Chapter 5

Food Restriction and Atherosclerotic Plaque Stabilization

Dorien G. De Munck, Guido R.Y. De Meyer and Wim Martinet

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76560

Abstract

Food restriction is a promising therapy for many age-associated pathologies as it stimulates the health-supportive mechanism autophagy. Because atherosclerosis is an inflammatory, age-related disease, dietary modification can be an important strategy in preventing atherosclerotic plaque development. A cholesterol-supplemented diet, used to induce plaque formation in rabbits, induces a pronounced hypercholesterolemia, which can be reversed after 4 weeks of normal diet. However, food restriction induces a further increase in circulating LDL cholesterol. These elevated cholesterol levels are associated with the induction of autophagy. Although neither a short-term normal diet nor food restriction alters plaque size, rabbits fed a normal diet show signs of increased plaque stability such as elevated collagen content and decreased expression of vascular cell adhesion molecule (VCAM)-1. Surprisingly, these favorable effects are not present after 4 weeks of food restriction. On the contrary, atherosclerotic plaques of food-restricted rabbits displayed enhanced apoptosis, a process known to further undermine plaque stability. In conclusion, severe short-term food restriction in rabbits prevents stabilization of atherosclerotic plaques as observed after regular cholesterol withdrawal via a normal diet.

Keywords: atherosclerosis, plaque stability, food restriction, cholesterol, autophagy

1. Introduction

Atherosclerosis is an inflammatory disease characterized by the formation of plaques in the large- and medium-sized arteries. Despite current pharmacological therapies, atherosclerosis remains the leading cause of death and morbidity among adults in the Western world [1]. Because a diet rich in calories, together with a sedentary lifestyle, contributes to the development

of atherosclerosis, dietary change is considered an important strategy in the prevention of atherosclerosis [2]. Moreover, dietary modification has shown to play an important role in several age-associated pathologies and in aging itself. Moderate calorie restriction results in a lifespan expansion of different species including yeast, fruit flies, nematodes, fish, rodents, and rhesus monkeys [3]. Besides favorable effects on longevity, long-term as well as short-term caloric restriction improves the cardiovascular disease risk profile in humans [4, 5]. Consistent with this finding, animal studies showed that dietary restriction attenuates atherosclerotic plaque development and decreases endothelial dysfunction [6, 7].

Starvation, as an extreme form of food restriction, is also one of the most important stimuli for autophagy induction [8]. Autophagy is a subcellular degradation pathway for long-lived proteins and damaged organelles. Under normal conditions, autophagy is a homeostatic process that is found in all cell types. However, under stress conditions, it functions as an important cell survival mechanism through nutrient recycling and the generation of energy [9]. Growing evidence indicates that autophagy deficiency plays a crucial role in plaque growth and destabilization [10–12]. Moreover, autophagy induction is suggested as a novel strategy for the prevention and treatment of atherosclerosis [13, 14].

2. Food restriction induces hypercholesterolemia

Cholesterol withdrawal by feeding atherosclerotic rabbits a normal diet for 4 weeks significantly reduces LDL cholesterol in serum (**Table 1**). In contrast, cholesterol withdrawal by severe food restriction (only 20% of normal diet) leads to elevated LDL cholesterol levels and a significant loss of bodyweight (**Table 1**), which confirms previous studies showing hypercholesterolemia in healthy subjects after fasting or moderate caloric restriction [15–17] as well as in patients with eating disorders such as anorexia nervosa [18]. Several mechanisms may account for hypercholesterolemia including downregulation of the hepatic LDL receptor leading to decreased LDL uptake in the liver, lipolysis in adipose tissue, or increased cholesterol synthesis [15, 17, 19].

	Weeks	Baseline	Normal diet	Restricted diet
LDL cholesterol (mg/dL)	20	1026 ± 147	589 ± 98	702 ± 13
	24	/	250 ± 105$^{\#\#}$	1101 ± 177$^{\#, ***}$
Triglycerides (mg/dL)	20	92 ± 29	53 ± 13	56 ± 9
	24	/	49 ± 7	44 ± 9
Bodyweight (kg)	20	4.0 ± 0.2	4.3 ± 0.1	4.0 ± 0.1
	24	/	4.4 ± 0.1	3.2 ± 0.1$^{\#\#\#}$, ***

Data are expressed as mean ± SEM.

$^{\#}P < 0.05$.

$^{\#\#}P < 0.01$.

$^{\#\#\#}P < 0.001$ versus 20 weeks (paired sample t-test, n = 10).

$^{***}P < 0.001$ versus normal diet (independent sample t-test, n = 10).

