	Bravais Lattices	132
9.2.3	Bragg Spectrometer	132
9.3	Structure of Nanocalcium in Milk	136
9.4	Conclusion	138
	Summary Points	140
	Key Facts	140
	Key Facts of Nanocalcium Additive and its Importance	140
	Key Facts of Structural Identification by Using X-ray Diffraction	141
	Definitions of Terms	141
	List of Abbreviations	142
	References	143

Chapter 10	Using Food-Frequency Questionnaires for Calcium Intakes	146
	<i>B. Pampaloni and M. L. Brandi</i>	
10.1	Introduction	146
10.2	Using FFQs to Assess Dietary Habits in Epidemiological Studies and Calcium Intakes	148
10.2.1	Dietary Assessment in Different Ethnic Groups	150
10.2.2	Obesity	151
10.2.3	Diabetes Type 2	151
10.2.4	Stroke	152
10.2.5	Cardiometabolic Risk Factors	153
10.2.6	Cardiometabolic Risk Factors in Young People	154
10.2.7	Gastroesophageal Reflux Disease	154
10.2.8	Kidney Stones	154
10.2.9	Colorectal Cancer (CRC)	155
10.2.10	Calcium and Bone	156
10.3	Conclusion	159
	Summary Points	159
	Key Facts	160
	Key Facts of Food-Frequency Questionnaires and their Use	160
	List of Abbreviations	160
	References	161
Chapter 11	Calcium Digestibility Using <i>In Vivo</i>, <i>In Vitro</i> and <i>Ex Vivo</i> Techniques	164
	<i>F. Rossi</i>	
11.1	Introduction	164
11.2	Methods for Estimating Ca Digestibility	165
11.2.1	<i>In Vitro</i> Methods	165
11.2.2	<i>In Vivo</i> Studies	169
11.2.3	Cell Culture	173
	Summary Points	174
	Key Facts	174
	List of Abbreviations	176
	References	177
Chapter 12	Determining Calcium Bioavailability Using Caco-2 Cells	179
	<i>Amparo Alegría, Guadalupe García-Llatas, and Reyes Barberá</i>	
12.1	Introduction	179
12.2	Caco-2 Cells	181

12.2.1 Generalities	181
12.2.2 Methodological Aspects of Caco-2 Cell Assays	181
12.3 Calcium Absorption Mechanisms in Caco-2 Cells	184
12.4 Bioavailability of Calcium-Enriched Foods	184
12.5 Influence of Food Components and Processing upon Calcium Bioavailability	185
12.5.1 Fiber and Phytic Acid	185
12.5.2 Calcium–Iron Interaction	186
12.5.3 Maillard Reaction Products	186
12.5.4 Peptides and Proteins	187
12.5.5 Processing	188
Summary Points	196
Key facts	196
Caco-2 Cells as a Model to Study Calcium Bioavailability	196
Definitions of Words and Terms	196
List of Abbreviations	197
References	197

Function and Effects

Chapter 13 Adolescents and Dietary Calcium	203
<i>Marta Mesías, Isabel Seiquer, and M. Pilar Navarro</i>	
13.1 The Role of Calcium in Adolescence	203
13.2 Recommended Calcium Intakes	204
13.3 Main Food Sources of the Daily Calcium Intake	206
13.4 Determinant Factors Affecting the Calcium Absorption during Adolescence	208
13.4.1 Hormonal Factors	208
13.4.2 Dietary Factors	209
13.5 Determinant Factors Affecting Calcium Retention during Adolescence	211
13.5.1 Hormonal Factors	213
13.5.2 Dietary Factors	214
13.6 Other Factors Affecting Bone-Mass Acquisition	216
13.7 Conclusions	216
Summary Points	217
Key Facts	217
Key Facts of Calcium	217
Key Facts of Adolescence	218
Key Facts of Osteoporosis	218
Definitions of Words and Terms	218
List of Abbreviations	219
Acknowledgements	219
References	219

Chapter 14	The Influence of Protein Intake on Calcium Balance	223
	<i>E. Rouy and D. Tome</i>	
14.1	Introduction	223
14.2	Protein Intake and Calcium Metabolism: Interacting at Multiple Levels	224
14.2.1	Protein Intake Increases Urinary Calcium Excretion	224
14.2.2	Does Protein Intake Increase Calcium Absorption?	224
14.2.3	Is Protein-Induced Acidosis a Threat to Calcium Metabolism?	226
14.2.4	The Calcium-Sensing Receptor also Senses Amino Acids	227
14.2.5	Overall Effect of Protein Intake on Calcium Balance	228
14.3	Effects of Protein Intake on Calcium Metabolism and Implications for Health	229
14.3.1	Protein Intake and Bone: Anabolic or Catabolic?	229
14.3.2	Protein Intake, Urinary Calcium and Kidney-Stone Formation	230
14.4	Conclusions	231
	Summary Points	231
	Key Facts	232
	Key Facts on Protein	232
	Key Facts on Osteoporosis	232
	Key Facts on Kidney Health	232
	Definitions of Words and Terms	233
	List of Abbreviations	234
	References	234
Chapter 15	Bioaccessibility of Calcium in Legumes	237
	<i>M^a Jesús Lagarda, Antonio Cilla, and Reyes Barberá</i>	
15.1	Introduction	237
15.2	Calcium Content in Legumes	238
15.3	Calcium Bioaccessibility Studies in Legumes	240
15.3.1	Dietetic Factors Affecting Calcium Bioaccessibility. Influence of Processing	242
	Summary Points	252
	Key Facts	252
	<i>In Vitro</i> Bioavailability of Ca in Legumes	252
	Definitions of Words and Terms	252
	List of Abbreviations	253
	References	253

Chapter 16	Calcium – Function and Effects: Rice Calcium and Phytic Acid Levels	256
	<i>Jianfen Liang, Yifan He, Qian Gao, Xuan Wang, and M. J. Robert Nout</i>	
16.1	Introduction	256
16.2	Calcium in Rice	257
16.2.1	Calcium Contents in Rice Products	258
16.2.2	Availability of Calcium from Rice Products	259
16.3	Phytic Acid in Rice	259
16.3.1	Phytic Acid and its Chemical Determination	259
16.3.2	Phytic Acid Contents of Rice and Rice Products	262
16.4	Location of Calcium, Phosphorous and Phytic Acid in Rice Kernel	265
16.4.1	Location of Elements with X-Ray Microscope	266
16.4.2	Location of Phytic Acid by Abrasive Method	266
16.5	Conclusion	269
	Summary Points	269
	Definitions of Words and Terms	270
	List of Abbreviations	271
	Acknowledgements	271
	References	271
Chapter 17	Adding Calcium to Foods and Effect on Acrylamide	274
	<i>Neslihan Göncüoğlu Taş, Aytül Hamzalıoğlu, Tolgahan Kocadağlı, and Vural Gökmen</i>	
17.1	Introduction	274
17.2	Acrylamide Formation Mechanism	275
17.3	Mitigation Mechanism of Acrylamide Formation by Calcium	278
17.4	Mitigation of Acrylamide Formation in Foods by Calcium Salts	281
17.5	Effect of Calcium Addition on Sugar Degradation in Foods and Model Systems	283
	Summary Points	285
	Key Facts of Mitigation of Acrylamide Formation with Calcium	286
	Definition of Words and Terms	286
	List of Abbreviations	287
	References	287

Chapter 18	Addition of Calcium to Gluten and Nongluten Flours for Breadmaking	291
	<i>Urszula Krupa-Kozak</i>	
18.1	Introduction	291
18.2	Calcium – Role and Demands	292
18.2.1	Calcium in the Human Body	292
18.2.2	Recommendations and Guidelines	293
18.3	Gluten Sensitivity	294
18.4	Calcium in Traditional Breadmaking	296
18.4.1	Nutritional Value of Cereals	296
18.4.2	The Breadmaking Process	297
18.4.3	Cereals Processing vs. Calcium Content	299
18.4.4	Calcium Supplements and Additives in Breadmaking	300
18.5	Calcium in Gluten-Free Breadmaking	301
18.5.1	Technological and Nutritional Quality of Gluten-Free Baked Products	301
18.5.2	Calcium in Gluten-Free Baked Products	302
	Summary Points	304
	Key Facts of Breadmaking	304
	Definitions and Explanations	305
	List of Abbreviations	306
	References	306
Chapter 19	Calcium-Fortified Soymilk: Function and Health Benefits	310
	<i>Lily Stojanovska, Mutamed Ayyash, and Vasso Apostolopoulos</i>	
19.1	Introduction	310
19.2	Calcium Fortification and Bioavailability	312
19.3	Soy Isoflavones	313
19.4	Soymilk and the Immune Response	314
19.5	Soymilk and Bone Health	315
19.6	Soymilk Properties in Health and Disease	316
19.7	Effects of Soymilk in Cholesterol	316
19.8	Effects of Soymilk in Metabolic Syndrome Disorders	318
19.9	Effects of Soymilk in Cancer	318
19.10	Adverse Effects of Soymilk	319
19.11	Conclusion	320
	Summary Points	320
	Key Facts	321
	Key Facts of Soymilk History	321
	Key Facts of Calcium-Fortification Method	322
	Key Facts of Osteoporosis	322

<i>Contents</i>	xvii
Definitions of Words and Terms	323
List of Abbreviations	324
References	324
Chapter 20 The Effect of Prebiotics on Calcium Absorption and Utilization	329
<i>Steven Jakeman and Connie Weaver</i>	
20.1 Introduction	329
20.2 What are Prebiotics?	330
20.3 Calcium Absorption	331
20.4 Prebiotic Mediated Calcium Absorption	331
20.4.1 Changes in the Lumen Environment	331
20.4.2 Changes to the Large Intestine	332
20.4.3 Changes to the Gut-Microbial Population	333
20.5 Types of Prebiotics	334
20.5.1 Disaccharides	334
20.5.2 Oligosaccharides	334
20.5.3 Polysaccharides	336
20.5.4 Synbiotics	336
20.5.5 Mixed Prebiotics	336
20.6 Factors that Influence Prebiotic Mediated Calcium Absorption	337
20.6.1 Age	337
20.6.2 Intervention Length and Calcium Status	339
20.6.3 Dose Amount	340
20.6.4 Genetics and Pre-Existing Conditions	341
20.7 Prebiotics on Bone	341
20.8 Conclusion and Future Work	343
Summary Points	343
Key Facts	344
Key Features of Prebiotics	344
Definitions of Words and Terms	344
List of Abbreviations	345
References	345
Chapter 21 Health Aspects of Calcium in Drinking Water	349
<i>A. Ata Alturfan and Ebru Emekli Alturfan</i>	
21.1 Drinking Water	349
21.2 Calcium and Water Hardness	350
21.3 Water as a Source of Calcium and Bioavailability of Calcium in Water	351
21.4 Calcium Content of Drinking Water in Different Regions	352

21.5	Potential Effects of Drinking-Water Hardness on Health	353
21.5.1	Effects of the Hardness of Drinking Water on Cardiovascular Diseases	353
21.5.2	Effects of Calcium in Water on Bone Metabolism	356
21.5.3	Effects of Calcium in Water on Kidney Stones	356
21.6	Conclusion	357
	Summary Points	358
	Key Facts	358
	Key Facts of Potential Health Effects of Drinking-Water Hardness	358
	Key Facts of Calcium and Water Hardness	358
	Definitions of Words and Terms	359
	List of Abbreviations	360
	References	360
Chapter 22	Calcium in Saliva and Impact on Health	364
	<i>Aysen Yarat, Ebru Emekli Alturfan, and Serap Akyuz</i>	
22.1	Importance of Calcium in Biological Systems	364
22.2	Saliva Production, Composition and Salivary Calcium Concentration	365
22.3	The Role of Salivary Calcium in Maintenance of Tooth Integrity	369
22.4	Salivary Calcium and Periondontitis	373
22.5	Salivary Calcium and Dental Caries	374
22.6	Salivary Calcium and Diabetes	375
22.7	Salivary Calcium as a Diagnostic Tool	376
22.8	Conclusion	377
	Summary Points	377
	Key Facts of Salivary Calcium in Maintenance of Tooth Integrity	378
	Definitions of Words and Terms	378
	List of Abbreviations	379
	References	379
Chapter 23	Intestinal Absorption of Calcium	384
	<i>Brian R. Stephens and James S. Jolliff</i>	
23.1	Introduction	384
23.2	Calcium Absorption	385
23.3	The Paracellular Pathway	386
23.4	The Transcellular Pathway	387
23.5	Facilitated Diffusion	388

23.6 Endoplasmic Reticulum-Mediated Transport of Calcium	388
23.7 Vesicular Transport	389
23.8 Calcium Homeostasis	389
23.9 Vitamin D	389
23.10 Other Factors Affecting Calcium Absorption	390
23.11 Studies from Other Animal Models	391
Summary Points	391
Key Facts of Calbindin	392
Definition of Words and Terms	392
List of Abbreviations	393
References	393
Chapter 24 The Calcium-Sensing Receptor in Intestinal Cells	396
<i>Tohru Hira, Shingo Nakajima, and Hiroshi Hara</i>	
24.1 Introduction	396
24.2 Multiple Agonists for CaSR	397
24.3 CaSR in the Gastrointestinal Tract	398
24.3.1 Gut-Hormone Secretion	398
24.3.2 Gastrin and Gastric-Acid Secretion	398
24.3.3 CCK Secretion	399
24.3.4 GLP-1 Secretion	401
24.4 Colonic-Fluid Secretion	403
24.5 Epithelial Proliferation and Differentiation	403
24.6 Future Perspectives	404
Summary Points	406
Key Facts	406
CaSR	406
Enteroendocrine System	407
Nutrient-Sensing Receptors	407
Definitions of Words and Terms	407
List of Abbreviations	408
References	409
Chapter 25 Taste Cells and Calcium Signaling	413
<i>Kathryn F. Medler</i>	
25.1 Introduction	413
25.2 Taste Cell Signaling	416
25.2.1 Ionic Stimuli	417
25.2.2 Chemically Complex Stimuli	419
25.3 Calcium Regulation in Taste Cells	421
25.4 Effects of Obesity on Taste Cell Signaling	422
25.5 Conclusions	425
Summary Points	425

Key Facts of Taste	425
Definitions of Words and Terms	426
List of Abbreviations	427
References	427
Chapter 26 Intracellular Calcium Modulation of Gene Expression	431
<i>Mariana Casas and Enrique Jaimovich</i>	
26.1 Introduction	431
26.2 Muscle-Cell Adaptations to Training	432
26.3 Gene Transcription Regulation by Calcium in Skeletal Muscle	433
26.4 What We Do Know about the Mechanism from Work in Myotubes and Adult Muscle Fibers	434
26.5 Fiber-Type Diversity	435
26.5.1 Ca^{2+} -Dependent Kinases and Phosphatases Involved in Muscle Phenotype Specification	437
26.5.2 Ras-MAPK Pathway	440
26.5.3 IP_3 -Dependent Ca^{2+} Signals and Muscle Plasticity	441
Summary Points	441
Key Facts for Muscle Calcium Signals and Gene Expression	442
Definitions of Words and Terms	443
References	444
Chapter 27 Mitochondrial Calcium Homeostasis and Implications for Human Health	448
<i>Tito Calì, Denis Ottolini, and Marisa Brini</i>	
27.1 Introductory Elements of Calcium Signaling	448
27.2 Mitochondrial Calcium Handling	450
27.2.1 The Molecular Identification of the Players	452
27.3 Mitochondrial Calcium in Human Health	457
Summary Points	460
Key Facts	461
Key Facts of Calciums	461
Key Facts of Mitochondrial Ca^{2+} History	461
Key Facts of the Molecular Identification of the Mitochondrial Ca^{2+} Players	462
Key Facts of ATP	462
Key Facts of Apoptosis	462
Key Facts of Autophagy	463
Definitions of Words and Terms	463

