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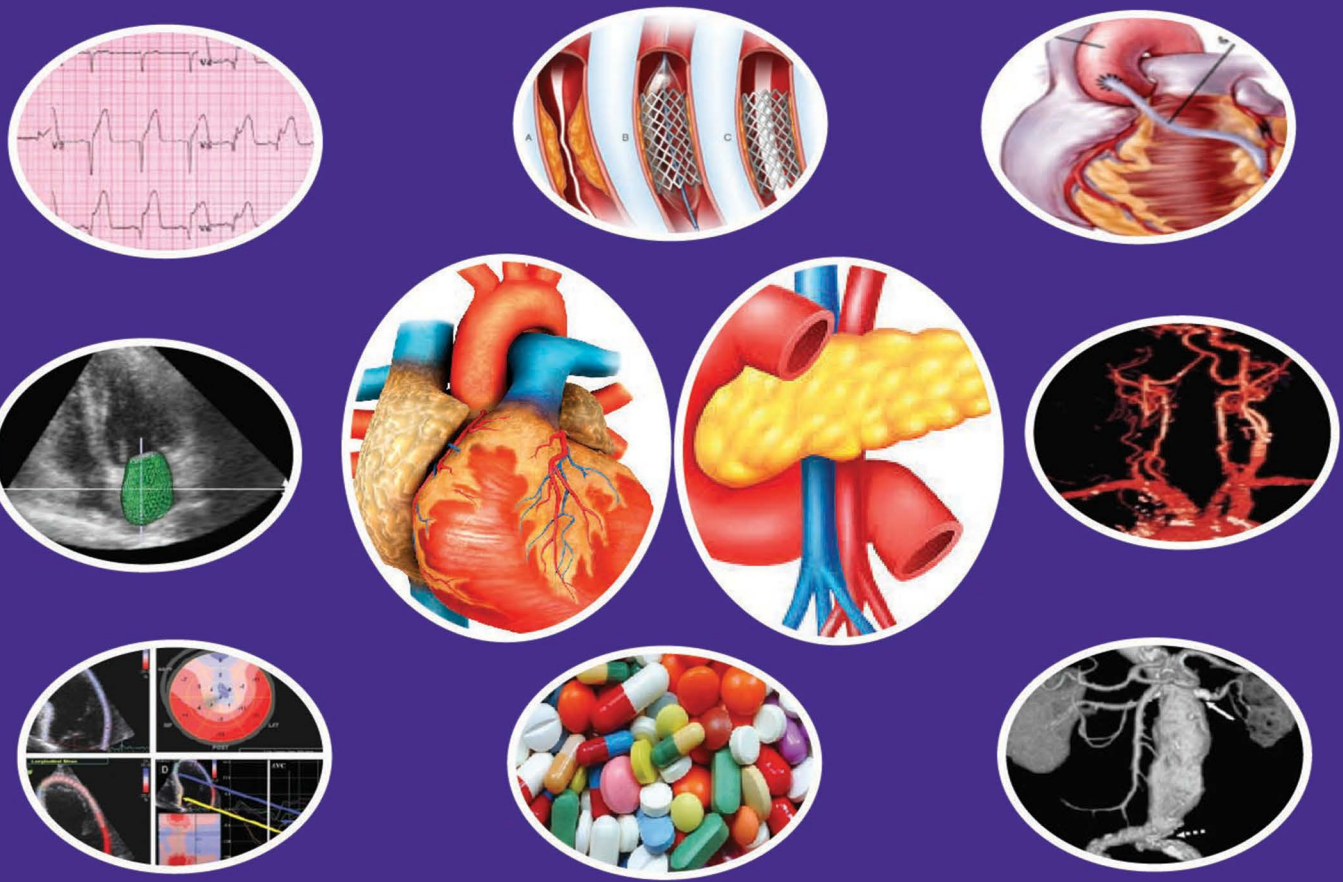
Cardiodiabetes Update