Table 1. Serum lipid values and body weight in cholesterol-fed rabbits (baseline, 20 weeks of cholesterol) followed by dietary lipid lowering for 4 weeks (normal diet) or a restricted diet for 4 weeks (restricted diet).

Despite increased levels of circulating LDL, there is no difference in lipid accumulation in the liver or aorta of rabbits undergoing severe food restriction. Both normal diet and food restriction do not affect serum triglycerides (**Table 1**).

3. Hypercholesterolemia induced by food restriction is associated with autophagy induction

LDL cholesterol levels are negatively correlated with SQSTM1/p62 protein levels in the liver (**Figure 1**), suggesting stimulation of autophagy as an alternative mechanism for the increase

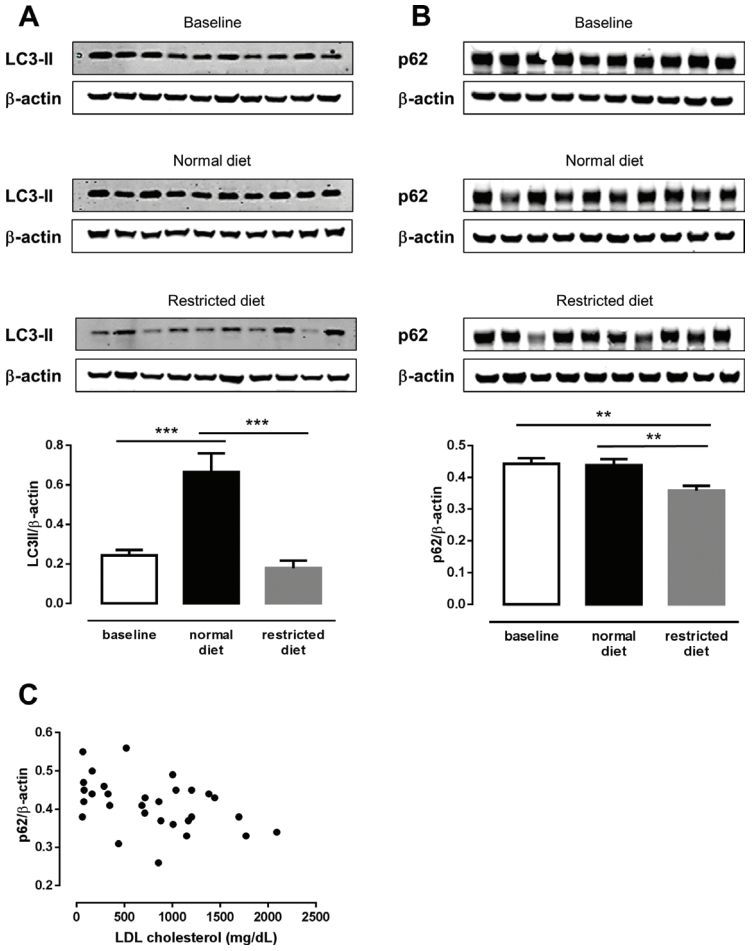


Figure 1. Induction of autophagy in liver of rabbits that were fed 0.3% cholesterol for 20 weeks (baseline), followed by cholesterol withdrawal for 4 weeks either via a normal diet or a restricted diet (20% of normal diet). Liver samples of ten rabbits per group were analyzed by Western blotting for the expression of autophagy marker proteins LC3-II (A) and p62 (B). $^{**}P < 0.01$, $^{***}P < 0.001$ (One-way ANOVA with post-hoc LSD, n = 10 in each group). (C) Serum LDL-levels show an inverse correlation with liver p62 protein levels (Pearson Correlation Coefficient −0.44, $P<0.05$).

in serum lipids. SQSTM1/p62 is a scaffold protein that binds directly to the autophagosomal marker Atg8/LC3 to facilitate degradation of ubiquitinated protein aggregates via autophagy. Nutrient deprivation is a powerful autophagy-inducing condition [20]. Rabbits that undergo cholesterol withdrawal via a normal diet show high LC3-II levels but unaltered amounts of SQSTM1/p62 (**Figure 1A**), indicating moderate induction of autophagy. In contrast, rabbits undergoing severe food restriction show low levels of LC3-II and a clear reduction of SQSTM1/p62 (**Figure 1B**), which points to strong autophagy stimulation. It has been described that autophagy is strongly involved in managing intracellular lipids [21, 22]. Lipid droplets are taken up by lysosomes, where lysosomal acid lipases hydrolyze cholesteryl esters to generate free cholesterol for ATP-binding cassette transporter 1 (ABCA1)-mediated cholesterol efflux [21]. Impairment of autophagy in macrophages reduces reverse cholesterol transport [21], a condition that refers to net cholesterol flux from the peripheral tissues to the liver (for excretion via the bile). Conversely, pharmacological activation of the autophagy pathway attenuates lipid accumulation [23] and in some conditions (e.g., after treatment with mTOR inhibitors) triggers hypercholesterolemia [24].