<i>Contents</i>	xxi
List of Abbreviations	464
Acknowledgements	465
References	465
Chapter 28 Pregnancy and Calcium	468
<i>Belal Alshaikh and Kamran Yusuf</i>	
28.1 Introduction	468
28.2 Maternal Adaptations during Pregnancy	469
28.2.1 Intestinal Calcium Absorption	469
28.2.2 Renal Excretion of Calcium	469
28.2.3 Skeletal Calcium Metabolism	470
28.3 Calcium Transfer from Mother to Fetus	470
28.4 Calcitropic Hormones – Changes during Pregnancy	472
28.4.1 Parathyroid Hormone (PTH)	472
28.4.2 Parathyroid Hormone-Related Protein (PTHrP)	472
28.4.3 1,25-Dihydroxyvitamin D ₃ (Calcitriol)	472
28.4.4 Calcitonin	473
28.5 Maternal Calcium Metabolism and Fetal Health	473
28.6 Maternal Calcium Metabolism and Infant Growth	475
28.7 Impact of Pregnancy on Disorders of Calcium Metabolism	475
28.7.1 Pre-eclampsia	475
28.7.2 Gestational Diabetes	476
28.7.3 Hyperparathyroidism	476
28.7.4 Hypoparathyroidism	476
28.7.5 Pseudohypoparathyroidism	477
Summary Points	477
Key Features of Pregnancy and Calcium	478
Definitions of Key Terms	478
List of Abbreviations	480
References	480
Chapter 29 Calcium Supplementation during Pregnancy and Lactation: Implications for Maternal and Infant Bone Health	484
<i>Flávia Fioruci Bezerra and Carmen Marino Donangelo</i>	
29.1 Introduction	484
29.2 Calcium Supplementation and Maternal Bone Outcomes	485
29.2.1 Effects of Calcium Supplementation during Pregnancy	486
29.2.2 Effects of Calcium Supplementation during Lactation	491

29.3	Calcium Supplementation and Fetal/Infant Bone Growth	495
29.3.1	Fetal Bone Growth	496
29.3.2	Evaluation of Fetal and Infant Bone Outcomes	496
29.3.3	Effects of Maternal Calcium Supplementation during Pregnancy on Fetal and Infant Bone Growth	500
29.3.4	Effects of Maternal Calcium Supplementation on Breast-Milk Calcium Concentration	502
29.4	Conclusions	503
	Summary Points	503
	Key Facts of Bone	504
	Definitions of Key Terms	504
	List of Abbreviations	505
	References	505
Chapter 30	The Effects of Dietary Calcium on Hypertension	509
	<i>Filippo Rossi</i>	
30.1	Introduction	509
30.2	Does Calcium Really Affect Blood Pressure?	510
30.3	Ca in the Regulation of the Renin–Angiotensin System	513
30.4	Conclusion	514
	Summary Points	515
	Key Facts	515
	Definition and Explanation of Key Terms	516
	List of Abbreviations	517
	References	517
Chapter 31	Interaction of Dietary Calcium with Genes of Transporters, Receptors and Enzymes Involved in Cholesterol Metabolism	519
	<i>Xiaobo Wang, Lin Lei, Yuwei Liu, Ka Ying Ma, Jingnan Chen, Rui Jiao, Yu Huang, and Zhen-Yu Chen</i>	
31.1	Introduction	519
31.2	Cholesterol Absorption	520
31.3	Cholesterol in Circulation	521
31.4	Cholesterol Homeostasis	523
31.5	Effect of Dietary Calcium on Plasma Lipoprotein in Ovariectomized Hamsters	523
31.6	Interaction of Dietary Calcium with Genes of Transporters, Receptors and Enzymes Involved in Cholesterol Metabolism	525
31.7	Conclusion	526

Summary Points	527
Key Facts of Cholesterol Absorption and Elimination	527
Definition of Words and Terms	527
List of Abbreviations	528
Acknowledgements	528
References	528
 Chapter 32 Bone Health: The Independent and Combined Effects of Calcium, Vitamin D and Exercise in Children and Adolescents	 530
<i>Dimitris Vlachopoulos, Luis Gracia-Marco, Alan R. Barker, Inge Huybrechts, Luis A. Moreno, and Theodora Mouratidou</i>	
32.1 Introduction	530
32.2 Bone Mass Increase during Childhood and Adolescence	532
32.3 Calcium, Vitamin D and Bone Status in Children and Adolescents	533
32.4 Impact of Physical Activity on Bone Status during Growth	535
32.4.1 The Role of Physical Activity on Bone Mass	535
32.4.2 Weight-Bearing Exercise and Bone Mass	536
32.5 Associations of Calcium, Vitamin D and Exercise with Bone Mass of Children and Adolescents	538
32.6 Conclusions	540
Summary Points	540
Key Facts of Bone Health during Growth	541
Definitions and Explanations of Key Terms	541
List of Abbreviations	542
References	542
 Chapter 33 Dietary Calcium and Osteoprotegerin	 547
<i>Dianjun Sun, Jun Yu, Yanhui Gao, and Yuanyuan Li</i>	
33.1 Osteoprotegerin in Health: A Brief Overview	547
33.1.1 Molecular Structure	548
33.1.2 Expression and Regulation	548
33.1.3 Function	549
33.2 Calcium Intake and Osteoprotegerin	550
33.3 Calcium and Osteoprotegerin and Bone Diseases	550
33.3.1 Calcium and Bone Diseases	550
33.3.2 Osteoprotegerin and Bone Diseases	552
33.4 Osteoprotegerin and Diabetes	554
33.5 Osteoprotegerin and Cardiovascular Diseases	555
33.6 Clinical Application of Osteoprotegerin	557
33.6.1 Osteoprotegerin and Hypercalcemia	557

33.6.2 Osteoprotegerin and Bone-Tissue Engineering	558
Summary Points	558
Key Facts	559
Definitions of Words and Terms	559
List of Abbreviations	559
References	560
Chapter 34 Inadequate Calcium Intake and Body Fat in Adults	565
<i>Diane K. Tidwell and Matthew J. McAllister</i>	
34.1 Introduction	565
34.2 Randomized Clinical Trials Investigating Calcium and Body Fat in Adults	566
34.3 Observational Studies Investigating Calcium and Body Fat in Adults	568
34.4 The Biological Plausibility of Calcium's Effect on Body Fat	570
34.5 Summary	575
Summary Points	576
Key Facts	576
Definitions and Explanations of Key Terms	577
List of Abbreviations	577
References	578
Chapter 35 Calcium in Critical Care	582
<i>Dima Youssef and Karin Amrein</i>	
35.1 Introduction	582
35.1.1 Recommended Intake	584
35.1.2 Sources of Calcium	584
35.1.3 Calcium Supplements	584
35.1.4 Calcium Absorption	585
35.1.5 Side Effects of Calcium Supplements	585
35.1.6 Special Situations	585
35.2 Hypocalcemia	585
35.2.1 Causes of Hypocalcemia	586
35.2.2 Clinical Manifestations of Hypocalcemia	589
35.2.3 Diagnostic Approach to Hypocalcemia	590
35.2.4 Treatment of Hypocalcemia	592
35.3 Hypercalcemia	593
35.3.1 Causes of Hypercalcemia	593
35.3.2 Clinical Manifestations of Hypercalcemia	596
35.3.3 Diagnostic Approach to Hypercalcemia	597
35.3.4 Treatment of Hypercalcemia	598

<i>Contents</i>	xxv
Summary Points	600
Key Facts for Calcium in Critical Care	601
Definitions of Words and Terms	601
List of Abbreviations	602
References	602
Chapter 36 Hypercalcemia: An Overview of its Pathology	605
<i>Franco Lumachi and Stefano M. M. Basso</i>	
36.1 Calcium Distribution in the Human Body	605
36.2 Regulatory Mechanisms of Calcium Metabolism	607
36.3 Evaluation of Hypercalcemia	610
36.4 Primary Hyperparathyroidism and Other Benign Diseases	611
36.5 Malignancy-Associated Hypercalcemia	614
36.6 Conclusions	617
Summary Points	617
Key Facts	618
Key Facts of Calcium Functions and Control of Ionized Calcium	618
Key Facts of Parathyroid Hormone Actions	618
Key Facts of Benign Hypercalcemia	619
Malignancy-Associated Hypercalcemia	619
Definitions and Explanations of Key Terms	620
List of Abbreviations	621
References	622
Subject Index	625

Section I

Calcium in Context

CHAPTER 1

Calcium in the Context of Dietary Sources and Metabolism

MACIEJ S. BUCHOWSKI^{*a}

^aDivision of Gastroenterology, Hepatology and Nutrition, Department of Medicine, Vanderbilt University, 1161 21st Avenue South, A4103 MCN, Nashville, Tennessee 37232, USA

*E-mail: maciej.buchowski@vanderbilt.edu

1.1 Overview of Calcium and Its Physiological Functions

Calcium is a divalent cation with an atomic weight of 40, one of the most abundant elements in the Earth's biosphere and it is present in both solid matter and in aqueous solutions. A solid, calcium carbonate, occurs in marble, chalk, limestone, and calcite, calcium sulfate in anhydrite and gypsum, calcium fluoride in fluor spar or fluorite and calcium phosphate occurs in apatite. Calcium also occurs in numerous silicates and aluminosilicates. Many organisms concentrate calcium compounds in their shells or skeletons. For example, calcium carbonate is formed in the shells of oysters and in the skeletons of coral, which are often used as a calcium source in dietary supplements. In soil, calcium usually is present as a cation in colloids. In plants, calcium is present in the leaves, stems, roots, and seeds in

concentration ranging from 0.1% to almost 10%. In living cells, calcium is one of 21 elements occurring as mineral elements in biosphere and is essential for conducting cell functions. In mammals, calcium is present in all cells and accounts for up to 4% of total body weight.

In humans, it ranks fifth after oxygen, carbon, hydrogen, and nitrogen and it makes up 1.9% of the body by weight. Approximately 99% of calcium is contained in bones and teeth as calcium hydroxyapatite ($\text{Ca}_{10}[\text{PO}_4]_6[\text{OH}]_2$) and the remainder is inside the cells (0.9%) and extracellular fluid (0.1%). In the bone and teeth, calcium constitutes 25% of the dry weight and 40% of the ash weight. The extracellular fluid contains ionized calcium at concentrations of about 4.8 mg/100 mL (1.20 mmol L^{-1}) maintained by the parathyroid–vitamin D axis as well as complexed calcium at concentrations of about 1.6 mg/100 mL (0.4 mmol L^{-1}). The plasma contains a protein-bound calcium fraction at a concentration of 3.2 mg/100 mL (0.8 mmol L^{-1}). In the cellular compartment, the total calcium concentration is lower than in extracellular fluid by several orders of magnitude (Robertson and Marshall, 1981).

In bone and teeth, the most calcified structure in the animal and human body, the role of calcium is structural and mechanical, determining their hardness and strength (Abrams, 2011; Hill *et al.*, 2013). The second most calcified structure is the vasculature. Once considered a passive process, vascular calcification has emerged as an actively regulated form of tissue biomineralization, in which skeletal morphogens and osteochondrogenic transcription factors are expressed by cells within the vessel wall, regulating the deposition of vascular calcium (Bithika and Dwight, 2012). Another physiological role of calcium is to act as an activator for several key cellular enzymes such as pancreatic lipase, acid phosphatase, cholinesterase, ATPase, and succinic dehydrogenase (Nicholls, 2002; Brownlee *et al.*, 2010; Hung *et al.*, 2010; Glancy and Balaban, 2012; Tarasov *et al.*, 2012). Through its role in enzyme activation, calcium stimulates muscle contraction (*i.e.* promotes muscle tone and normal heartbeat) and regulates the transmission of nerve impulses from one cell to another through its control over acetylcholine production (Harnett and Biancani, 2003). Calcium is also essential for the normal clotting of blood, by stimulating the release of thromboplastin from the blood platelets (Østerud, 2010; Diamond, 2013). In conjunction with phospholipids, calcium plays a key role in the regulation of the permeability of cell membranes and consequently over the uptake of other nutrients by the cell (Brenner and Moulin, 2012; Kiselyov *et al.*, 2012). On a molecular level, calcium is an important second messenger participating in many activities. For example, when physicochemical insults deregulate calcium delicate homeostasis, it acts as an intrinsic stressor producing or increasing cell damage (Cerella *et al.*, 2010).

1.1.1 Sources of Calcium in the Diet

Dietary calcium comes from food sources associated with dairy products, other foods such as vegetables and cereals, foods fortified with inorganic or organic calcium, and from dietary supplements containing calcium.

Dairy foods are excellent sources of calcium and a major supplier of dietary calcium in the developed and majority of less developed countries (Table 1.1). For example, more than 40% of dietary calcium in North American and British diet come from milk, cheese, and yogurt and from foods to which dairy products have been added such as pizza, lasagna, and dairy desserts (Anonymous, 2011a).

A major nondairy source of calcium is green vegetables such as kale, turnip greens, bok choy, and Chinese cabbage, which provide approximately ~7% of dietary calcium (Table 1.2).

Other nondairy sources of calcium are grains, legumes, fruits, meat, poultry, fish (Tables 1.3 and 1.4), and eggs each providing 1% to 5% of calcium in a typical Western-style diet (Anonymous, 2009).

Other excellent sources of calcium are nuts (Table 1.5) and spices (Table 1.6).

In African diet, calcium-rich foods include crabs, edible caterpillars, locust beans, millet, and cowpea, baobab, and amaranth leaves (Anonymous, 2000).

Table 1.1 Calcium content of selected dairy food sources commonly present in diet. This table contains contents of calcium in dairy foods and eggs. The data is extracted from the USDA Nutrient Data Laboratory: <http://fnic.nal.usda.gov/food-composition/usda-nutrient-data-laboratory>.

Food source	Calcium (mg/100 g)
Milk, nonfat (with added vitamin A and D)	170
Milk, reduced-fat (2% milk fat)	140
Milk, whole (3.25% milk fat)	120
Yogurt, plain, low fat (with or without added fruit)	120–190
Milk, dry, nonfat, regular, without added vitamin A and D	1250
Cottage cheese, nonfat, 1% or 2% milk fat	60–85
Ice creams, milk based, all natural	130–170
Cheese (e.g. cheddar, Swiss, muenster, provolone, mozzarella)	400–800
Egg, whole; raw or cooked	56–62

Table 1.2 Calcium content of selected vegetables and fruits commonly present in diet. This table contains contents of calcium in vegetables and fruits. The data is extracted from the USDA Nutrient Data Laboratory: <http://fnic.nal.usda.gov/food-composition/usda-nutrient-data-laboratory>.