A Textbook of Cardiology

HK Chopra • Shashank R Joshi • GS Wander
Ravi R Kasliwal • Viveka Kumar • AK Pancholia



PDF CD-ROM (Complete Book)

Forewords

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Contents

SECTION 1 CLINICAL SPECTRUM

1. **Clinical Spectrum of Cardiodiabetes: How Indians are Different** 3
   JPS Sawhney, Arjun Sreekumar, Saurabh Bagga
2. **Risk Factors for Cardiodiabetes** 7
   Sanjiv Sharma, Varsha Koul, Varun Gupta
3. **Cardiodiabetes in Children** 13
   IB Vijayalakshmi
4. **New Genes for Type 2 Diabetes: Indian Scenario** 20
   Om J Lakhani, Surender Kumar
5. **Stress and Cardiodiabetes** 25
   Satish Kr Gupta, Rahul Gupta
6. **Hypothyroidism and Cardiodiabetes** 36
   M Somasundaram, C Elamaran
7. **Cardiodiabetes and Insulin Resistance in Obesity: Clinical Relevance** 41
   Ajay Kumar Sinha, Anand Gopal, Dinanath Kumar, Shaheen Ahmad, Asim Perwez, Vikas Singh
8. **Anemia and Cardiodiabetes: Management Strategies** 46
   RK Saran, Mahim Saran, Vasudha Jain
9. **Endothelial Dysfunction in Atrial Fibrillation with Type 2 DM** 49
   Shishu Shankar Mishra, Biswaranjan Mishra, Satyanarayan Routray, Dipak Ranjan Das
10. **ACS, Cardiodiabetes, and Women** 55
    BP Singh, Ravi Vishnu Prasad, Nishant Tripathy, Nirav Kumar
11. **Coronary Artery Disease in Diabetes: How Different is It from Nondiabetics?** 62
    Binoy John
12. **Cardiodiabetes and Heart Failure in the Elderly** 66
    Thachathodiyl Rajesh, Umesh C Samal
13. **Prognosis of Heart Failure in Diabetes: Newer Perspectives** 74
    Jaideep C Menon, Umesh C Samal
14. **Cardiodiabetes Management and STEMI: Prognostication** 97
    PB Jayagopal, T Kallarakkal Jain

15. **Small Vessel CAD in Cardiodiabetes** 100
Arvind Sethi, Upendra Kaul

16. **Cardiodiabetes and Deep Venous Thrombosis** 105
Nagesh S Waghmare, Anil Kumar

17. **Pregnancy and Cardiodiabetes** 112
Ruchi Tandon

18. **Cardiodiabetes and Autonomic Insufficiency** 119
Ankit Bansal, Vivek Chaturvedi

19. **Cardiodiabetes and Pulmonary Embolism: Is the Outcome Different?** 126
Mrinal Kanti Das, Tapan Sinha

20. **Cardiodiabetes and Cutaneous Manifestations** 132
Gulshant Panesar

21. **Benidipine for Hypertension in Chronic Kidney Disease with Cardiodiabetes** 138
DS Rana

22. **Cardiorenal Diabetes: Triple Jeopardy** 145
Ramesh Hotchandani, Nikhil Bhat, Neelam Bisht, Abhimanyu Bhatia

23. **Contrast-induced Acute Kidney Injury** 150
Pawan K Sharma, Kapil Sharma, HK Chopra

24. **Cardiodiabetes and Hypertension: Double Jeopardy** 159
Praveen Jain, Mohammad Jibran

25. **Cardiodiabetes and Obstructive Sleep Apnea** 168
Avi Kumar, Tanu Satija, HK Chopra

26. **Cardiodiabetes and Mind-Heart Connection** 174
Chockalingam A, Chockalingam P, Chockalingam V

27. **Aortic Aneurysm Surgery in Cardiodiabetes: Is the Outcome Different?** 180
Jayesh Suresh, Anita Dhar, Anil Bhan