4. Cholesterol withdrawal increases plaque stability

Numerous studies indicate that dietary modification is an important strategy for the prevention of cardiovascular disease [2, 25]. However, studies examining the effects of food restriction on atherosclerosis are scarce. Although short-term cholesterol withdrawal (4 weeks) does not alter plaque size (**Table 2**), a normal unrestricted diet results in a more stable plaque phenotype. Indeed, collagen content of the atherosclerotic plaques is increased, mainly due to an increase in type I collagen (**Figure 2**), which is essential for plaque stability. Moreover, VCAM-1 expression in endothelial cells declines (**Figure 3**). VCAM-1 is important for leucocyte recruitment and thereby contributes to plaque inflammation and macrophage accumulation. However, despite a decrease in VCAM-1 expression, the total amount of macrophages in the plaque does not alter within 4 weeks of cholesterol withdrawal (4 weeks). Indeed, only prolonged cholesterol withdrawal (12–24 weeks) results in a dramatic loss of plaque macrophages [26–28].

	Baseline	Normal diet	Restricted diet
Plaque area (mm^2)	3.3 ± 0.8	3.6 ± 0.6	3.6 ± 1.0
Macrophages (%)	22 ± 3	24 ± 4	34 ± 6
Smooth muscle cells (%)	26 ± 4	23 ± 2	26 ± 4
Fibrous cap thickness	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.1

Data are expressed as mean ± SEM.

Table 2. Plaque area and cellular composition in the proximal ascending in cholesterol-fed rabbits (baseline, 20 weeks of cholesterol) followed by dietary lipid lowering for 4 weeks (normal diet) or a restricted diet for 4 weeks (restricted diet).

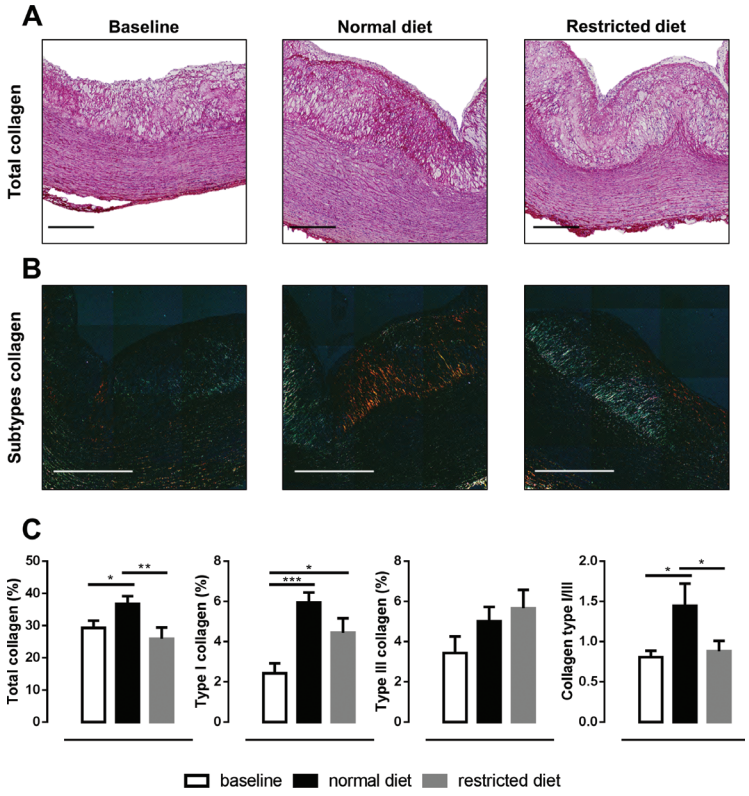


Figure 2. Collagen content of atherosclerotic plaques in rabbits that were fed 0.3% cholesterol for 20 weeks (baseline), followed by cholesterol withdrawal for 4 weeks either via a normal diet or a restricted diet (20% of normal diet). (A) Sections of the proximal ascending aorta were stained with Sirius red for total collagen determination. Scale bar = 500 μm. (B) Analysis of Sirius red staining via polarized light microscopy. Collagen type I is displayed in red, type III in green. Scale bar = 500 μm. (C) Quantification of total collagen, type I and type III collagen as well as the type I/III collagen ratio in Sirius red stained sections. *P < 0.05, **P < 0.01, ***P < 0.001 (One-way ANOVA with post-hoc LSD, n = 8–10 in each group).