Food source	Calcium (mg/100 g)
Turnip greens, kale, collards; cooked or boiled and drained	130–150
Kale, arugula, turnip greens, soybeans, beet green; raw	120–200
Okra, Chinese cabbage, broccoli, spinach; raw	80–100
Carrots, tomatoes, brussels sprouts, endive, squash; raw	30–40
Onions, asparagus, lima beans, green peas; raw	15–30
Tangerines, blackcurrants, oranges; raw	40–60
Blackberries, kiwifruit, grapes; raw	27–37
Papaya, grapefruit, gooseberries; raw	20–25
Apples, pears, apricots, peaches; raw	4–8

Table 1.3 Calcium content of fish, seafood, and meats commonly present in diet. This table contains contents of calcium in selected fish, seafood, and meat. The data is extracted from the USDA Nutrient Data Laboratory: <http://fnic.nal.usda.gov/food-composition/usda-nutrient-data-laboratory>.

Food source	Calcium (mg/100 g)
Fish, salmon, pink, canned, drained solids	283
Mollusks, oyster, eastern, wild, cooked, moist heat	140
Fish: trout, herring, pike; cooked	50–90
Fish: grouper, ocean perch, tuna, skipjack; cooked	27–44
Chicken, turkey: all meats broiled cooked or roasted	10–30
Pork: loin, other cuts, separable lean and fat, cooked or broiled	30–70
Beef: tenderloin, steak, separable lean and fat, trimmed to 1/8" fat, all grades, cooked, broiled	10–20
Veal, lamb: all grades, cooked, broiled	20–30
Game: all grades, cooked, broiled	10–15

Table 1.4 Calcium content of bread, bakery, cereal, and pasta products commonly present in diet. This table contains contents of calcium in selected bread, bakery, and pasta products and cereal. The data is extracted from the USDA Nutrient Data Laboratory: <http://fnic.nal.usda.gov/food-composition/usda-nutrient-data-laboratory>.

Food source	Calcium (mg/100 g)
Muffins, English muffins, mixed grains toasted	30–250
Bread, mixed grains, commercially prepared	50–600
Crackers, standard snack type	80–250
Pancakes, plain, standard commercial dry mix	70–220
Tortillas, ready-to-bake or -fry, corn	50–175
Cereals, ready-to-eat, single or mixed grains, regular	30–80
Pasta, noodles, macaroni, spaghetti (dry)	5–40

Table 1.5 Calcium content of nuts and seeds commonly present in diet. This table contains contents of calcium in selected nuts and seeds. The data is extracted from the USDA Nutrient Data Laboratory: <http://fnic.nal.usda.gov/food-composition/usda-nutrient-data-laboratory>.

Food source	Calcium (mg/100 g)
Almonds	260–340
Lotus, sesame seeds	140–160
Hazelnuts, filberts	117
Pumpkin, butternuts, sunflower seed kernels	52–87
Chestnuts raw, unpeeled	12–27

In several developed countries, an important source of dietary calcium are foods fortified with calcium, which do not naturally contain calcium such as orange juice, other beverages, soy milk and tofu and ready-to-eat cereals (Table 1.7) (Calvo *et al.*, 2004; Rafferty *et al.*, 2007; Poliquin *et al.*, 2009).

In recent decades, dietary supplements became an important source of dietary calcium. The use of vitamin and mineral supplements that include

Table 1.6 Calcium content of spices commonly present in diet. This table contains contents of calcium in selected dried and fresh spices. The data is extracted from the USDA Nutrient Data Laboratory: <http://fnic.nal.usda.gov/food-composition/usda-nutrient-data-laboratory>.

Food source	Calcium (mg/100 g)
Savory, dried	2100
Marjoram, dried	1990
Thyme, dried	1890
Tarragon, dried	1139
Cinnamon, dried	1002
Curry powder, dried	525
Caraway seed, dried	689
Dill weed, fresh	252
Bay leaf, dried	834

Table 1.7 Calcium content of selected fortified foods. This table contains contents of calcium in selected foods fortified with calcium either during the technological process (tofu) or to increase amount of calcium (orange juice, infant formula, ready-to-eat cereal, flour). The data is extracted from the USDA Nutrient Data Laboratory: <http://fnic.nal.usda.gov/food-composition/usda-nutrient-data-laboratory>.

Food source	Calcium (mg/100 g)
Tofu, raw, firm, prepared with calcium sulfate	680
Orange juice, chilled, includes from concentrate, fortified with calcium and vitamin D	140
Infant formula	125–432
Cereals, ready-to-eat, single or mixed grains, fortified	150–450
Corn or wheat flour, white, all-purpose, enriched, fortified	130–250

calcium becomes commonplace in several populations, especially in the developed countries. For example, among the United States (US) population based on a national survey, about 40% of adults, but almost 70% of older women reported calcium intake from supplements (Bailey *et al.*, 2010). Current estimates from the National Health and Nutrition Survey (NHANES) showed that in the US adult population between 2007 and 2010, dietary supplements users have approximately 10% higher calcium intake than nonusers (Wallace *et al.*, 2014).

The most common forms of supplemental calcium are calcium carbonate and calcium citrate. Generally, less calcium carbonate is required to achieve a given dose of elemental calcium because calcium carbonate provides 40% of elemental calcium, compared with 20% for calcium citrate. However, compared with calcium citrate, calcium carbonate is more often associated with gastrointestinal side effects, including constipation, flatulence, and bloating (Straub, 2007). In contrast, calcium citrate is less dependent than calcium carbonate on stomach acid for absorption (Recker, 1985) and thus, can be taken without food. Other forms of calcium in dietary supplements

include calcium lactate, gluconate, glucoheptonate, and hydroxyapatite and their relevance for life stage groups may vary. The health benefits of calcium supplements are still debatable. For example, in a 2013 update, the *US Preventive Services Task Force* concludes that the current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men (Moyer, 2013). Some recent studies have raised concern about an increased cardiovascular risk with the use of calcium supplements, but the findings are considered inconsistent and inconclusive (Xiao *et al.*, 2013).

1.1.2 Calcium Absorption and Excretion

Calcium is absorbed in the intestine by passive diffusion (paracellular) or by active transport (transcellular) across the intestinal mucosa (Bronner, 2009). The rate of paracellular calcium uptake is considered nonsaturable, while transcellular transport can be upregulated under conditions of dietary calcium constraints. The paracellular route is tied to a downhill concentration gradient between the luminal and the extracellular compartments throughout the entire intestine. Although canonically thought to be constant, the recent evidence suggests that paracellular calcium transport is regulated, at least in part, by $1,25(\text{OH})_2$ vitamin D (Christakos, 2012).

Transcellular calcium absorption can also take place against an uphill gradient, but requires molecular machinery in the form of distinct calcium transport proteins and energy from hydrolyzable adenosine triphosphate (ATP) (Auchère *et al.*, 1998). The absorption occurs mostly in the duodenum and the jejunum (Pansu *et al.*, 1983) and the process is activated by calcitriol and is dependent on the intestinal vitamin D receptor (VDR) and physiologic factors such as the presence of calcium-regulating hormones and the life stage (Whiting, 2010; Gallagher, 2013). Since a concentration gradient is not a prerequisite for this process, transcellular transport accounts for most of the absorption of calcium at low and moderate intake levels (Table 1.8).

The solubility of calcium salts is increased in the acid environment of the stomach, but the dissolved calcium ions to some extent reassociate and precipitate in the jejunum and ileum where the pH is closer to neutral. Recent observations indicate that a reduction of gastric acidity may impair effective calcium uptake throughout the entire intestine (Kopic and Geibel, 2013). In the neutral environment, the absorbability of calcium is determined mainly by the presence of other food components such as lactose, glucose, fatty acids, phosphorus, and oxalate, which can bind to soluble calcium, are released resulting in complex luminal interactions. For example, absorption of calcium supplements, and especially those that are less soluble, is substantially better if they are taken with a meal perhaps by food-stimulated gastric secretion and delayed emptying allowing dispersion and dissolution

Table 1.8 Physiological and dietary factors affecting calcium absorption. This table lists the key factors that affect calcium absorption in humans and lists calcium roles in living cells, and describes calcium physiological role in the human body. Calcium absorption is a complex process influenced by several physiological and dietary factors either promoting or inhibiting this process.

Factors promoting absorption	Factors interfering with absorption
Physiological	
Growth-promoting hormones	Lack of stomach acid
Vitamin D ₃	Diminishing absorption with aging
Optimal gastric acidity	Vitamin D deficiency
Dietary	
Lactose	High-fiber diet
Ingestion with a meal	Oxalates and phosphates
Phosphorus in optimal ratio with calcium	High protein intake

of calcium. In the gastrointestinal lumen, calcium can compete or interfere with the absorption of other minerals such as iron, zinc, and magnesium.

Calcium is excreted in urine, feces, and body tissues and fluids, such as sweat. Calcium excretion in the urine is a function of the balance between the calcium load filtered by the kidneys and the efficiency of reabsorption from the renal tubules. Most of the calcium (~98%) is reabsorbed by either passive or active processes occurring at four sites in the kidney, each contributing to maintaining neutral calcium balance. The majority of the filtered calcium (~70%) is reabsorbed passively in the proximal tubule and the remaining 30% actively in the ascending loop of Henle, the distal tubule, and collecting duct (Allen and Woods, 1994).

1.1.3 Calcium Homeostasis and Systemic Balance

Regulation of calcium homeostasis during a lifetime is a complex process reflecting a balance among intestinal calcium absorption, bone calcium influx and efflux, and renal calcium excretion. Maintaining the level of circulating ionized calcium within a narrow physiological range between 8.5 and 10.5 mg dL⁻¹ (2.12 and 2.62 mmol L⁻¹) is critical for normal body function (Jeon, 2008). Homeostasis of serum calcium level is maintained through an endocrine system comprised of controlling factors, epithelial calcium channels, and feedback mechanisms that includes vitamin D metabolites, primarily calcitriol, and parathyroid hormone (PTH) (Peacock, 2010). Any perturbations in calcium homeostasis can result in hypocalcemia or hypercalcemia and adaptations in calcium handling must occur during a lifetime that include growth and aging (Felsenfeld *et al.*, 2013).

Calcium systemic balance is essential for a multitude of physiological processes, ranging from cell signaling to maintenance of bone health. A

systemic calcium balance (positive, neutral, or negative) is the measure derived by taking the difference between the total intake and the sum of the urinary, fecal, and sweat calcium excretion. These measures have some limitations and are generally cross-sectional in nature, and their precision differs. Long-term balance studies for calcium are rarely carried out because of the difficult study protocol. Calcium balance can also be estimated by using stable isotopes to trace the amount of calcium absorbed from a single feeding. In general, a positive calcium balance is indicative of calcium accretion also termed net calcium retention, neutral balance suggests maintenance of bone, and a negative balance indicates bone loss.

The relevance of the calcium balance state varies depending upon the developmental stage. Infancy through late adolescence periods are characterized by positive calcium balance due to enhanced bone formation. In female adolescents and adults, even within the normal menstrual cycle, there are measurable fluctuations in calcium balance owing to the effects of fluctuating sex steroid levels and other factors on the basal rates of bone formation and resorption. Later in life, menopause and age-related bone loss lead to a net loss of calcium due to enhanced bone resorption.

In an average adult human, daily calcium intake is approximately 800–1000 mg per day (20–25 mmol). From this amount, about 25–50% is absorbed and passes into the exchangeable calcium pool (Figure 1.1). This pool consists of the small amount of calcium in the blood, lymph,

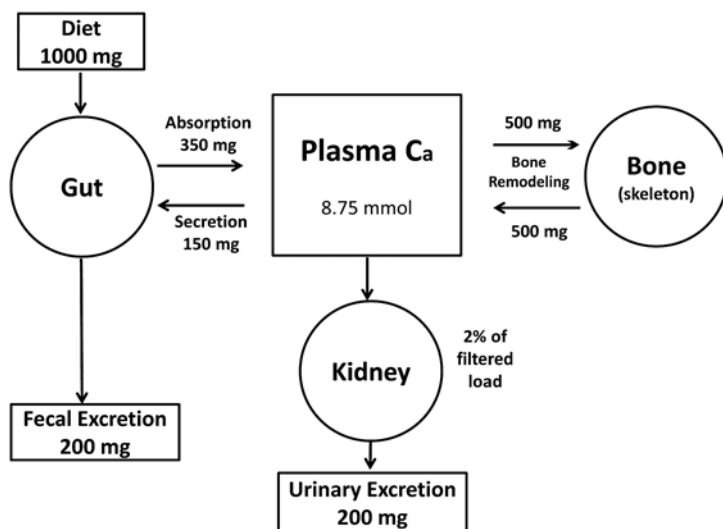


Figure 1.1 Calcium metabolism in an adult human under neutral balance (input = output). Outline of calcium absorption (mg per day) from diet by the gut, reabsorption by the kidney, turnover in bone, and urinary and fecal excretion.

and other body fluids, and accounts for 1% of the total body calcium. Calcium located in bones and teeth (99%) is inaccessible to most physiological processes. Approximately 150 mg per day (3.75 mmol) of calcium enter the intestinal lumen in intestinal secretions such as digestive enzymes and bile, but about 30% of this calcium is reabsorbed (Allen and Woods, 1994). The kidneys filter about 8.6 g per day (215 mmol) of calcium, almost all (~98%) of which is reabsorbed so that only 100 to 200 mg per day (2.5 to 5 mmol) is excreted in approximately equal amounts in the urine and stool. Calcium loss from the skin is about 15 mg per day (0.4 mmol) depending on sweating. In the adult human, the extracellular calcium pool turns over approximately 20 to 30 times per day, while the bone pool turns over every 5 to 6 years.

1.1.4 Calcium Bioavailability and Dietary Factors Affecting Calcium Absorption

Calcium availability from diet varies with form of calcium ingested. In general, bioavailability is increased when calcium is well solubilized and inhibited in the presence of agents that bind calcium or form insoluble calcium salts. The absorption of calcium is about 30% from dairy and fortified foods (e.g., orange juice, tofu, and soymilk) and nearly twice as high from certain leafy green vegetables and calcium supplements (Table 1.9).

Dietary fiber has an adverse effect on calcium absorption in humans and can impair the calcium balance significantly. The majority of marked adverse effects of dietary fiber could be explained by the calcium-binding capacity of phytic acid. However, other constituents of dietary fiber also have the ability to bind calcium. For example, uronic acids present in hemicellulose can bind calcium strongly and may explain the inhibition of dietary fiber calcium absorption from cellulose-containing foods. Pectin present in dietary fiber especially in fruits and vegetables do not affect calcium absorption most likely because 80% of uronic acids in pectin are methylated and cannot bind calcium (Allen and Woods, 1994).

Table 1.9 Foods ranked according to absorbability of calcium. This table lists the key facts about foods in relation to their calcium absorbability divided into four categories.