28. **Cardiodiabetes and Syncope** 183
Rakesh Varma, Rajat Jain

29. **Cardiodiabetes and Sexual Dysfunction** 188
Deepak K Jumani

30. **Cardiodiabetes and Erectile Dysfunction** 199
Naveen Garg, KK Kapur, HK Chopra

31. **Endothelial Cell Dysfunction in DM, HT and CAD, and Its Pathophysiology** 203
GS Sainani, Manisha Sawhney, Nitin Joshi, Aneesa Kapadia, Rajesh Sainani

SECTION 2 DIAGNOSIS

32. Current Status of Diabetic Cardiomyopathy 213
PC Mondal, Manotosh Panja, Madhumanti Panja

33. Insulin Therapy and Cardiodiabetes 220
Vitull K Gupta, Meghna Gupta, Varun Gupta

34. Echo-guided CRT in Cardiodiabetes 227
Rahul Mehrotra, Raj Kumar Dahiya, Meeta Maheshwari

35. Echocardiography in Diabetes 233
Srikanth Sola, Vatchsala Sree Varadharajan

36. Echo/Doppler Assessment of Increased Left-sided Filling Pressures and Diastolic Heart Failure in Patients with Normal Systolic Function in Cardiodiabetes 241
Omar Tageldin, Ahmed Abdelhaleem, Mohammed J Arisha, Ayman Battisha, Swetha Srialluri, Adel A Farhoud, Mohamed S Mahmoud, Hassan Kamel, HK Chopra, Navin C Nanda

37. 3D Echo and Cardiodiabetes 246
V Amuthan, RVA Ananth

38. Emergency Echocardiography in Cardiodiabetes 253
Rekha Mishra, Sanjeev Asotra, Krishna CK, Manish Bansal, HK Chopra

39. Diabetic Cardiomyopathy: Studies on Global Longitudinal Strain in Asymptomatic Diabetic Subjects 263
G Vijayaraghavan

40. Strain and Strain Rate Imaging in Cardiodiabetes 267
Nitin Burkule

41. Dobutamine Stress Echo for Coronary Artery Disease Evaluation in Diabetics 274
Naveen Garg, KK Kapur

42. Noninvasive Cardiovascular Imaging for Risk Assessment in Asymptomatic Diabetic Patients 290
Pawan K Sharma, HK Chopra

43. Value of Ankle–Brachial Index in Cardiodiabetes 299
Shraddha Ranjan, Manish Bansal, Ravi R Kasliwal, HK Chopra

44. Computed Tomography Evaluation of Abdominal Arterial Wall Calcification in Patients with Type 2 Diabetes Mellitus 305
Charu Paruthi, Shivya Tucker, HK Chopra, Reeta Kanaujiya, Gauri Gupta

45. Cardiac MRI: A Promise, Hope or Hype in Cardiodiabetes 309
Mona Bhatia

46. **CT for CVD Evaluation in Cardiodiabetes** 313
Priya Jagia, Arun Sharma, Kartik Ganga, Pankaj Kumar

47. **Recent Advances in Nuclear Cardiology and Cardiodiabetes** 321
GN Mahapatra, Mary Anne Joseph

48. **Blood Pressure Variability in Cardiodiabetes** 328
Rajan Joseph Manjuran, Sulthan Raslin Salih

49. **Central Aortic Blood Pressure Evaluation for Hypertension in Cardiodiabetics** 331
Bahekar Anurag D, George Koshy, K Venugopal

50. **Telemedicine in Diabetes Management** 336
Krishnam Raju P, Prasad SG

51. **HbA1c: Clinical Relevance in Cardiodiabetes** 342
AK Bali

52. **Emerging Role of Cardiac Troponin in Cardiodiabetes** 345
Arvind Lal, Nimmi Kansal