5. Effect of food restriction on plaque development is controversial

In contrast with a normal unrestricted diet, severe food restriction does not promote beneficial effects such as increased collagen synthesis and decreased VCAM-1 expression. On the contrary, plaques of rabbits undergoing food restriction reveal an increase in apoptosis (**Figure 3**). Depending on the cell type and stage of the plaque, apoptosis could be detrimental for plaque stability [29]. Moreover, apoptosis can stimulate the release of inflammatory cytokines and chemotactic factors, thereby further aggravating plaque inflammation [30].

Given that food restriction stimulates autophagy, a well-known cellular survival mechanism, increased apoptosis may seem surprising. However, autophagy induction after intensive nutrient deprivation may be insufficient to counteract apoptosis.

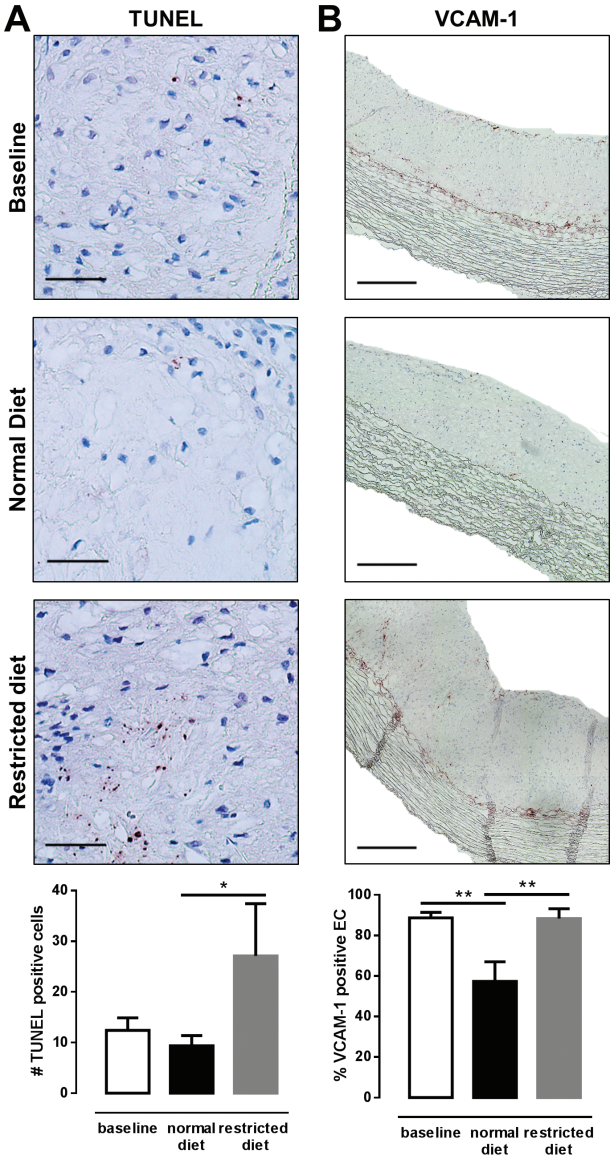


Figure 3. Atherosclerotic plaque composition of rabbits that were fed 0.3% cholesterol for 20 weeks (baseline), followed by cholesterol withdrawal for 4 weeks either via a normal diet or a restricted diet (20% of normal diet). (A) Sections of the proximal ascending aorta were TUNEL stained for the detection of apoptosis and the number of TUNEL positive cells in each group was quantified. Scale bar = 50 μm. *P < 0.05 (One-way ANOVA with post-hoc LSD, n = 10 in each group). (B) Sections of the proximal ascending aorta were immunohistochemically stained for VCAM-1 expression on endothelial cells. The number of VCAM-1 positive endothelial cells in each group was quantified. Scale bar = 500 μm. **P < 0.01 (One-way ANOVA with post-hoc LSD, n = 8–10 in each group).

The abovementioned findings are in agreement with previous studies in rabbits showing increased plaque development after a 50% reduction in food intake [31], even though Lacombe et al. [16] reported that aggravated atherosclerosis only occurs in rabbits when dietary restriction is combined with cholesterol feeding. Prenatal under nutrition is also known to program a pro-atherosclerotic phenotype and to accelerate plaque development in young adult offspring [32, 33]. Nonetheless, a large body of evidence indicates that food restriction is associated with a range of positive effects on cardiovascular health. Dietary restriction in apolipoprotein E-deficient mice, for example, results in the development of smaller and less advanced atherosclerotic lesions [7, 34]. A lower incidence of atherosclerotic plaque development is also seen in genetically obese rats consuming a low calorie diet, as compared to rats fed ad libitum [35]. Studies in humans clearly describe a reduction in cardiovascular risk factors but often fail to demonstrate a direct effect on atherosclerotic plaque development [4, 5]. Still, the incidence of atherosclerosis was decreased during the years following World War I and World War II, which supports the general benefit of food deprivation [36]. Importantly, at least two main differences in the experimental design or setup of different studies should be mentioned that may explain a different outcome. First, differences might be related to the severity of food restriction (50% food restriction = moderate, 80% food restriction = severe). Accordingly, severe food restriction holds a higher risk of vitamin deficiency that should be taken into account. Indeed, vitamin D deficiency may contribute to atherosclerosis [37], and also vitamin C and vitamin E depletions are demonstrated to aggravate plaque development [38]. Second, the time span of dietary restriction could be an important factor. Four weeks of food restriction is relatively short in comparison with other studies showing beneficial effects of food restriction. Fontana et al. [4], for example, reported a reduced risk for atherosclerosis in individuals who had been on food restriction for an average of 6 years.