Absorbability of calcium	Food
Excellent >50%	Kale, broccoli, turnip greens, brussels sprouts, rutabaga, mustard greens, bok choy, cauliflower, watercress
Good ~30%	Milk, dairy products, yogurt, soy milk, calcium-set soy tofu, soy isolates
Fair ~20%	Almonds, sesame seeds, pinto beans, sweet potatoes, nuts
Poor ~5%	Spinach, rhubarb, collard greens

Other food compounds such as oxalic acid that also bind calcium could significantly interfere with absorption and decrease calcium bioavailability. The poor absorption of calcium from spinach (5% compared to 27% absorption from milk) has been attributed to its binding to oxalic acid in spinach. However, other factors may also be involved because calcium absorption from calcium oxalate is twice as high as that from that the plant. It has been documented that during the absorption of calcium oxalate there is no tracer exchange, suggesting that absorption occurs without dissociation of the molecule (Heaney and Weaver, 1989). Similarly, solubility of salts such as citrate or citrate-malate is not related to their absorbability. Thus, the form in which the calcium approaches the mucosal brush border and in which it is transported by the paracellular mechanism may be a better predictor of its bioavailability than the solubility of the salt.

Some food constituents increase calcium bioavailability. For example, lactose enhances the absorption of calcium in animals and human infants. Lactose increases the diffusional component of calcium and perhaps of phosphorus, especially in the ileum, and probably acts osmotically to alter the junctions between the epithelial cells (Kobayashi *et al.*, 1975). Solubility of the dominant chemical form of calcium in specific foods, or of calcium supplements, has a negligible effect on calcium absorption after lactase treatment can be ascribed to the fact that most metabolizable sugars enhance calcium absorption. However, it is doubtful that lactose improves the absorbability of calcium from dairy products beyond infancy. For example, in adults the absorption of calcium from yogurt is the same as that from milk, even though the lactose in yogurt is hydrolyzed in the stomach by lactase originating from the bacteria in the yogurt (Smith *et al.*, 1985).

Dark green, leafy vegetables are often relatively high in calcium. Absorption from many of these is expected to be good, if they are low in oxalic acid (e.g., kale, broccoli, turnip and mustard greens, and collard). For example, absorption from kale is as good as from milk. Other factors may also be involved because calcium absorption from calcium oxalate is twice as high as that from spinach (Heaney and Weaver, 1989). There is no interference of calcium oxalate with the absorption of calcium in milk when the two are consumed together.

Protein intake stimulates acid release in the stomach, and this, in turn, enhances calcium absorption. However, it has long been known that protein also increases urinary calcium excretion. The effect of protein on calcium retention and hence bone health has been controversial (Allen and Woods, 1994). Sodium and potassium in the diet may also affect the calcium balance. High intakes of sodium increase urinary calcium excretion. In contrast, adding more potassium to a high-sodium diet might help decrease calcium excretion, particularly in postmenopausal women (Sellmeyer *et al.*, 2002; Anonymous, 2011b). Phosphate in food is a mixture of inorganic and organic and similarly to calcium, the portion of phosphorus absorption is due to saturable, active transport facilitated by

calcitriol. However, fractional phosphorus absorption is virtually constant across a broad range of intakes, suggesting that absorption occurs primarily by a passive, concentration-dependent process. Interestingly, several observational studies have suggested that the consumption of carbonated soft drinks with high levels of phosphate is associated with reduced bone mass and increased fracture risk. However, it is likely that the effect is due to replacing milk with soda, rather than to phosphorus itself (Heaney and Rafferty, 2001).

Alcohol intake can affect calcium nutriture by reducing calcium absorption although the amount of alcohol required to cause an effect and whether moderate alcohol consumption is helpful or harmful to bone are unknown (Hirsch and Peng, 1996). Caffeine from coffee and tea modestly increases calcium excretion and reduces absorption (Heaney and Recker, 1982). Other studies have indicated that caffeine intake from two to three cups of coffee per day might result in bone loss, but only in individuals with low milk or low total calcium intake (Harris and Dawson-Hughes, 1994).

However, the extent to which these food compounds affect calcium absorption varies, and food combinations affect overall absorption efficiency. For example, eating spinach with milk at the same time reduces the absorption of the calcium in the milk (Weaver and Heaney, 1991). In contrast, wheat products (with the exception of wheat bran) do not appear to have a negative impact on calcium absorption (Weaver *et al.*, 1991). Nevertheless, calcium from foods of plant origin is less bioavailable than calcium from foods of animal origin such as milk and dairy products (Weaver, 2009).

The calcium salts most commonly used for food fortification or as supplements exhibit similar absorbability when tested in pure chemical form (Rafferty *et al.*, 2007). In contrast, the absorbability of calcium from pharmaceutical preparations is usually lower than predictions from studies of pure salts (Weaver and Heaney, 2006). Calcium citrate appears to be better absorbed than calcium carbonate when they are taken with food (Harvey *et al.*, 1988). Other research suggests similar bioavailability of the forms of calcium carbonate and citrate (Heaney *et al.*, 1999). Another form of supplemental calcium, calcium formate, showed a better ability to deliver calcium to the bloodstream after oral administration than both calcium carbonate and calcium citrate (Hanzlik *et al.*, 2005).

Summary Points

- This chapter focuses on calcium in the context of dietary sources and providing bases of calcium metabolism in the human body.
- Calcium is an inorganic element essential to living cells present in the Earth's biosphere as a solid matter and aqueous solution.
- In humans, calcium is an essential constituent of bones and teeth, participates in vascular calcification, and is necessary for activation catalytic and mechanical properties of proteins in key enzymes.

- Dietary sources of calcium include dairy and nondairy foods, fortified foods, and supplements.
- Calcium is readily absorbed through the gastrointestinal tract (through vitamin D₃ action) and calcium absorption is facilitated by some food components by forming calcium complexes with some food components and by high gastric acidity through aiding solubilization of the calcium salts.
- The calcium balance is measured as the difference between calcium absorbed and excreted is essential for many physiological processes, ranging from cell signaling to maintenance of bone health.
- Regulation of calcium homeostasis is based on the interrelationship among intestinal calcium absorption, bone influx and efflux of calcium, and renal calcium excretion.

Key Facts

Key facts about calcium and its forms in biosphere, lists calcium roles in living cells, and describes calcium physiological role in the human body.

1. Calcium is a mineral widely abandoned in the biosphere and occurs mostly as calcium salts such as carbonate, sulfate, fluorite, and phosphate.
2. Calcium is present in all living cells including plant cells.
3. In humans, 99% of the body's calcium is stored in the bones and teeth where it supports their structure and functions.
4. The remaining 1% of supports critical metabolic functions such as vascular contraction and vasodilation, muscle function, nerve transmission, blood clotting, and intracellular signaling and hormonal secretion.

Key facts about calcium sources of dietary calcium. Key facts about major sources of calcium that include dairy and dairy products, nondairy foods such as vegetables, grains and soy foods, foods fortified with calcium such as juices and cereals, and calcium supplements such calcium carbonate and citrate.

1. The major source of calcium in the diet is dairy milk, milk products, and food sources associated with dairy products.
2. Major nondairy foods containing calcium include green leafy vegetables, grains, cereals, and legumes.
3. Other sources of calcium include foods fortified with inorganic or organic calcium such as fruit juices, beverages, and cereals.
4. Dietary supplements containing calcium are becoming important sources of dietary calcium especially in older adults.
5. Calcium carbonate and calcium citrate are major sources of calcium in dietary supplements.

Key facts about calcium absorption and excretion. Key facts about intestinal calcium absorption by two independent pathways and calcium excretion from the human body mainly in urine and stools.

1. Calcium absorption occurs across the intestinal mucosa *via* either passive nonsaturable diffusion (paracellular) or by active transport (transcellular) pathways.
2. Transcellular active transport takes place against an uphill gradient and requires calcium-transport proteins, energy from ATP. The process is activated by calcitriol, dependent on the intestinal vitamin D receptor (VDR) and the presence of calcium-regulating hormones.
3. The paracellular passive transport depends primarily on calcium quantity and availability in the diet.
4. The solubility of calcium salts is increased in the acid environment of the stomach and the intestine absorbs between 25 and 35% of the ingested calcium.
5. Calcium leaves the body mainly in urine and feces, but also in other body tissues and fluids, such as sweat.
6. Calcium excretion in the urine is a function of the balance between calcium load and reabsorption from the renal tubules (~98%).

Key facts about calcium homeostasis and systemic balance in the human body.

1. Regulation of calcium homeostasis during a lifetime is a complex process reflecting a balance among intestinal calcium absorption, bone calcium influx and efflux, and renal calcium excretion.
2. Homeostasis of serum calcium level is maintained through an endocrine system comprised of controlling factors, epithelial calcium channels, and feedback mechanisms that includes calcitriol and parathyroid hormone (PTH).
3. Exchangeable calcium pool accounts for ~1% of calcium in the human body and turnovers 20–30 times a day.
4. Systemic calcium balance (positive, neutral, or negative) is the measure derived by taking the difference between the total intake and the sum of the urinary, fecal, and sweat calcium excretion.

Key facts about calcium bioavailability from food sources and calcium salts and dietary factors affecting its absorption such as fiber, oxalic acid, lactose, and protein.

1. Calcium availability from diet varies with form of calcium ingested.
2. The absorption of calcium is about 30% from dairy and fortified foods (*e.g.*, orange juice, tofu, and soymilk) and nearly twice as high from certain leafy green vegetables and calcium supplements.

3. Dietary fiber has an adverse effect on calcium absorption in humans and can impair significantly calcium balance.
4. Other food compounds that bind calcium (*e.g.* oxalic acid) could significantly interfere with calcium absorption and decrease calcium bioavailability from some foods (*e.g.* spinach).
5. Lactose from milk increases calcium bioavailability especially in infants.
6. Other food components affecting calcium bioavailability include protein, sodium and potassium, phosphates, caffeine, and alcohol.
7. The calcium salts most commonly used for food fortification or as supplements exhibit similar absorbability.

Definitions of Words and Terms

Vitamin D₃. This is a fat-soluble vitamin that could be either provided with the diet or synthesized from 7-dehydrocholesterol with adequate sunlight exposure in humans.

Calcitriol. This is the hormonally active form of vitamin D, also termed 1,25-dihydroxyvitamin D₃, that increases the level of calcium (Ca²⁺) in the blood by increasing the uptake of calcium from the gut into the blood. Calcitriol is used to treat and prevent low levels of calcium in the blood of patients whose kidneys or parathyroid glands are not working normally.

Parathyroid Hormone (PTH). This is an 84 amino acid peptide acting primarily in kidney. PTH major physiological functions to raise plasma calcium *via* bone resorption and renal calcium reabsorption and to stimulate the metabolism of vitamin D to its active hormonal form 1,25-dihydroxyvitamin D₃.

NHANES. The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the United States since early 1960s. The survey is unique in that it combines interviews and physical examinations. Findings from NHANES are used to determine the prevalence of major diseases and risk factors for diseases.

Calcitonin. This is a hormone (32 amino acid peptide) produced by the thyroid gland under conditions of hypercalcemia that lowers the levels of calcium and phosphate in the blood and promotes bone formation. Calcitonin inhibits bone removal by the osteoclasts and at the same time promotes bone formation by the osteoblasts.

Bone remodeling. This is a process by which bone is renewed to maintain strength and mineral homeostasis. The bone remodeling unit is composed of a tightly coupled group of highly specialized osteoclasts and osteoblasts that sequentially carry out resorption of old bone and formation of new bone.

Osteoclasts. These are large bone-resorbing cells triggered by parathyroid hormone (PTH) in response to hypocalcemia. Osteoclasts are formed from

the conjoining of several cells created by the bone marrow and travel in the circulatory system working in perfect synchronization with osteoblasts to maintain the skeletal system.

Osteoblasts. These are bone-forming connective tissue cells found at the bone surface that can be stimulated to proliferate and differentiate as osteocytes.

Osteocytes. These are cells enclosed in bone that manufacture type 1 collagen and other substances that make up the bone extracellular matrix.

References

- Abrams, S. A., 2011. Calcium and vitamin D requirements for optimal bone mass during adolescence. *Current Opinion in Clinical Nutrition & Metabolic Care*. 14: 605–609.
- Allen, L. and Woods, R., 1994. Calcium and phosphorus. In: Shills, M. E., Olson, J. and Shike, M. (ed.) *Modern Nutrition in Health and Disease*. Lea & Fibiger, Philadelphia, pp. 144–163.
- Anonymous, 2000. Agriculture, food and nutrition for Africa: a resource book. In: Nations, Faaootu (ed.). FAO Corporate Document Repository.
- Anonymous, 2009. *Nutrient Availability Data (2009)*. U.S. Department of Agriculture/Economic Research Service.
- Anonymous, 2011a. *Dietary Reference Intakes for Calcium and Vitamin D*. National Academies Press Online, Washington, DC, 1132 pp.
- Anonymous, 2011b. Dietary reference intakes for calcium and vitamin D. In: Ross, A. C., Taylor, C. L., Yaktine, A. L. and Valle, H. B. D. (ed.). The National Academies Press, Washington, DC.
- Auchère, D., Tardivel, S., Gounelle, J., Drüeke, T. and Lacour, B., 1998. Role of transcellular pathway in ileal Ca^{2+} absorption: stimulation by low- Ca^{2+} diet. *American Journal of Physiology*. 275: G951–G956.
- Bailey, R., Dodd, K., Goldman, J., Gahche, J., Dwyer, J., Moshfegh, A., Sempos, C. and Picciano, M., 2010. Estimation of total usual calcium and vitamin D intakes in the United States. *Journal of Nutrition*. 140: 817–822.
- Bithika, T. and Dwight, A. T., 2012. Arterial calcification and bone physiology: role of the bone–vascular axis. *Nature Reviews Endocrinology*. 8: 529–543.
- Brenner, C. and Moulin, M., 2012. Physiological roles of the permeability transition pore. *Circulation Research*. 111: 1237–1247.
- Bronner, F., 2009. Recent developments in intestinal calcium absorption. *Nutrition Reviews*. 67: 109–113.
- Brownlee, I. A., Forster, D. J., Wilcox, M. D., Dettmar, P. W., Seal, C. J. and Pearson, J. P., 2010. Physiological parameters governing the action of pancreatic lipase. *Nutrition Research Reviews*. 23: 146–154.
- Calvo, M. S., Whiting, S. J. and Barton, C. N., 2004. Vitamin D fortification in the United States and Canada: current status and data needs. *American Journal of Clinical Nutrition*. 80: 1710S–1716S.