SECTION 3 MANAGEMENT STRATEGIES

53. **Role of Yoga in Cardiodiabetes** 351
SC Manchanda, Kushal Madan

54. **Metabolic Effects of Antihypertensive Drugs** 358
Mohsin Wali, C Venkata S Ram

55. **Potential Role of Rosuvastatin in Cardiodiabetes** 362
Saumitra Ray, Sumanta Chatterjee

56. **Diabetic Hypertriglyceridemia: Management Strategies** 370
HK Chopra, Ashok Jaiswal, Harmeet Singh

57. **High-density Lipoprotein in Cardiodiabetes** 378
Ruvan AI Ekanayaka

58. **Glucose-lowering Strategies and Cardiovascular Outcomes** 387
Apoorv Mittal

59. **Improving CV Outcomes in Diabetes with New Antidiabetic Medications: A New Era has Begun** 396
PC Manoria, Pankaj Manoria

60. **Positioning of Once Weekly GLP–1- based Therapies for Whom and When?** 405
Brij Mohan Makkar, Jugal Kishore Sharma

61. **DPP-IV Inhibitors beyond Glycemic Efficacy** 413
Geetha Subramanian, Balaji Lohiya, Vikas Agrawal, Aviraj Chaudhary

62. **Insulin Therapy and Cardiodiabetes in Critical Care** 418
Surabhi Awasthi, Nikhil Bhat

63. **Lixisenatide: A Cardiodiabetes Perspective** 427
Vijay Panikar, Jimit Vadgama, Tejas Kamat

64. **SGLT2-i Agents and Cardiovascular Diabetology** 430
Sanjay Kalra

65. **SGLT2-i for the Reduction of Cardiovascular Events in High-risk Patients with Diabetes Mellitus** 436
AK Pancholia

66. **Diabetes and Heart Failure: New Data on the Role of SGLT 2 Inhibitors—A Change of Concept?** 447
Tiny Nair, Akash Nair

67. **Bisoprolol: Is It Superior in Cardiodiabetes?** 450
Jamshed J Dalal

68. **Bisoprolol: A Choice of Beta Blocker in Hypertension and ACS in Cardiodiabetes** 455
CN Manjunath, Prabhavathi

69. **Bisoprolol in Heart Failure in Cardiodiabetes** 461
CK Ponde, Maulik Parekh

70. **Nebivolol for Hypertension in Cardiodiabetes** 466
Abhirup Chatterjee, Soumitra Kumar

71. **ARB for Hypertension in Cardiodiabetes** 471
Sandeep Bansal, Preeti Gupta

72. **CKD and Hypertension: Is Benidipine Beneficial?** 479
Asha Moorthy, T Kallarakkal Jain

73. **Azilsartan: Promise and Power for Hypertension in Cardiodiabetes** 481
Lal C Daga, Suman Bhandari

74. **Benidipine for Hypertension in Cardiodiabetes** 485
HK Chopra, Ravi R Kasliwal, Manish Bansal

75. **Azilsartan: A Molecule of First Choice for Hypertension in Cardiodiabetes** 491
HK Chopra, Viveka Kumar, AK Pancholia

76. **Superiority of Telmisartan: ARB, the First Choice in Cardiodiabetes** 499
Kajal Ganguly, Santanu De, Auriom Kar, Biswadev Basu

77. **ARNI in Heart Failure with Cardiodiabetes: The Way Forward** 505
Srikant Sharma, Surabhi Chhabra

78. **Indapamide versus Hydrochlorothiazide versus Chlorthalidone in Cardiodiabetes** 514
Debabrata Roy, Md Saiyed Rana