In conclusion, severe short-term food restriction seems to counteract the plaque stabilizing benefits of cholesterol withdrawal in rabbits.

Acknowledgements

The authors acknowledge Rita Van den Bossche, Hermine Fret, and Anne-Elise Van Hoydonck for excellent technical support. This study was funded by the University of Antwerp (BOF) and the Flanders Fund for Scientific Research (FWO) (project G.0412.16N). Dorien G. De Munck is a fellow of the Agency for Innovation by Science and Technology (IWT).

Author details

Dorien G. De Munck, Guido R.Y. De Meyer and Wim Martinet*

*Address all correspondence to: wim.martinet@uantwerpen.be

Laboratory of Physiopharmacology, University of Antwerp, Antwerp, Belgium

References

[1] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics-2015 update: A report from the American Heart Association. Circulation. 2015;**131**(4):e29-e322. DOI: 10.1161/CIR.0000000000000152

[2] Rees K, Dyakova M, Wilson N, Ward K, Thorogood M, Brunner E. Dietary advice for reducing cardiovascular risk. The Cochrane Database of Systematic Reviews. 2013; **12**:CD002128. DOI: 10.1002/14651858.CD002128.pub5

[3] Fontana L, Partridge L, Longo VD. Extending healthy life span–From yeast to humans. Science. 2010;**328**(5976):321-326. DOI: 10.1126/science.1172539

[4] Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**(17):6659-6663. DOI: 10.1073/pnas.0308291101

[5] Lefevre M, Redman LM, Heilbronn LK, Smith JV, Martin CK, Rood JC, et al. Caloric restriction alone and with exercise improves CVD risk in healthy non-obese individuals. Atherosclerosis. 2009;**203**(1):206-213. DOI: 10.1016/j.atherosclerosis.2008.05.036

[6] Shinmura K. Cardiovascular protection afforded by caloric restriction: Essential role of nitric oxide synthase. Geriatrics & Gerontology International. 2011;**11**(2):143-156. DOI: 10.1111/j.1447-0594.2010.00675.x

[7] Guo Z, Mitchell-Raymundo F, Yang H, Ikeno Y, Nelson J, Diaz V, et al. Dietary restriction reduces atherosclerosis and oxidative stress in the aorta of apolipoprotein E-deficient mice. Mechanisms of Ageing and Development. 2002;**123**(8):1121-1131. DOI: 10.1016/S0047-6374(02)00008-8

[8] Rubinsztein DC, Codogno P, Levine B. Autophagy modulation as a potential therapeutic target for diverse diseases. Nature Reviews Drug Discovery. 2012;**11**(9):709-730. DOI: 10.1038/nrd3802

[9] Mizushima N, Komatsu M. Autophagy: Renovation of cells and tissues. Cell. 2011;**147**(4): 728-741. DOI: 10.1016/j.cell.2011.10.026

[10] Grootaert MO, da Costa Martins PA, Bitsch N, Pintelon I, De Meyer GRY, Martinet W, et al. Defective autophagy in vascular smooth muscle cells accelerates senescence and promotes neointima formation and atherogenesis. Autophagy. 2015;**11**(11):2014-2032. DOI: 10.1080/15548627.2015.1096485

[11] Liao X, Sluimer JC, Wang Y, Subramanian M, Brown K, Pattison JS, et al. Macrophage autophagy plays a protective role in advanced atherosclerosis. Cell Metabolism. 2012; **15**(4):545-553. DOI: 10.1016/j.cmet.2012.01.022

[12] Razani B, Feng C, Coleman T, Emanuel R, Wen H, Hwang S, et al. Autophagy links inflammasomes to atherosclerotic progression. Cell Metabolism. 2012;**15**(4):534-544. DOI: 10.1016/j.cmet.2012.02.011