- Cerella, C., Diederich, M. and Ghibelli, L., 2010. The dual role of calcium as messenger and stressor in cell damage, death, and survival. *International Journal of Cell Biology*. DOI: 10.1155/2010/546163.
- Christakos, S., 2012. Recent advances in our understanding of 1,25-dihydroxyvitamin D₃ regulation of intestinal calcium absorption. *Archives of Biochemistry and Biophysics*. 523: 73–76.
- Diamond, S. L., 2013. Systems biology of coagulation. *Journal of Thrombosis and Haemostasis*. 11: 224–232.
- Felsenfeld, A., Rodriguez, M. and Levine, B., 2013. New insights in regulation of calcium homeostasis. *Current Opinion in Nephrology and Hypertension*. 22: 371–376.
- Gallagher, J. C., 2013. Vitamin D and aging. *Endocrinology and Metabolism Clinics of North America*. 42: 319–332.
- Glancy, B. and Balaban, R. S., 2012. Role of mitochondrial Ca²⁺ in the regulation of cellular energetics. *Biochemistry*. 51: 2959–2973.
- Hanzlik, R. P., Fowler, S. C. and Fisher, D. H., 2005. Relative bioavailability of calcium from calcium formate, calcium citrate, and calcium carbonate. *Journal of Pharmacology and Experimental Therapeutics*. 313: 1217–1222.
- Harnett, K. M. and Biancani, P., 2003. Calcium-dependent and calcium-independent contractions in smooth muscles. *American Journal of Medicine*. 115: 24–30.
- Harris, S. S. and Dawson-Hughes, B., 1994. Caffeine and bone loss in healthy postmenopausal women. *American Journal of Clinical Nutrition*. 60: 573–578.
- Harvey, J. A., Zobitz, M. M. and Pak, C. Y. C., 1988. Dose dependency of calcium absorption: a comparison of calcium carbonate and calcium citrate. *Journal of Bone and Mineral Research*. 3: 253–258.
- Heaney, R. and Recker, R., 1982. Effects of nitrogen, phosphorus, and caffeine on calcium balance in women. *Journal of Laboratory and Clinical Medicine*. 99: 46–55.
- Heaney, R. P., Dowell, M. S. and Barger-Lux, M. J., 1999. Absorption of calcium as the carbonate and citrate salts, with some observations on method. *Osteoporosis International*. 9: 19–23.
- Heaney, R. P. and Rafferty, K., 2001. Carbonated beverages and urinary calcium excretion. *American Journal of Clinical Nutrition*. 74: 343–347.
- Heaney, R. P. and Weaver, C. M., 1989. Oxalate: effect on calcium absorbability. *American Journal of Clinical Nutrition*. 50: 830–832.
- Hill, T. R., Aspray, T. J. and Francis, R. M., 2013. Vitamin D and bone health outcomes in older age. *Proceedings of the Nutrition Society*. 72: 372–380.
- Hirsch, P. and Peng, T., 1996. Effects of alcohol on calcium homeostasis and bone. In: Anderson, J. J. B. and Garner, S. C. (ed.) *Calcium and Phosphorus in Health and Disease*. CRC Press, Boca Raton, FL.
- Hung, C. H.-L., Ho, Y.-S. and Chang, R. C.-C., 2010. Modulation of mitochondrial calcium as a pharmacological target for Alzheimer's disease. *Ageing Research Reviews*. 9: 447–456.

- Jeon, U., 2008. Kidney and calcium homeostasis. *Electrolyte & Blood Pressure*. 6: 68–76.
- Kiselyov, K. K., Ahuja, M., Rybalchenko, V., Patel, S. and Muallem, S., 2012. The intracellular Ca^{2+} channels of membrane traffic. *Channels*. 6: 344–351.
- Kobayashi, A., Kawai, S., Obe, Y. and Nagashima, Y., 1975. Effects of dietary lactose and lactase preparation on the intestinal absorption of calcium and magnesium in normal infants. *American Journal of Clinical Nutrition*. 28: 681–683.
- Kopic, S. and Geibel, J., 2013. Gastric acid, calcium absorption, and their impact on bone health. *Physiological Reviews*. 93: 189–268.
- Moyer, V. A., 2013. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*. 158: 691–696.
- Nicholls, D. G., 2002. Mitochondrial function and dysfunction in the cell: its relevance to aging and aging-related disease. *International Journal of Biochemistry & Cell Biology*. 34: 1372–1381.
- Østerud, B., 2010. Tissue factor expression in blood cells. *Thrombosis Research*. 125(suppl. 1): S31–S34.
- Pansu, D., Bellaton, C., Roche, C. and Bronner, F., 1983. Duodenal and ileal calcium absorption in the rat and effects of vitamin D. 244: G695–G700.
- Peacock, M., 2010. Calcium metabolism in health and disease. *Clinical Journal of the American Society of Nephrology*. 5: S23–S30.
- Poliquin, S., Joseph, L. and Gray-Donald, K., 2009. Calcium and vitamin D intakes in an adult Canadian population. *Canadian Journal of Dietetic Practice and Research*. 70: 21–27.
- Rafferty, K., Walters, G. and Heaney, R. P., 2007. Calcium fortificants: overview and strategies for improving calcium nutriture of the U.S. population. *Journal of Food Science*. 72: R152–R158.
- Recker, R. R., 1985. Calcium absorption and achlorhydria. *New England Journal of Medicine*. 313: 70–73.
- Robertson, W. and Marshall, R., 1981. Ionized calcium in body fluids. *Critical Reviews in Clinical Laboratory Sciences*. 15: 85–125.
- Sellmeyer, D., Schloetter, M. and Sebastian, A., 2002. Potassium citrate prevents increased urine calcium excretion and bone resorption induced by a high sodium chloride diet. *Journal of Clinical Endocrinology and Metabolism*. 87: 2008–2012.
- Smith, T. M., Kolars, J. C., Savaiano, D. A. and Levitt, M. D., 1985. Absorption of calcium from milk and yogurt. *American Journal of Clinical Nutrition*. 42: 1197–1200.
- Straub, D. A., 2007. Calcium supplementation in clinical practice: a review of forms, doses, and indications. *Nutrition in Clinical Practice*. 22: 286–296.
- Tarasov, A. I., Griffiths, E. J. and Rutter, G. A., 2012. Regulation of ATP production by mitochondrial Ca^{2+} . *Cell Calcium*. 52: 28–35.
- Wallace, T. C., McBurney, M. and Fulgoni, V. L., 2014. Multivitamin/mineral supplement contribution to micronutrient intakes in the United States, 2007–2010. *Journal of the American College of Nutrition*. 33: 94–102.

- Weaver, C. and Heaney, R. P., 2006. Calcium. In: Shils, M., Shike, M., Ross, A., Caballero, B. and Cousins, R. (ed.) *Modern Nutrition in Health and Disease*. Lippincott Williams & Wilkins, Baltimore, MD.
- Weaver, C. M., 2009. Should dairy be recommended as part of a healthy vegetarian diet? Point. *American Journal of Clinical Nutrition*. 89: 1634S–1637S.
- Whiting, S. J., 2010. Calcium: a nutrient deserving a special issue. *Nutrients*. 2: 1044–1047.
- Xiao, Q., Murphy, R. A., Houston, D. K., Harris, T. B., Chow, W. and Park, Y., 2013. Dietary and supplemental calcium intake and cardiovascular disease mortality: the national institutes of health–AARP diet and health study. *JAMA Internal Medicine*. 173: 639–646.

CHAPTER 2

The Biological Roles of Calcium: Nutrition, Diseases and Analysis

LEONARDO M. MOREIRA^{*a}, RAPHAEL P. ARAUJO^a,
FERNANDO P. LEONEL^a, HENRIQUE V. N. MACHADO^a,
ALEXANDRE O. TEIXEIRA^a, FABIO V. SANTOS^b,
VANESSA J. S. V. SANTOS^b, AND JULIANA P. LYON^c

^aDepartamento de Zootecnia, Universidade Federal de São João Del Rei, Av. Visconde do Rio Preto s/n, Fábricas, São João Del Rei, Minas Gerais, Brazil;

^bUniversidade Federal de São João Del Rei, Campus Centro Oeste D. Lindu, Rua Sebastião Gonçalves Coelho, 400, Chanadour, Divinópolis, Minas Gerais, Brazil; ^cUniversidade Federal de São João Del Rei, Departamento de Ciências Naturais, Campus Dom Bosco, Praça Dom Helvécio, 74, Fábricas, Sala C 2.16 bloco C, São João Del Rei, Minas Gerais, Brazil

*E-mail: leonardomarmo@ufsj.edu.br

2.1 Introduction

Humphry Davy is considered to be the discoverer of calcium (1808), in spite of some previous experiments with animal bones involving calcium having been developed after the year 1700 (McDowell, 1992). Calcium is an alkaline-earth metal with atomic number 20, being its electronic distribution $[\text{Ar}]4s^2$ ($1s^22s^22p^63s^23p^64s^2$). Calcium presents 1.97 angstroms of metallic

Food and Nutritional Components in Focus No. 10

Calcium: Chemistry, Analysis, Function and Effects

Edited by Victor R. Preedy

© The Royal Society of Chemistry 2016

Published by the Royal Society of Chemistry, www.rsc.org

radius (1.00 angstroms of ionic radius to Ca^{2+}), and a Pauling's electronegativity of 1.0 (Lee, 1996).

The alkaline-earth metals constitute the Group IIA in the periodic table. These elements present a well-defined behavior of highly reactive metals, although they are less reactive than the metals of the Group IA (Lee, 1996). In any case, they react easily with a great variability of nonmetals (Mahan and Myers, 1987), producing colorless ionic compounds, which present the alkaline-earth metal as a divalent cation (Lee, 1996). Indeed, the relative ease with which both s electrons are lost from these elements atoms leads to compounds in which only the +2 oxidation state is found (it occurs because M^+ is unstable with respect to disproportionation) (Huheey *et al.*, 1993). The metals of this group are less strongly reducing than the alkali metals (Group IA), but still must be considered strongly reducing (Huheey *et al.*, 1993). The metals of the group IIA (alkaline-earth metals) are significantly harder than the metals of the Group IA (Alkaline metals) (Mahan and Myers, 1987).

Calcium is the fifth most abundant element by mass in the Earth's crust (4.66%), being one component of several common mineral salts (Lee, 1996). It is important to notice that the calcium is not found free in nature (the elements of the Group IIA (Be; Mg; Ca; Sr; Ba; Ra) are not found in the metallic state in nature (Mahan and Myers, 1987)), in spite of the great number of compounds with calcium in their respective compositions (Lee, 1996). Some of the most common compounds encountered on Earth are limestone (calcium carbonate (CaCO_3)); gypsum (calcium sulfate ($\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$)); fluorite (calcium fluoride (CaF_2)) and apatite (calcium fluorophosphates ($\text{Ca}_5(\text{PO}_4)_3\text{F}$) or calcium chlorophosphate ($\text{Ca}_5(\text{PO}_4)_3\text{Cl}$)) (Holden, 2001). Chloride and sulfate salts of calcium are water soluble; most other inorganic calcium salts are only slightly soluble in water (NRC, 2005).

Fairly pure deposits of calcium carbonate in the form of limestone are common and are a major source of calcium used in animal-diet formulation. Nearly pure calcium sulfate is also found in the form of gypsum that is used in Portland cement, drywall, and plaster production as well as animal feeds. Organic salts of calcium, such as calcium propionate, are very soluble and are increasingly being used in diet form (NRC, 2005).

In any case, the calcium in its metallic state is a silvery white metallic solid, which presents its surface covered with a thin layer of oxide that protects this metal from several types of chemical attacks by air, such as the oxidative attack.

The study focused on calcium is particularly relevant for some areas of interest, such as agriculture and soil science, since the levels of calcium in the soil constitute one important aspect related to the fertility of the soil, being a key nutrient to several cultures. Indeed, the reactivity of agricultural limestones and the respective relation between calcium and other metallic contents, such as the magnesium level, has been evaluated in order to optimize the soil acidity neutralization and the availability of mineral nutrients to plant-growing cultures (Bellingieri *et al.*, 1988).

2.1.1 Calcium in the Biological Medium

Calcium is a biologically relevant element to plants and animals. In plants, for example, the calcium ion presents a crucial regulator role of the growth and development through being associated to a great number of physiological processes (Hepler, 2005). In animals, the calcium ions are associated with various physiological and pathological processes, being focus of interest of a high number of research works. Extracellular calcium is essential for formation of skeletal tissues, transmission of nervous tissue impulses, excitation of skeletal and cardiac muscle contraction, blood clotting, eggshell formation, and as a component of milk. Intracellular calcium, while 1/10 000 the concentration of extracellular calcium, is involved in the activity of a wide array of enzymes and serves as an important “second messenger” conveying information from the surface of the cell to the interior of the cell (NCR, 2005).

The mineral salts constitute around 4% of the corporal composition of vertebrate animals, with the calcium and phosphorus representing more than 50% of this content (Underwood, 1981). In the biological medium, calcium presents great relevance, as its divalent cation, Ca^{2+} is associated with many biochemical roles, such as a messenger for hormonal action, a trigger for muscle contraction, in the initiation of blood clotting, and in the stabilization of protein structures (Shriver and Atkins, 1999). The amount of ionized calcium in normal serum is approximately 1.3 mM L^{-1} (Ettori and Scooggan, 1959). X-ray diffraction and NMR results illustrate how these functions are controlled by conformational changes induced by Ca^{2+} , when it binds to calmodulin, troponin C, and related proteins: these proteins are involved in the activation of membrane channels and receptors on cell surfaces (Shriver and Atkins, 1999).

The higher concentration of calcium in the animal organism is present in an inorganic form, as salts of hydroxyapatite in the bone matrix. This form of calcium represents 99% of the calcium that is present in several types of animals, such as mammals. The remaining 1% of all calcium found in the animal organism is divided between the vascular and intracellular environments, being associated with cell membranes and endoplasmic reticulum (Berchielli *et al.*, 2006).

In agreement with Shriver and Atkins, the many roles of the Ca^{2+} ion appear to arise from its affinity for the hard ligand oxygen in conjunction with the lability of its complexes, which fall between the alkali-metal ions and the d-metal ions, and the less-labile ions of its lighter congeners in Group 2 (Be^{2+} and Mg^{2+}) (Shriver and Atkins, 1999). In fact, the divalent cation of calcium (Ca^{2+}) is a Lewis's acid considered significantly “hard”, in Pearson's concept, making this cation present a great affinity for “soft” Lewis's bases, in Pearson's classification, which is the case of the bases that presents an oxygen atom as a donor site. Indeed, as a consequence of its low selectivity, Ca^{2+} can bind neutral oxygen donor ligands (carbonyls and alcohols) in competition with water (Shriver and Atkins, 1999), implying a great potentiality to formations of chemical bonds with several relevant biological molecules.

Intracellular calcium plays a role in signaling and as a second messenger in many types of cells and its concentration is closely regulated in cells (Gunter and Gunter, 2001). In fact, techniques for measuring intracellular free calcium are using radiometric and nonradiometric fluorescence with significant success (Gunter and Gunter, 2001).

2.1.2 Calcium in the Diet

In total there are 20 minerals that are essential for maintenance and normal functioning of the body (De Groote *et al.*, 2002). Insufficient supply of these minerals results in deficiency symptoms leading to reduced performance. Therefore, sufficient amounts should be supplied. Conversely, an oversupply of minerals may harm the production efficiency together with a possible negative effect on the environment. Therefore, apart from the requirement for various minerals their availability should also be known to prevent oversupply. Different terms used to express the nutritive value of the minerals are described together with various factors that may affect their nutritive value (De Groote *et al.*, 2002).