79. Polypill for Cardiovascular Protection in Diabetes **519**
Jugal Bihari Gupta, Rajeev Gupta

80. Clopidogrel in Patients of Diabetes with Acute Coronary Syndrome **525**
A Gupta, MP Girish, Mohit D Gupta

81. Acute Coronary Syndrome in Cardiodiabetes: Is It Different? **533**
Gaurav Mohan, Ravina Sharma, GS Wander

82. Newer Drugs in Heart Failure and Changes in Our Clinical Approach **538**
Vatchsala Sree Varadharajan

83. Role of Oral Anticoagulants in Atrial Fibrillation with Cardiodiabetes **543**
Chetan P Shah, Priyank Mody

84. Low-molecular-weight Heparin in Acute Coronary Syndrome in Cardiodiabetes **550**
Jabir A, Sajan Ahmad

85. Myocardial Bridging **554**
Pawan K Sharma, HK Chopra

86. Benidipine for Hypertension in STEMI with Cardiodiabetes **563**
Viveka Kumar, Vivek Kumar

87. Thrombolytic Therapy of Choice in STEMI with Cardiodiabetes **566**
KN Srinivasan, I Sathyamurthy

88. Tenecteplase and ST-elevation Myocardial Infarction with Cardiodiabetes **572**
SS Iyengar

89. Cardiodiabetes and Stroke **575**
Neeraj Tyagi

90. Hemorrhagic Stroke and Cardiodiabetes **580**
Sanjeev Kumar

91. Prognostication of STEMI in Cardiodiabetes **592**
Kewal C Goswami, Deepti Siddharthan

92. Management of Hypertension in Diabetes: Special Consideration **596**
Naveen Mittal, Rohin Vinayak, GS Wander

93. Benidipine: A New Calcium Channel Blocker for Management of Hypertension and Angina in Cardiodiabetes **600**
CK Ponde, Maulik Parekh

94. Azilsartan for Hypertension Management in Cardiodiabetes **604**
Harsh Wardhan, Nitin Aggarwal

95. Need for Registry of Cardiodiabetes in India **610**
PP Mohanan

96. Nonpharmacological Management of Cardiodiabetes **614**
Dharmendra Jain, Geetha Subramanian, Aviraj Chaudhary

97. Maternal Diabetes Mellitus and Fetal Cardiac Malformations: Antenatal and Postnatal Management and Outcome 619
Smita Mishra, Neha Gupta

98. Role of Enhanced External Counterpulsation: Future Perspectives 625
Sanjay Mittal, S Ramasamy

SECTION 4 NUTRACEUTICAL AND OBESITY CARE

99. Role of Vitamin D as Cardioprotection Strategy: Hope or Hype? 637
Vinod Sharma, Hakim Irfan Showkat

100. Omega-3 Fatty Acids and Cardiovascular Disease 643
Pawan K Sharma, HK Chopra

101. Role of Red Yeast Rice and Phytosterols in Dyslipidemia 655
Pawan K Sharma, Paul N Hopkins, HK Chopra

102. Meal Replacement Therapy for Obesity Care in Cardiodiabetes 663
Shashank R Joshi

103. Ideal Edible Oil in Cardiodiabetes 667
Shashank R Joshi

104. Cardiodiabetic Diet 674
Rekha Sharma

SECTION 5 ARRHYTHMIA MANAGEMENT

105. Cardiodiabetes and Heart Rate Variability 683
Vidyut Jain, Avani Jain

106. Natural History of Atrial Fibrillation in Cardiodiabetes: Is it Different? 688
Ashokan Nambiar

107. Atrial Fibrillation: Management Strategies in Cardiodiabetics 690
Satya Nand Pathak

108. Ventricular Tachycardia in Heart Failure with Cardiodiabetes 701
Rohit Walia

109. Sudden Cardiac Death in Patients with Diabetes Mellitus: Prevalence, Predictors and Preventive Strategies 707
S Shanmugasundaram

110. Prevention of Sudden Cardiac Death in Cardiodiabetes 712
Rabin Chakraborty, Arindam Pande

111. **Pacing in Cardiodiabetes** 717
Deep Chandh Raja, Ulhas M Pandurangi

112. **Radiofrequency Ablation in Atrial Fibrillation in Cardiodiabetes** 721
Viveka Kumar, Rajendra Kumar Agarwal