[13] De Meyer GRY, Grootaert MO, Michiels CF, Kurdi A, Schrijvers DM, Martinet W. Autophagy in vascular disease. Circulation Research. 2015;**116**(3):468-479. DOI: 10.1161/CIRCRESAHA.116.303804

[14] Vindis C. Autophagy: An emerging therapeutic target in vascular diseases. British Journal of Pharmacology. 2015;**172**(9):2167-2178. DOI: 10.1111/bph.13052

[15] Savendahl L, Underwood LE. Fasting increases serum total cholesterol, LDL cholesterol and apolipoprotein B in healthy, nonobese humans. The Journal of Nutrition. 1999;**129**(11):2005-2008

[16] Lacombe C, Corraze G, Nibbelink M. Increases in hyperlipoproteinemia, disturbances in cholesterol metabolism and atherosclerosis induced by dietary restriction in rabbits fed a cholesterol-rich diet. Lipids. 1983;**18**(4):306-312

[17] Markel A, Brook JG, Aviram M. Increased plasma triglycerides, cholesterol and apolipoprotein E during prolonged fasting in normal subjects. Postgraduate Medical Journal. 1985;**61**(715):395-400

[18] Ohwada R, Hotta M, Oikawa S, Takano K. Etiology of hypercholesterolemia in patients with anorexia nervosa. The International Journal of Eating Disorders. 2006;**39**(7):598-601. DOI: 10.1002/eat.20298

[19] Stoudemire JB, Renaud G, Shames DM, Havel RJ. Impaired receptor-mediated catabolism of low density lipoproteins in fasted rabbits. Journal of Lipid Research. 1984;**25**(1):33-39

[20] Mizushima N, Yamamoto A, Matsui M, Yoshimori T, Ohsumi Y. In vivo analysis of autophagy in response to nutrient starvation using transgenic mice expressing a fluorescent autophagosome marker. Molecular Biology of the Cell. 2004;**15**(3):1101-1111. DOI: 10.1091/mbc.E03-09-0704

[21] Ouimet M, Franklin V, Mak E, Liao X, Tabas I, Marcel YL. Autophagy regulates cholesterol efflux from macrophage foam cells via lysosomal acid lipase. Cell Metabolism. 2011;**13**(6):655-667. DOI: 10.1016/j.cmet.2011.03.023

[22] Singh R. Autophagy and regulation of lipid metabolism. Results and Problems in Cell Differentiation. 2010;**52**:35-46. DOI: 10.1007/978-3-642-14426-4_4

[23] Li BH, Liao SQ, Yin YW, Long CY, Guo L, Cao XJ, et al. Telmisartan-induced PPARgamma activity attenuates lipid accumulation in VSMCs via induction of autophagy. Molecular Biology Reports. 2015;**42**(1):179-186. DOI: 10.1007/s11033-014-3757-6

[24] Martinet W, De Loof H, De Meyer GRY. mTOR inhibition: A promising strategy for stabilization of atherosclerotic plaques. Atherosclerosis. 2014;**233**(2):601-607. DOI: 10.1016/j.atherosclerosis.2014.01.040

[25] Reidlinger DP, Darzi J, Hall WL, Seed PT, Chowienczyk PJ, Sanders TA, et al. How effective are current dietary guidelines for cardiovascular disease prevention in healthy middle-aged and older men and women? A randomized controlled trial. The American Journal of Clinical Nutrition. 2015;**101**(5):922-930. DOI: 10.3945/ajcn.114.097352

[26] Kockx MM, De Meyer GRY, Buyssens N, Knaapen MWM, Bult H, Herman AG. Cell composition, replication, and apoptosis in atherosclerotic plaques after 6 months of cholesterol withdrawal. Circulation Research. 1998;**83**(4):378-387. DOI: 10.1161/01.RES.83.4.378

[27] Riedmuller K, Metz S, Bonaterra GA, Kelber O, Weiser D, Metz J, et al. Cholesterol diet and effect of long-term withdrawal on plaque development and composition in the thoracic aorta of New Zealand White rabbits. Atherosclerosis. 2010;**210**(2):407-413. DOI: 10.1016/j.atherosclerosis.2010.01.009

[28] Aikawa M, Rabkin E, Okada Y, Voglic SJ, Clinton SK, Brinckerhoff CE, et al. Lipid lowering by diet reduces matrix metalloproteinase activity and increases collagen content of rabbit atheroma: A potential mechanism of lesion stabilization. Circulation. 1998; **97**(24):2433-2444. DOI: 10.1161/01.CIR.97.24.2433

[29] Kockx MM, Herman AG. Apoptosis in atherosclerosis: Beneficial or detrimental? Cardiovascular Research. 2000;**45**(3):736-746