The mineral relationships is related to the acid–base interaction, as the maintenance of physiological acid–base equilibrium requires the excretion of excessive dietary cations and anions. The consumption of excess mineral cations in comparison to the anions amount or exceeding the quantity of anions in comparison to the cations amount results in acid–base disturbances (Shohl, 1939), as the mineral interrelationships were found to affect numerous metabolic processes (Leach, 1979; Mongin, 1980).

In this context, the control of the dosages of calcium in the diet is a relevant subject to animal health. In fact, the absence or the insufficient quantities of this micronutrient affects the bones, being related to bone diseases, such as osteoporosis, include, increasing significantly the risk of fractures. On the other hand, the excessive ingestion of this element is also extremely dangerous to animal organisms. The high biological levels of calcium affects the absorption of other important divalent cations, such as iron(II), zinc(II) and Mn(II), which can provoke direct and indirect adverse consequences. An elevated ingestion of calcium (more than 2000 mg by day), for example, mainly calcium of mineral origin, especially when associated to high levels of vitamin D, can generate calculus in kidneys. Another adverse effect related to the high levels of calcium is intestinal constipation.

Ions such as, for example, Mg(II) can be dislocated and, for consequence, absorbed in insufficient quantities. In fact, Ca(II) and Mg(II) are alkaline-earth metals that present proximal affinities regarding Lewis acids, which is the case of several cations of biological interest. A particular topic related to pathological occurrences due to excess calcium is associated to circulatory affections, in which Ca(II) presents a central role. Indeed, in the animal body, the magnesium is deeply related to the calcium and the phosphorus, with respect to the distribution and metabolism (Maynard, 1979). The dietary cation–anion balance (DCAB) effect on the macromineral (calcium, phosphorus

and magnesium) balance, urinary and fecal pH, serum concentration of calcium, phosphorus and magnesium has been evaluated in several animals, as the manipulation of the DCAB significantly affected the macromineral metabolism, mainly the calcium metabolism (Gomide *et al.*, 2004).

2.1.3 The Calcium Metabolism

The metabolism of calcium is associated with three basic factors: The absorption of calcium from the alimentation process; the calcium elimination by the urinary system; the fixation and/or release associated to bones and teeth.

The absorption of calcium happens, mainly, in the duodenum, involving passive and active absorption. When the level of calcium of the diet is relatively low, a large proportion of the calcium is absorbed by active transport. The absorption of calcium in the animal intestine occurs accordingly with necessity, *i.e.*, with the change of the levels of requirements (McDowell, 1992). The absorption of calcium is dependent on the medium pH, as the acid medium favors the solubility of the calcium ions and, consequently, increases its absorption that occurs, principally, in the acid medium of the duodenal environment (McDowell, 1992).

The presence of calcium in the blood is regulated by vitamin D and by the hormones calcitonin and parathormone. When the levels of calcium in blood are high, the thyroid gland secretes calcitonin, leading to the following major consequences: inhibition of vitamin D activation; impairment of the calcium absorption in the kidneys and intestine; and inhibition of the calcium liberation by the osteoclasts. In its turn, when the calcium levels in blood are lowered, the parathyroid gland secretes the parathormone, leading to vitamin D activation. Vitamin D, together with parathormone, stimulates calcium absorption by kidneys and intestine and stimulates osteoclasts to resorb bone tissues liberating calcium to the blood (Whitney and Rolfes, 2008) (Figure 2.1).

2.1.4 The Calcium Action in Several Cardiovascular Diseases

A group of academic and industry experts in the fields of nutrition, cardiology, epidemiology, food science, bone health, and integrative medicine examined the data on the relationship between calcium-supplement use and risk of cardiovascular events. The results of these studies indicated a small increase in the risk of adverse cardiovascular events (Heaney *et al.*, 2012). On the other hand, Jorde and Bona (2000) claim that calcium possesses a protective effect against hypertension. Research studies sponsored by the National Heart, Lung, and Blood Institute (NHLBI) led to the development of the DASH eating plan (dietary approach to stop hypertension), which consists in eating foods that are low in saturated and *trans* fats and rich in potassium, calcium, magnesium, fiber, and protein. Jacqmain *et al.* (2003) suggested that the calcium intake is related to less cholesterol, less diabetes and protection against colon cancer.

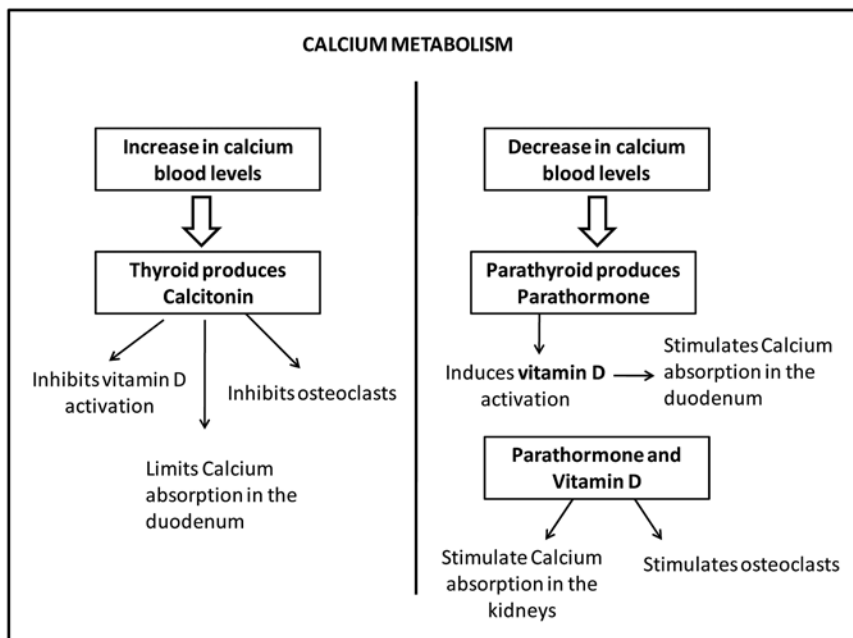


Figure 2.1 Schematic metabolism of calcium.

2.1.5 Calcium and Osteoporosis

Osteoporosis is a systemic skeletal disease characterized by a low bone mass. The disease is related to ageing and it is known to affect 44 million of people in the United States, mostly woman beyond 50 (Whitney and Rolfes, 2008). Osteoporosis is a silent disease and the bone mass loss is not shown in blood tests or by symptoms in the organism. There are several predisposing factors for the risk of developing osteoporosis, as we can mention: age, gender, genetic influence, hormones, physical activity level and diet.

According to Gennari (2001), reduced intake of calcium can be correlated to reduced bone mass and osteoporosis. Calcium intake should be appropriate, especially in the growth stage of development in order that a person achieves the ideal peak of bone mass at the age of 20 (Teegarden *et al.*, 1999).

2.1.6 Methods of Analysis and Evaluation of Calcium in Feeds and Biological Tissues

Determination of calcium in feeds and biological tissues is usually accomplished by wet or dry ashing of the sample followed by suspension of the ash in an acidic solution for analysis by atomic absorption spectrophotometry. Indeed, atomic absorption measurement is conducted at a wavelength of 422.7 nm and can detect as little as 0.01 mg Ca per L (NRC, 2005).

2.1.7 Conclusions

The biological action of the calcium ion and its derivative compounds constitute one of the more relevant studies related to the areas of bioinorganic chemistry (inorganic biochemistry), human and animal nutrition and medicinal chemistry.

Summary Points

- Calcium is an alkaline-earth metal with atomic number 20 and is the fifth most abundant element by mass in the Earth's crust, being one component of several common mineral salts.
- Calcium is important in plant physiology as well as to several metabolic and cellular functions of the human organism, as well as to the formation of bone tissues.
- Insufficient calcium intake may lead to the development of osteoporosis. On the other hand, the excessive ingestion of calcium increases the risk of renal calculus and intestinal constipation.
- The presence of calcium in the blood is regulated by vitamin D and by the hormones calcitonin and parathormone.
- The intake of calcium is important to prevent cardiovascular diseases.

Key Facts of Calcium in the Human Body

1. Calcium is the most abundant mineral in the human organism, as 99% of calcium is stored in bones and teeth.
2. Extracellular calcium is essential for formation of skeletal tissues, transmission of nervous tissue impulses, excitation of skeletal and cardiac muscle contraction, blood clotting, eggshell formation, and as a component of milk.
3. Diet is the main source of calcium to the organism.
4. Although dairy products are excellent sources of calcium, vegans may also obtain this nutrient from soy and its derivatives, beans and other grains as well as from green leaves such as broccoli, collards cabbage kale and mustard greens.
5. Calcium and phosphate are salivary buffers. Tooth decay occurs because of the demineralization promoted by bacterial acid products and the calcium present in saliva helps in the remineralization of teeth.

Definitions of Words and Terms

Calcitonin is a polypeptide hormone produced by the parafollicular cells of thyroid.

Osteoporosis progressive disease characterized by the decrease in bone mass, which can lead to an increase in the risk of bone fracturing.

Parathormone also known as parathyroid hormone, is a polypeptide hormone produced by the chief cells of the parathyroid gland.

Ratiometric fluorescence. Method based on the use of a ratio between two fluorescence intensities.

Nonradiometric fluorescence. Method that employs indicators with a shift in their fluorescence intensity. The cytosolic-free calcium concentration is related with fluorescence intensity.

List of Abbreviations

Ar	Argon
Ca²⁺	Divalent cation of calcium
Be	Beryllium
Be²⁺	Divalent cation of beryllium
Mg	Magnesium
Mg²⁺	Divalent cation of magnesium
Sr	Strontium
Ba	Barium
Ra	Radium
CaCO₃	Calcium carbonate
CaF₂	Calcium fluoride
NCR	National Research Council of the National Academies
NMR	Nuclear magnetic resonance

References

- Bellingieri, P. A., Alcarde, J. C. and Souza, E. C. A., 1988. Agricultural limestones reactivity and the relation between calcium and magnesium contents. *Anais da Escola Superior de Agricultura, "Luiz de Queiroz," Universidade de Sao Paulo*. 45: 499–515.
- Berchielli, T. T., Pires, A. V. and de Oliveira, S. G., 2006. *Nutrição de Ruminantes*. Funep, 583 pp.
- De Groote, G., Lippens, M., Jongbloed, A. W. and Meschy, F., 2002. *Study on the Bioavailability of Major and Trace Minerals*, International Association of the European (EU) Manufacturers of Major, Trace and Specific Feed Mineral Materials.
- Ettori, J. and Scooggan, S. M., 1959. Ionized calcium in biological media. *Nature*. 184: 1315–1316.
- Gennari, C., 2001. Calcium and vitamin D nutrition and bone disease of the elderly. *Public Health and Nutrition*. 4: 547–549.
- Gomide, C. A., Zanetti, M. A., Penteado, M. V. C., Carrer, C. R. O., Del Claro, G. R. and Netto, A. S., 2004. Influence of the dietary cation–anion difference on calcium, phosphorus and magnesium balance in sheep. *Arquivo Brasileiro de Medicina Veterinaria e Zootecnia*. 56(3): 363–369.

- Gunter, K. K. and Gunter, T. E., 2001. Measurements of intracellular free calcium concentration in biological systems. *Current Protocols in Toxicology*, Ch. 2.
- Heaney, R. P., Kopecky, S., Maki, K. C., Hathcock, J., MacKay, D. and Wallace, T. C., 2012. A review of calcium supplements and cardiovascular disease risk. *Advances in Nutrition – An International Review Journal*. 3: 763–771.
- Hepler, P. K., 2005. Calcium: a central regulator of plant growth and development. *Plant Cell*. 17: 2142–2155.
- Holden, N. E., 2001. *History of the Origin of the Chemical Elements and Their Discoverers*.
- Huheey, J. E., Keiter, E. A. and Keiter, R. L., 1993. *Inorganic Chemistry – Principles of Structure and Reactivity*. HarperCollinsCollegePublishers.
- Jacqmain, M., *et al.*, 2003. Calcium intake, body composition and lipoprotein lipid concentrations. *American Journal of Clinical Nutrition*. 77: 1448–1452.
- Jorde, R. and Bonaa, K. H., 2000. Calcium from dairy products, vitamin D and blood pressure: the Tromso study. *American Journal of Clinical Nutrition*. 71: 1530–1535.
- Leach, R. M., 1979. Dietary electrolytes: story with many facets. *Feedstuffs*. 27.
- Lee, J. D., *Concise Inorganic Chemistry*, Chapman & Hall, 1996.
- Mahan, B. M. and Myers, R. J., 1987. *University Chemistry*. 4th edn. Benjamin-Cummings Publishing Company.
- Maynard, L. A., Loosli, J. K., Hintz, H. F. and Warner, R. G., 1979. *Animal Nutrition*. 7th edn. McGraw-Hill, New York, 602 pp.
- McDowell, L. R., 1992. Calcium and phosphorus. In: *Minerals in Animal and Human Nutrition. Chapter 2*. Academy Press, Inc., pp. 26–77.
- Mongin, P., 1980. Electrolytes in nutrition: review of basic principles and practical application in poultry and swine. In: *Third Ann. Int. Mineral Conf. Orlando, FL*, p. 1.
- National Research Council of the National Academies, 2005. *Mineral Tolerance of Animals*. 2nd edn.
- Shohl, A. T., 1939. *Mineral Metabolism*. Reinhold Publishing Corp., New York.
- Shriver, D. F. and Atkins, P. W., *Inorganic Chemistry*. 3rd edn. Oxford University Press, 1999.
- Teegarden, D., *et al.*, 1999. Previous milk consumption is associated with greater bone density in young women. *American Journal of Clinical Nutrition*. 69: 1014–1017.
- Underwood, J. E., 1981. *Los minerales en la nutricion del Ganado*. Acribia, Zaragoza, 210 pp.
- Whitney, E. and Rolfes, S. R., 2008. *Nutrição*. Ed Cengage Learning, São Paulo, 342 pp.

CHAPTER 3

Food Sources of Calcium Vary by Ethnicity and Geography

NOREEN WILLOWS*^a

^aFaculty of Agricultural, Life & Environmental Sciences, University of Alberta, 4-378 Edmonton Clinic Health Academy, Mailbox #54, 11405 87 Avenue, Edmonton, Alberta, Canada T6G 2P5

*E-mail: noreen.willows@ualberta.ca

3.1 Introduction

This chapter discusses food sources of calcium among populations world-wide. The focus is on the contribution of dairy, vegetables, cereal grains and legumes to calcium intake. The chapter also describes the contribution to calcium nutrition of less common but potentially important sources of calcium such as insects. Discussed in brief are the genetic, sociodemographic and religious reasons a calcium-contributing food is consumed. In the modern context, calcium supplements and foods intentionally fortified with calcium (*e.g.*, calcium-fortified orange juice) contribute to calcium intake; however, a discussion of these calcium sources is not included in this chapter.