113. **LA Appendage Closure for AF in Cardiodiabetes: Is the Outcome Different?** 725
Balbir Singh

114. **AICD after Cardiac Arrest in Cardiodiabetes** 729
Rajeeve Kumar Rajput

SECTION 6 INTERVENTION

115. **Coronary Interventions in Cardiodiabetes Prognostication** 739
Harinder K Bali, Hiteshi KC Chauhan

116. **Primary PCI for STEMI in Cardiodiabetes: What is the Outcome?** 751
Shirish (MS) Hiremath, Gaurav M Ganeshwala

117. **Optimizing Results of Percutaneous Coronary Intervention in Multivessel Disease with Diabetes** 757
Dev Pahlajani

118. **STEMI Management in Diabetes Mellitus: Is it Different?** 762
Santanu Guha, Sumanta Chatterjee

119. **CTO with STEMI in Cardiodiabetes: Is the Outcome Different?** 769
Satyendra Tewari, Ankit Kumar Sahu

120. **Coronary Intervention in Venous Grafts in Diabetes** 774
Aniruddha Pawar, Prafulla Kerkar

121. **Cardiodiabetes and Peripheral Vascular Interventions** 781
NN Khanna, Suparna Rao

122. **Cardiodiabetes and Vasculopathy** 794
Sameer Shrivastava, Biswajit Paul

123. **Cardiodiabetes and Carotid Artery Interventions** 799
Aditya Kapoor, Arpit Agarwal

124. **Coronary Revascularization in Diabetics** 805
Brian Pinto, Neeraj Desai, Kunal Sinkar, Dinesh Parikh

125. **Endovascular Intervention in Stroke in Cardiodiabetes: New Frontiers** 813
Chandril Chugh

SECTION 7 CARDIAC SURGERY

126. Coronary Artery Bypass Grafting in Cardiodiabetes 821
OP Yadava

127. Cardiac Surgery and Diabetes 828
Yugal Mishra, Jatin Yadav

128. ECMO for Cardiodiabetes 835
Poonam Malhotra Kapoor, Shivani Aggarwal

SECTION 8 REHABILITATION

129. Cardiac Rehabilitation in Cardiodiabetes 847
Aashish Contractor, Sagri Negi

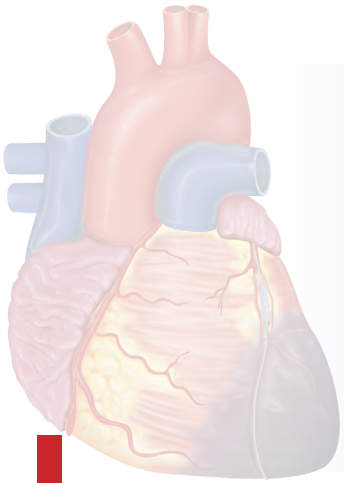
130. Post-STEMI Intervention: Rehabilitation in Cardiodiabetes 853
JPS Sawhney, Kushal Madan, Simran Sawhney

131. Role of Nurses in a Structured Manner for Cardiac Rehabilitation in Cardiodiabetes 857
Harvinder Kaur

SECTION 9 FUTURE DIRECTIONS

132. Type 2 Diabetes and Coronary Artery Bypass Grafting: Relation and Outcomes 865
Naresh Trehan, Jasjeet S Wasir, Tarannum Bano, Paras Aggarwal