[30] Seimon T, Tabas I. Mechanisms and consequences of macrophage apoptosis in atherosclerosis. Journal of Lipid Research. 2009;**50**(Suppl):S382-S387. DOI: 10.1194/jlr.R800032-JLR200

[31] Bailey JM, Butler J. Intensification of experimental atherosclerosis by semi-starvation diet. Proceedings of the Society for Experimental Biology and Medicine. 1967;**124**(4):1119-1121

[32] Blackmore HL, Piekarz AV, Fernandez-Twinn DS, Mercer JR, Figg N, Bennett M, et al. Poor maternal nutrition programmes a pro-atherosclerotic phenotype in ApoE−/− mice. Clinical Science (London, England). 2012;**123**(4):251-257. DOI: 10.1042/CS20110487

[33] Yates Z, Tarling EJ, Langley-Evans SC, Salter AM. Maternal undernutrition programmes atherosclerosis in the ApoE*3-Leiden mouse. The British Journal of Nutrition. 2009;**101**(8):1185-1194. DOI: 10.1017/S0007114508066786

[34] Lyngdorf LG, Gregersen S, Daugherty A, Falk E. Paradoxical reduction of atherosclerosis in apoE-deficient mice with obesity-related type 2 diabetes. Cardiovascular Research. 2003;**59**(4):854-862. DOI: 10.1016/S0008-6363(03)00506-6

[35] Koletsky S, Puterman DI. Reduction of atherosclerotic disease in genetically obese rats by low calorie diet. Experimental and Molecular Pathology. 1977;**26**(3):415-424

[36] Schettler G. Atherosclerosis during periods of food deprivation following World Wars I and II. Preventive Medicine. 1983;**12**(1):75-83

[37] Mozos I, Marginean O. Links between vitamin D deficiency and cardiovascular diseases. BioMed Research International. 2015;**2015**:109275. DOI: 10.1155/2015/109275

[38] Babaev VR, Li L, Shah S, Fazio S, Linton MF, May JM. Combined vitamin C and vitamin E deficiency worsens early atherosclerosis in apolipoprotein E-deficient mice. Arteriosclerosis, Thrombosis, and Vascular Biology. 2010;**30**(9):1751-1757. DOI: 10.1161/ATVBAHA.110.209502

Open access peer-reviewed Edited volume

Atherosclerosis

Yesterday, Today and Tomorrow

Edited by Luigi Gianturco

ICBM - GSD

Atherosclerosis is a subject of enormous contention for cardiologists and in general for all medical doctors. With this publication we have given you a concise "state-of-the-art" look at the world of atheroma. Many other elements could be included and so it is only a brief analysis of "today" (the preventive medicine era) and "tomorrow" (transforming the cure medicine era into the care medicine era) but also remembering "yesterday" (the ex-cathedra medicine era). Let's hope our arteries are free from atherosclerotic events: have a good read!

ORDER HARDCOPY

Published: August 1st 2018

DOI: 10.5772/intechopen.68346

ISBN: 978-1-78923-561-6

Print ISBN: 978-1-78923-560-9

128

Total Chapter Downloads

Chapters	Downloads
Open access peer-reviewed	
1. Focus on Coronary Atherosclerosis *By Hakan Saçlı, İbrahim Kara and Mehmet Kaan Kırali*	21
Open access peer-reviewed	
2. Early Stages of Atherosclerosis Documented in Early Embryologic Life *By Bahar Uslu*	17
Open access peer-reviewed	
3. Inflammatory Mechanisms in Atherosclerosis *By Ida Gregersen and Bente Halvorsen*	15
Open access peer-reviewed	
4. Effects of Nicotine Contained in Tobacco Mainstream Smoke on Vascular Smooth Muscle Cells *By Akio Nakamura*	21
Open access peer-reviewed	
5. Food Restriction and Atherosclerotic Plaque Stabilization *By Dorien G. De Munck, Guido R.Y. De Meyer and Wim Martinet*	19
Open access peer-reviewed	
6. Atherothrombosis as a Leading Cause of Acute Coronary Syndromes and Stroke: The Main Killers in Developed Countries *By Ewelina Dziedzic, Michał Machowski, Małgorzata Oleszczak-Kostyra and Marek J. Dąbrowski*	19
Open access peer-reviewed	
7. Cerebrovascular Atherosclerosis: Cognitive Dysfunction Progress and Autophagic Regression *By Kyoung Joo Cho and Gyung Whan Kim*	16

Edited volume and chapters are indexed in

WorldCat®

BASE

Order a hardcopy of the Edited volume

Free shipping with DHL Express

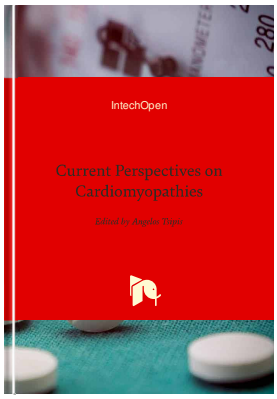
Hardcover (ex. VAT)

£140

ORDER NOW

Residents of European Union countries need to add a Book Value-Added Tax of 5%. Institutions and companies, registered as VAT taxable entities in their own EU member state, will not pay VAT by providing IntechOpen with their VAT registration number. This is made possible by the EU reverse charge method.