3.2 Milk and Dairy Foods Consumed Worldwide

Dairy is a concentrated source of calcium; hence, populations that consume dairy have the highest calcium intakes (Prentice, 2014). For example, a 250 mL serving of milk or buttermilk contains 300 mg of calcium (Osteoporosis

Canada, 2014). Although global dairy production has increased in recent decades, especially in developing countries, there are still large between-country differences in dairy consumption (Prentice, 2014). Dairy is included in European, Middle Eastern, and South Asian cuisines; however, it is not a part of traditional Polynesian cuisines, nonpastoral African cuisines, the cuisines of the indigenous peoples of the Americas, or most East or Southeast Asian cuisines (Kittler and Sucher, 2008). Dairy consumption is greatest among cultures that historically maintained mammals for milking, and where the ability to hydrolyze lactose persists in the adult population. Lactase activity persists into adulthood at high frequency in Northern European and African pastoralist populations; at moderate frequency in Southern European and Middle Eastern populations; and, at low frequency in nonpastoral Asian, Pacific, indigenous American, and African populations (Ingram *et al.*, 2009; Prentice, 2014). Cheese, fermented milk beverages like kefir and fermented dairy products like yoghurt are lower in lactose than milk and therefore better tolerated in populations that produce low levels of lactase (Savaiano, 2010).

3.2.1 Europe

In countries predominantly populated by persons of Northern, Central European and Scandinavian ancestry, milk (including buttermilk and fermented milk) and dairy products in the form of hard cheese, cheese curd, whipped cream, ice cream and sour cream make a significant contribution to calcium intake. Dairy is used in sauces, soups, stews, noodle dishes, dumplings and baked products. Many adults in Southern Europe do not drink milk but do eat cheese (Barer-Stein, 1999; Kittler and Sucher, 2008).

Dairy is the main source of calcium for British adults aged 19 to 64 years old. Milk and milk products contribute to 43% of mean overall calcium intake, with semiskimmed milk and cheese being the main contributors, providing 17% and 11% of calcium, respectively (Henderson, 2003). Among 12 year old Northumbrian children in the United Kingdom milk contributes to 25% of calcium intake, more than any other food (Moynihan *et al.*, 1996). Among Flemish preschoolers 2.5 to 6.5 years old milk, sweetened milk drinks and cheese are the main sources of calcium in the diet (26, 25 and 11% of calcium, respectively) (Huybrechts *et al.*, 2011).

Dairy provides the majority of dietary calcium in Southern Europe countries. Among Spanish children 7 to 11 years old dairy provides 64.7% of calcium (Ortega *et al.*, 2012). Dairy provides 58.7% of calcium among Spanish adults (Estaire *et al.*, 2012). In central Italy the principal source of calcium among adults is hard cheese (parmigiano), since the quantity of milk consumed daily is small and yoghurt consumption is infrequent (Matteucci and Giampietro, 2008). Dairy is the primary source of calcium among adults in Greece (Magkos *et al.*, 2006). Milk is not a preferred beverage among Greek adults, whose dairy-product choices are yoghurt and hard and soft cheeses, some like feta that are preserved in salt brine (Barer-Stein, 1999).

Dietary practices of members of the Eastern Christian Orthodox Church influence dairy consumption. Russian, Greek, Serbian, Romanian, Bulgarian, Ukrainian, and Moldavian ethnic groups commonly practice this religion. Dietary rules of this religion require vegetarianism during religious fasts through the avoidance of most animal foods including milk and all dairy products. Adherents of these dietary rules avoid dairy every Wednesday and Friday throughout the year and during the Christmas, Lent and Assumption fasts, resulting in a significant reduction in calcium intake (Kittler and Sucher, 2008; Lazarou and Matalas, 2010).

3.2.2 Middle East

In the Middle East fresh milk is seldom consumed as a beverage, in part because the hot climate causes milk to spoil quickly. One study of 316 Lebanese adults 30 to 50 years old found that only 15.9% drank a daily cup of milk, while 53.1% never drank milk (Gannagé-Yared *et al.*, 2005). Milk in the Middle East is used in puddings and custards. In Jewish, Iraqi, Jordanian, Lebanese and Syrian cuisines cultured (soured) milk such as leben (buttermilk made from soured milk) and yoghurt are eaten with bread, pilafs, meats, or fruits. Cheeses from camel, goat, or sheep milk may be preserved in brine or olive oil. Labneh is consumed. This fresh cheese is prepared by straining yoghurt. In Israel, cottage cheese is eaten for breakfast and incorporated into dishes, particularly filled pastries (Barer-Stein, 1999; Kittler and Sucher, 2008).

Dairy consumed in Iran includes milk, cheese, yoghurt, ice cream, cocoa milk, a dairy product made from fermented and dried sheep milk (kashk), and a beverage made by diluting yoghurt with water (dough) (Karandish *et al.*, 2005). A study of postmenopausal Iranian women found that dairy contributed to $61 \pm 19\%$ of dietary calcium (Karandish and Naghashpoor, 2010). A study of pregnant Iranian women found that dairy provided 49% of dietary calcium; however, 43% of women consumed <1 serving of dairy per day. Milk and yoghurt were the main dairy products consumed by pregnant women, followed by cheese (Karandish *et al.*, 2005).

In Israel, the consumption by Jews of dairy is dictated by religious dietary laws (Stern, 2004). Food is kosher, meaning acceptable to eat, when prepared according to these laws. Keeping kosher concerning dairy applies also to individuals living outside of Israel who practice the Jewish religion. To be kosher, only the milk of a cow, goat or sheep can be consumed. Jewish religious observances require the strict separation of dairy from meat and poultry. These foods cannot be cooked together, eaten at the same meal, or eaten close together in time to ensure that dairy does not mix with meat or poultry in the digestive tract. The requirement for separation means that cheese made from animal-derived rennet is forbidden (Stern, 2004). Following an ultra-Orthodox Jewish lifestyle may therefore result in fewer opportunities to consume dairy and consequently a lower calcium intake. Indeed, a large survey of Jewish adults in Israel examined dietary intake in relation to religious observance. It found higher dairy product

consumption among less religiously adherent individuals (Shmueli and Tamir, 2007).

3.2.3 Canada, United States of America, and Australia

A large proportion of the population of Canada, the United States of America and Australia have European heritage, hence, high dairy consumption. Results from a large national survey in the United States indicated the highest ranked sources of calcium for adults were milk (22.5% of calcium) and cheese (21.6% of calcium) (O'Neil *et al.*, 2012). Results from the same national survey indicated that among children the two top sources of calcium were also milk (33.2% of calcium) and cheese (19.4% of calcium) (Keast *et al.*, 2013). In the United States, African-Americans of most age groups consume significantly less dairy overall, milk and cheese compared with their non-African-American counterparts. Yoghurt consumption is negligible among African-Americans (Fulgoni *et al.*, 2007). The Food Habits of Canadians study found that among participants aged 18 to 65 years old milk contributed to about 35% of calcium consumption whereas cheese contributed to 12 to 19% of calcium consumption (Johnson-Down *et al.*, 2006). Most (84–98%) Australian children aged 2 to 16 years old participating in a 2007 national survey consumed dairy. Milk was the predominant dairy food consumed by 58–88% of children, followed by cheese (consumed by 36–53% of children) and yoghurt (consumed by 12–39% of children). Children typically consumed 243–384 g per day of milk, which was the primary source of calcium (Baird *et al.*, 2012).

3.2.4 South Asia

Dairy is an ingredient of most South Asian cuisines. The consumption of milk, buttermilk, ghee (clarified butter), curds, and fermented milk products like yoghurt is common. Milk may be drunk fresh or as a diluted yoghurt drink known as lassi. Although in South Asia milk from the cow is common, milk from goats, sheep, buffalo, mares and camels is also used (Kilara and Iya, 1992; Kittler and Sucher, 2008). In India, milk (whether unpasteurized or pasteurized) is often boiled before its consumption to prevent spoilage. Sugar and/or condiments are sometimes added to improve its flavor and perceived digestibility. Dilution of milk is also a common practice in many Indian households, which significantly diminishes its nutritional profile (Bahman *et al.*, 2012). In traditional South Asian cooking hard cheese is not used, rather a fresh cheese known as paneer is incorporated into many dishes. Desserts made with milk are common including sweet milk and rice pudding (khir), a fudge made with condensed milk or cream and sugar (barfi), a sweetened frozen dairy product made with sweetened evaporated milk (kulfi), and dumplings made of thickened or reduced milk, soaked in rose-flavored sugar syrup (gulab jamun). Tea (chai) is made with boiled milk and heavily sweetened (Barer-Stein, 1999; Kilara and Iya, 1992; Kittler and Sucher, 2008).

Dairy consumption in South Asia is driven by religion, socioeconomic status, social practices, and availability. Hinduism, one of the major religions of India, considers milk and dairy products from the cow to be spiritually pure. Consuming milk, dairy products and ghee are all important to maintaining ritual purity in Hinduism (Kilara and Iya, 1992; Kittler and Sucher, 2008). Food availability and economic status exert an important impact on food intake. While impoverished individuals often have very low dairy intake, due to lack of availability dairy consumption can even be low among individuals from better off socioeconomic groups. Girls may be deprived of nourishing foods like dairy when it is in limited supply so that boys can eat (Gupta, 1987).

Two hundred adolescents from lower and upper economic stratum in India were included in a study of calcium intake and sources of calcium. The contribution of dairy products to daily calcium intake was the highest in upper economic strata boys (271 mg, 219–382 mg) and the lowest in lower economic strata girls (43 mg, 14–66 mg) (data presented as median, 25th and 75th percentiles). The main source of calcium was dairy products in upper economic strata adolescents while it was dark green leafy vegetables in lower economic strata adolescents. Girls from both groups had less access to dairy products than boys (Sanwalka *et al.*, 2010). Dairy consumption may be lowest in rural areas. One study of healthy adults in south India found that milk and milk products contributed to 15% of energy intake of urban living individuals but to 5% of energy intake of rural-living individuals. Calcium intake was significantly lower in rural than urban individuals. It ranged from 262 mg per day for rural woman to 323 mg per day for urban men (Kumar, 2007).

A study of impoverished nonpregnant and nonlactating women between the ages of 30 and 60 years residing in a large urban slum in India found that consumption of milk and milk products was only 62 g per day. Considering few other sources of calcium in the diet, and the low overall intake of food among women, total calcium intake was very low (270 mg per day) (Shatrugna *et al.*, 2005). In a study in Bangladesh, very low income women consumed, on average, 3.6 g per day of dairy whereas high-income women consumed, on average, 89.3 g per day. Milk was the second highest source of calcium among higher-income women, contributing to more than 19% of calcium. In contrast, among low-income women milk supplied only 3% of calcium. For both groups of women low consumption of dairy was the result of a lack of availability of milk and dairy products in the region coupled with their high cost (Islam *et al.*, 2003).

3.2.5 East and Southeast Asia

The diet of East and Southeast Asia is traditionally nondairy based; consequently, most nutrition surveys in Asia indicate low dairy consumption. An exception is a long history of milk production and consumption in some areas of China, namely Inner Mongolia, Shanghai, Beijing and Tianjin (Fuller *et al.*, 2007). Among postmenopausal women in Vietnam included in a nutrition study in 2004 only 0.38% of calcium consumed was from cow's milk and

milk powder combined (Khan *et al.*, 2008). Results of the 2008–2009 Korea National Health and Nutrition Examination Survey indicated that adults consume milk and dairy products less than once per day (4.1 times per week for men and 4.7 times per week for women) (Yoon *et al.*, 2012). Data from the 2005–2008 National Nutrition Surveys in Taiwan found that 45.4% of respondents ate no dairy. Forty seven percent of first-grade children consumed a serving or more of dairy daily, while 37% of 6th graders did. Only 20% of nonelderly adults ate at least a daily serving of dairy. Physiological limitations (diarrhea, 22%; bloating, 2.9%; constipation, 1.3%), some seemingly due to lactose intolerance, accounted for about 25% of dairy avoidance. Most (66.7%) avoidance was due to dietary habits or dislike. Only 3% of respondents avoided dairy because they could not afford it (Lee *et al.*, 2009).

As Asian diets and consumption patterns become more westernized, the consumption of dairy is increasing. The rapidly developing dairy industry in China has become an important source of dairy for China and other countries (Fuller *et al.*, 2007). Even small amounts of dairy can make a significant contribution to calcium intake. In Japan, dairy was the predominant source of calcium for all age groups in a 2002 national nutrition survey (Sato *et al.*, 2005). Data from the 2001–2002 Nutrition and Health Survey in Taiwan Elementary School Children showed that children 6–12 years old had a very low calcium intake and a low intake of dairy, yet dairy (fresh milk, yogurt, cheese and other dairy products) was the primary source of calcium. Dairy provided children with 164 mg calcium per day, on average. The mean daily intake of dairy in children 6–9 years old was 0.9 servings, whereas it was 0.6 servings in children 10–12 years old (Wu *et al.*, 2007). Data from the Korean National Health and Nutrition Examination Survey 2007–2010 showed that among children and adolescents 1 to 18 years of age the highest ranked source of calcium was dairy (milk, modified milk powder, formula, breast milk, goat's milk, yoghurt, ice cream, and cheese). Dairy contributed to 35% of calcium intake followed by vegetables (17.3%), grains (11.3%) and seafood (9.9%). Dairy contributed to 57% of calcium intake at age 1–2 years and to 24% of calcium intake at age 15–18 years (Im *et al.*, 2013). Milk consumption in Singapore was determined in 2009 from a random sample of children. The mean weekday consumption of milk for 3 to 6 year-old children was 635 mL and the mean intake of calcium from all sources was 1032 mg per day. The mean weekday consumption of milk for 7 to 10 year-old children was 359 mL and the mean intake of calcium from all sources was 733 mg per day (Goh and Jacob, 2011). Milk contributed the majority of calcium in Singapore children's diets.

In China, there is great variation in milk consumption across regions and between rural and urban areas. There have been increases in milk consumption, largely in urban areas, and school programs promote milk consumption among children (Fuller *et al.*, 2007). The 2007 Chinese Food Guide Pagoda recommends the daily consumption of 300 g of milk and milk products (Ge, 2011). A survey of households in Beijing, Shanghai, and Guangzhou in the fall of 2001 focused on dairy consumption. Survey data revealed that all but five of 300 households reported purchasing one or more dairy

products. About 91% of the households purchased milk, but less than 60% purchased yogurt or ice cream (Fuller *et al.*, 2007). Data from the 2004 China Economic, Population, Nutrition and Health Survey showed that adults aged 18–45 years consumed, on average, 12 g per day of milk and dairy products (Zhai *et al.*, 2009). A survey of Chinese adolescents living in Guangzhou city in 2006–2007 demonstrated that nearly 70% consumed less than the recommended daily 300 g intake of dairy. The average intake of dairy (sources included whole milk, whole milk powder, skim/low-fat milk, skim/low-fat milk powder, yoghurt, milk tea, cheese, and ice cream) among adolescents was 261 g per day (Zhang *et al.*, 2012).

3.2.6 Africa

Intake of milk and dairy is low among ethnic Africans except for among herding populations (Prentice, 2014). The pastoral Maasai of East Africa rely on meat, milk and blood from cattle for sustenance. Cow's milk is consumed fresh, boiled and mixed with blood and meat in stews, and made into sour milk and yoghurt. Goat milk is also consumed. Wild herbs high in calcium are added to fresh or boiled milk and soups (Oiye *et al.*, 2009). The adult diet of the pastoral Fulani of Nigeria is rich in dairy, in particular milk, cheese, butter oil, and yogurt. The vast majority of adults drink milk (Glew *et al.*, 2001). Dairy products are losing their dominance in the diets of the Fulani of Central Africa who have become nonnomadic. The need for cash income to meet the requirements of sedentary living requires the Fulani to sell most of their dairy and milk products. These factors have resulted in less availability of milk and dairy products for Fulani children (Ekpo *et al.*, 2008).

3.3 Nondairy Sources of Calcium Consumed Worldwide

The remainder of this chapter will focus on nondairy sources of calcium in regions that are not large dairy consumers.

3.3.1 Asia

In Asia, traditional food sources of calcium are grains, vegetables, legumes, seafood and the soft bones of small fish. The Chinese Food Pagoda 2007 depicts eight food categories for dietary adequacy with recommended daily intakes for each one: 250–400 g for cereals, 300–500 g for vegetables, 200–400 g for fruits, 50–75 g for meat, 70–100 g for fish and shrimps, 25–50 g for eggs, 30–50 g for soybean products and nuts, and 300 g for dairy (Ge, 2011). Apart from dairy, in China food categories that contribute to calcium nutrition are cereals (*e.g.*, white rice, porridge, noodles, bread, cake and biscuits); vegetables (*e.g.*, dark green leafy vegetables, cruciferous vegetables such as gai lan and bok choy, melon, radish, pepper, carrot, tomato, starchy tubers, fresh

corn, fresh beans, allium – onion, garlic, leek, and chives, mushroom and fungi); fish and shrimp (*e.g.*, freshwater and saltwater fish, canned fish, salted fish, crab, shrimp, prawn, squid, cuttlefish, scallops, mussel and whelk); and, soybean products (*e.g.*, hard tofu, fried tofu pop, soft tofu, soy products such as tofu curd and vegetarian chicken, soy drink, bean curd pudding, fresh and dried soybean) (Zhang *et al.*, 2012).

Among Korean children and adolescents participating in the Korea National Health and Nutrition Examination Survey 2007–2010 the highest ranking source of calcium after dairy was vegetables (*e.g.*, kimchi – pickled vegetables, radish leaves, welsh onion, onion, radish, soybean sprouts, carrot, spinach) (contributing 17.3% of calcium). Two plants very high in calcium (mg per standard serving) were radish leaves (149 mg/60 g) and mugwort (103.5 mg/45 g) (Im *et al.*, 2013). The next highest ranking sources of calcium were grains (*e.g.*, rice, barley, wheat and their products) (11.3% of calcium) and seafood (*e.g.*, boiled and dried anchovy, fish paste, dried and raw shrimp, loach mudfish, squid, opossum shrimp, mackerel) (9.9% of calcium). Soy (*e.g.*, soybeans, tofu, fried tofu, bean-curd dregs, soya milk, bean flour) provided 6.4% of calcium (Im *et al.*, 2013). Data from the Nutrition and Health Survey in Taiwan Elementary School Children 2001–2002 showed that after dairy, the main sources of calcium in the diet of children were green and yellow vegetables (81.4 mg calcium per day), soybean and soybean products (42.2 mg calcium per day), and fish and seafood (not including seaweed) (38.7 mg calcium per day) (Wu *et al.*, 2007).

Whole small fish are an excellent calcium source. Japanese Dietary Guidelines recommend individuals to drink milk and eat green/yellow vegetables, beans, and small fish to get a sufficient amount of calcium (Japan Dietetic Association, 2014). In Japan, whole fish are eaten, as well as cakes made from whole fish, including the bones. In the traditional Korean diet fish high in calcium (mg per standard serving) are dried icefish (98.2 mg/10 g) and dried anchovy (64.5 mg/5 g) (Im *et al.*, 2013). In low-income countries such as Bangladesh, small fish play an important role in the diet since they are often used in sauces and curries, which are eaten with the main staple. Among some Bangladeshi women fish are the main source of calcium (Islam *et al.*, 2003).

The soybean (or soya bean) is a legume native to East Asia that has been cultivated for millennia. In China, soybeans are referred to as “poor man’s cow” as they are high in protein and are made into products resembling milk and cheese (Kittler and Sucher, 2008). Buddhism has been influential in the development of soy foods in China and other Asian countries where it is practised. This is because soy foods can substitute for animal foods making a vegetarian diet possible (Huang and Ang, 1992). Soybeans in Asia are consumed as sprouts, boiled beans and boiled bean pods (edamame). They are processed to make soymilk, soybean curd (tofu), fermented tofu, fermented cooked soybeans (*e.g.*, black beans, natto, tempeh), fermented soybean paste (*e.g.*, miso), soy flour and condiments (*e.g.*, soya sauce). Cooked soybeans provide 85 mg of calcium per 125 mL. To make tofu, ground soybeans are soaked in water to which a coagulant, either calcium or magnesium sulfate,

is added. Made with calcium sulfate, 125 g of tofu provides 193 mg of calcium (Osteoporosis Canada, 2014). In Korea, a typical serving of tofu is 60 g and provides 75.6 mg of calcium (Im *et al.*, 2013). In Japan, a medium serving of tofu (100 g) provides 90 mg of calcium, whereas a medium serving (60 g) of deep-fried tofu provides 160 mg of calcium (Sato *et al.*, 2005).

Potential sources of calcium in the Asian diet are bones and bird eggshells cooked or pickled in vinegar. In China, postpartum mothers eat whole eggs that have been placed into a vinegar solution that dissolves the shell (Newman, 2004). In southern China, postpartum mothers eat a special mixture called *geung cho* of ginger, pig's feet, and boiled eggs with the shells on cooked in black vinegar (Fong, 2001). One preservation technique to make duck or chicken eggs taste sour involves immersing eggs in vinegar and salt until the shells soften. The eggs are called *zao dan*. Some eggs are kept in the solution so long that the shells dissolve (Newman, 2004).

The contribution of preserved and pickled eggs to calcium nutrition could be substantial. Eggshells are about 95% calcium carbonate and a single chicken eggshell contains up to 3 g (3000 mg) calcium (Roberts, 2010). The softened shells of pickled eggs are edible (McGee, 2007). Calcium carbonate from the eggshell might penetrate the pickled egg and be ingested. The acid in vinegar may dissolve calcium from bone and eggshells when soup is made using it; however, it is unknown how much calcium is provided by *geung cho*. Pork bones cooked in vinegar are stated to provide 130 mg calcium per 110 g (as cited in Kuhnlein, 1984).

3.3.2 Africa

Both wild and cultivated dark green leafy vegetables are an important part of the traditional starch-based African diet. Wild greens eaten throughout Africa often have more calcium than cultivated greens (Kinabo *et al.*, 2006; Van Der Walt *et al.*, 2009). Among two- to five-year-old children in KwaZulu-Natal in South Africa dark-green leafy vegetables such as Swiss chard and imifino (a collective term for various dark-green leaves) contribute 21 to 39% of total dietary calcium (Faber *et al.*, 2007).

Insects are a neglected but potentially important source of calcium in Africa and elsewhere. Humans eat over 1600 species of insects deliberately, although cultures are highly variable in their consumption of insects (Raubenheimer and Rothman, 2013). Insects are consumed in central and southern Africa, Asia, Australia (by the indigenous Aborigines) and Latin America. The calcium content of five species of insects consumed by the Luo of Kenya varies from 33 mg/100 g dry matter for *Onyoso mammon* (ant) to 341 mg/100 g dry matter for *Onjiri mammon* (cricket) (Christensen *et al.*, 2006). The calcium content of 16 of 22 insect species eaten in Nigeria has been reported. Two insects relatively high in calcium are *A. trifasciata* (stem girdler) containing 61.3 mg of calcium per 100 g and *Z variegatus* (grasshopper) containing 42.4 mg of calcium per 100 g (Alamu *et al.*, 2013). To fully appreciate the contribution of insects to nutritional status there is the need for additional standardized data on both the types and quantities

of insects consumed in Africa and elsewhere and their macro- and micro-nutrient composition (Raubenheimer and Rothman, 2013).

3.3.3 Mexico and Central America

In Mexico and some Central American countries (*e.g.*, Guatemala) maize (corn) tortillas are daily dietary staples and a major source of calcium for persons whose intake of dairy is limited. To make tortillas using the traditional method maize undergoes a process called nixtamalization, or liming, whereby the kernels are cooked and soaked overnight in a lime (calcium hydroxide) water solution before being ground to form dough. Commercial corn flour is also available for the preparation of tortillas; it is usually lime treated for only 1 h. Tortillas prepared using lime-treated, home-prepared corn flour have 1.7 times more calcium than tortillas prepared from commercial lime-treated corn flour (Rosado *et al.*, 2005). In Mexico it is common to consume six tortillas daily with a combined weight of 180 g. When made from commercial flour six tortillas provide 187.6 mg of calcium; when made with homemade flour six tortillas provide 326.8 mg of calcium (Rosado *et al.*, 2005).

Summary Points

- This chapter focuses on variations in food sources of calcium worldwide.
- Genetic, cultural, sociodemographic and religious reasons help to explain differences in the calcium-containing foods that are consumed worldwide.
- The diets of ethnic Europeans are relatively high in dairy sources of calcium, whereas the diets of ethnic Africans and individuals living in East and Southeast Asia are low in dairy.
- Global dairy production has intensifying in recent decades increasing the amount of milk and dairy products consumed in regions where they were not traditionally incorporated into the diet.
- Even where dairy is consumed, nondairy sources of calcium must be ingested to meet calcium adequacy.
- Nondairy sources of calcium are fish with edible bones, leafy greens, legumes such as the soybean and soybean derivatives like tofu made with calcium sulfate, grains such as maize treated with calcium hydroxide used to prepare tortillas, and insects.
- To widen our understanding of food sources of calcium increased knowledge of the calcium content of edible insects, wild greens, pickled eggs and Asian bone soups is required.

Key Facts

Key facts about the digestion of milk and dairy foods in adulthood, in particular the requirement for the persistent production of the enzyme lactase by the intestinal epithelium.

1. The main carbohydrate in milk is lactose.
2. Lactase is the enzyme produced by the intestinal epithelium that hydrolyzes lactose to glucose and galactose.
3. Lactase production decreases after the weaning phase in most humans.
4. It has been estimated that 65% or more of the human adult population are lactase nonpersistent.
5. Lactase activity persists into adulthood at high frequency in Northern European dairying and African pastoralist populations; at moderate frequency in Southern European and Middle Eastern populations; and at low frequency in nonpastoral Asian, Pacific, indigenous American, and African populations.
6. When lactase production is nonpersistent into adulthood, drinking milk can cause significant gastrointestinal discomfort such as diarrhea, cramps, bloating and flatulence.
7. Cheese and fermented milk products like yoghurt are lower in lactose than milk and therefore better tolerated by individuals who produce low levels of lactase.
8. Differences in lactase persistence help to explain variations in milk and dairy product consumption within and between populations.

Definitions of Words and Terms

Cuisine. A cuisine is a characteristic style or method of cooking often named after the geographic region from which it originated.

Dairy. Dairy pertains to milk and milk products.

Dairy product. A dairy product is a food or beverage produced from the milk of mammals such as cows, goats, sheep, yaks, horses, and camels.

Ethnicity. An ethnicity is a social group of people who identify with each other based on common ancestral, religious, linguistic, social, cultural, or national experience.

Lactase. Lactase is an enzyme produced by the epithelial cells of the small intestine that hydrolyzes lactose into glucose and galactose.

Lactase persistence. Lactase persistence is the continued production of the enzyme lactase in adulthood.

Lactose. Lactose is the primary carbohydrate in milk. This disaccharide must be hydrolyzed to its two constituent monosaccharides, glucose and galactose, to be transported across the intestinal epithelium.

Lactose intolerance. Lactose intolerance is a group of symptoms (cramps, diarrhea, flatulence, gurgling, bloating, nausea, and combinations thereof) that are caused by the inability to enzymatically cleave lactose into its two constituent sugars.

Nomad. A pastoral group that moves their herds seasonally to avoid depleting pasturage.

Pastoralist. Pastoralists are nomads who raise livestock such as camels, goats, sheep and cattle. Many of these animals are milk producing.

List of Abbreviations

g	Grams
mg	Milligrams

References

- Alamu, O. T., Amao, A. O., Nwokedi, C. I., Oke, O. A. and Lawa, I. O., 2013. Diversity and nutritional status of edible insects in Nigeria: a review. *International Journal of Biodiversity and Conservation*. 5(4): 215–222.
- Bahman, S., Yadav, N., Kumar, A., Ganguly, S., Garg, V. and Marwaha, S. S., 2012. Impact of household practices on the nutritional profile of milk. *Indian Journal of Public Health*. 56(1): 82–87.
- Baird, D. L., Syrette, J., Hendrie, G. A., Riley, M. D., Bowen, J. and Noakes, M., 2012. Dairy food intake of Australian children and adolescents 2–16 years of age: 2007 Australian National Children's Nutrition and Physical Activity Survey. *Public Health Nutrition*. 15(11): 2060–2073.
- Barer-Stein, T., 1999. *You Eat What You Are: People, Culture and Food Traditions*. 2nd edn, Firefly Books, Richmond Hill, Ontario, 544 pp.
- Christensen, D. L., Orech, F. O., Mungai, M. N., Larsen, T., Friis, H. and Aagaard-Hansen, J., 2006. Entomophagy among the Luo of Kenya: a potential mineral source? *International Journal of Food Sciences and Nutrition*. 57: 198–203.
- Ekpo, U. F., Omotayo, A. M. and Dipeolu, M. A., 2008. Prevalence of malnutrition among settled pastoral Fulani children in Southwest Nigeria. *BMC Research Notes*. 1(1): 7.
- Estaire, P., González-Rodríguez, L. G., López-Sobaler, A. M. and Ortega, R. M., 2012. Food sources and intake of calcium in a representative sample of Spanish adults. *Food and Nutrition Sciences*. 3: 1269–1276.
- Faber, M., Van Jaarsveld, P. J. and Laubscher, R., 2007. The contribution of dark-green leafy vegetables to total micronutrient intake of two- to five-year-old children in a rural setting. *Water SA*. 33(3): 407–412.
- Fong, S., 2001. Celebrating baby beginnings. *Flavor and Fortune*. 8: 13–14.
- Fulgoni, III, V., Nicholls, J., Reed, A., Buckley, R., Kafer, K., Huth, P., DiRienzo, D. and Miller, G. D., 2007. Dairy consumption and related nutrient intake in African-American adults and children in the United States: continuing survey of food intakes by individuals 1994–1996, 1998, and the National Health and Nutrition Examination Survey 1999–2000. *Journal of the American Dietetic Association*. 107(2): 256–264.
- Fuller, F., Beghin, J. and Rozelle, S., 2007. Consumption of dairy products in urban China: results from Beijing, Shanghai and Guangzhou. *Australian Journal of Agricultural and Resource Economics*. 51(4): 459–474.
- Gannagé-Yared, M. H., Chemali, R., Sfeir, C., Maalouf, G. and Halaby, G., 2005. Dietary calcium and vitamin D intake in an adult Middle Eastern population: food sources and relation to lifestyle and PTH. *International Journal for Vitamin and Nutrition Research*. 75(4): 281–289.