Related books

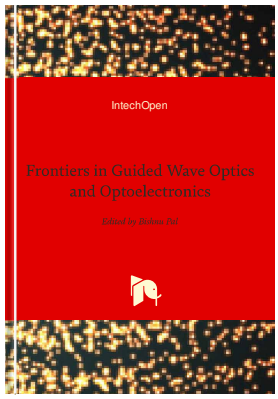


Current Perspectives on Cardiomyopathies

Edited by Angelos Tsipis

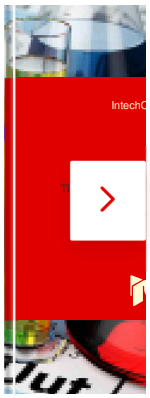
Cholesterol

Edited by Madan L. Nagpal



Frontiers in Guided Wave Optics and Optoelectronics

Edited by Bishnu Pal



Ionic L

Edited by Alexa

Your recently viewed content

Chapter

Food Restriction and Atherosclerotic Plaque Stabil...

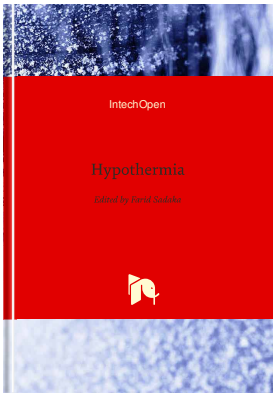
By Dorien G. De Munck, Guido R.Y. De Meyer and Wim Ma...

Call for authors
Submit your work to IntechOpen

We're endorsed by Web Of Science, the world's leading citation index. The authors who publish with us range from globally-renowned Nobel Prize winners to up-and-coming researchers at the cutting edge of scientific discovery. We'd love for you to be one of them.

VIEW ALL BOOKS OPEN FOR SUBMISSIONS

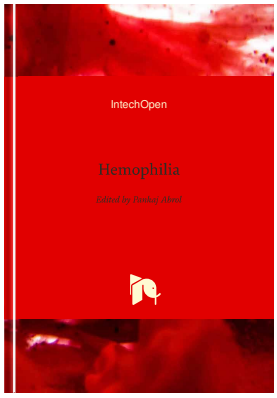
Books open for chapter submissions



Hypothermia

Edited by Farid Sadaka

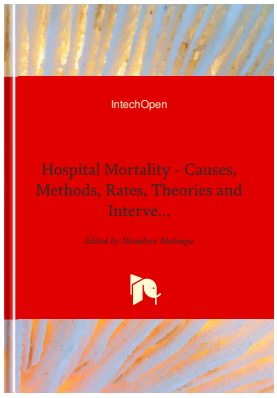
Open for chapter submissions



Hemophilia

Edited by Pankaj Abrol

Open for chapter submissions



Hospital Mortality - Causes, Methods, Rates, Theories and Interventions

Edited by Ntambwe Malangu

Open for chapter submissions

From
Hear

I

Op

Book subject areas

Physical Sciences, Engineering and Technology

Chemistry (114)

Computer and Information Science (362)

Earth and Planetary Sciences (120)

Engineering (658)

Materials Science (194)

Mathematics (31)

Nanotechnology and Nanomaterials (76)

Physics (92)

Robotics (87)

Technology (52)

More ›

Life Sciences

Agricultural and Biological Sciences (224)

Biochemistry, Genetics and Molecular Biology (189)

Environmental Sciences (103)

Immunology and Microbiology (39)

Neuroscience (39)

More ›

Health Sciences

Medicine (1085)

Pharmacology, Toxicology and Pharmaceutical Science (46)

Veterinary Medicine and Science (17)

Social Sciences and Humanities

Business, Management and Economics (85)

Psychology (13)

Social Sciences (37)

Home

News

Contact

Careers

About us

Our Authors and Editors

Scientific Advisors

Team

Events

Partnerships

Publish with us

About Open Access

How it works

OA Publishing fees

Open Access funding

Peer reviewing

Editorial policies

Headquarters
IntechOpen Limited
The Shard
25th floor
32 London Bridge Street
London, SE1 9SG, UNITED KINGDOM

Phone: +44 (0) 20 3457 0462

Search AUTHOR PANEL SIGN IN