Index *873*



CHAPTER 2

Risk Factors for Cardiodiabetes

Sanjiv Sharma, Varsha Koul, Varun Gupta

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INTRODUCTION

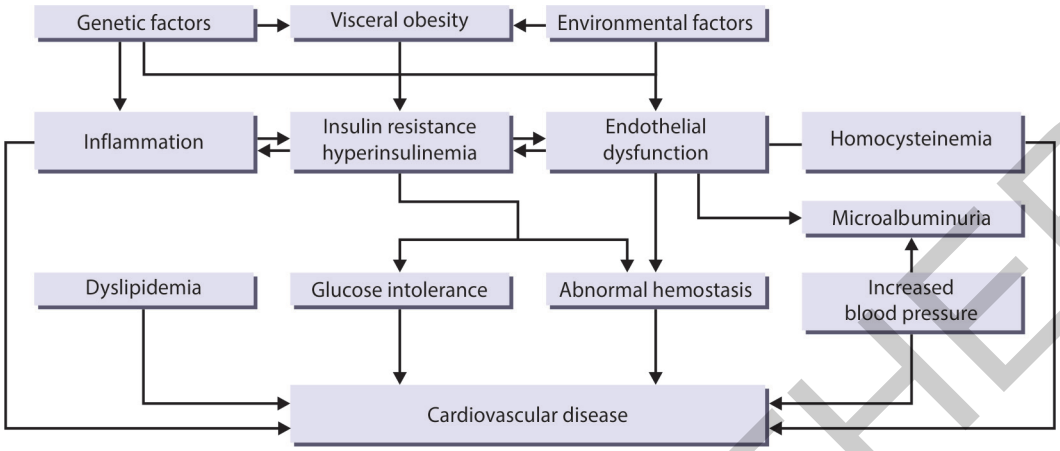
Diabetes is a known independent risk factor for cardiovascular disease. Since diabetes and serious cardiovascular disease (CVD) are frequently observed together, researchers are increasingly using the term "cardiodiabetes" to describe the co-occurrence of diabetes and significant CVD.[1] People with cardiodiabetes have both diabetes and CVD, which may be subclinical and undiagnosed, but it is still present. In 2015, an estimated 415 million people had diabetes and this number is predicted to increase to 642 million by 2040, with type 2 diabetes mellitus (T2DM) accounting for the vast majority of cases.[2,3] India leads the world with 40.9 million people with diabetes in 2007. Moreover, it is projected that, by the year 2025, 80.9 million will have diabetes in India.[4,5] People with T2DM have a higher cardiovascular morbidity and mortality compared to nondiabetic subjects. The accelerated rate of atherosclerosis seen in diabetes mellitus leads to higher rates of coronary artery disease (CAD), stroke, peripheral vascular disease, and cardiovascular death.[6,7] The outcomes in patients with both diabetes and CVD are worse than those of other patients. Diabetic vascular disease is responsible for two- to fourfold rise in the occurrence of CAD and stroke, and two- to eightfold increase in the risk of heart failure.[8,9] Patients with T2DM and no previous history of CAD have similar risk for cardiac events as subjects with a prior myocardial infarction (MI).[10] Hence, diabetes is increasingly being considered as a coronary heart disease risk equivalent.[11,12] CVD is increased in T2DM subjects due to a complex combination of various traditional and nontraditional risk factors that have an important role to play in the beginning and the evolution of atherosclerosis over its long natural history from endothelial dysfunction to clinical events (Flow chart 1).[8]

The traditional risk factors include dyslipidemia, hypertension, obesity and abdominal obesity, physical exercise, and cigarette smoking, whereas the nontraditional risk factors include insulin resistance (IR) and hyperinsulinemia, postprandial hyperglycemia, microalbuminuria (MA), hematological and thrombogenic factors, inflammatory cascade, atherosclerosis and endothelial dysfunction, hyperhomocysteinemia (HHC) and vitamin D deficiency, erectile dysfunction (ED), genetics and epigenetics, and cardiovascular autonomic neuropathy (CAN).[8]

DYSLIPIDEMIA

Diabetic patients are at increased risk of developing dyslipidemia.[13,14] There is increased release of free-fatty acids (FFA) present in insulin-resistant fat cells, which promote triglyceride (TG) production, which in turn stimulates the secretion of apolipoprotein B (ApoB) and very low-density lipoproteins (VLDL) cholesterol. High levels of ApoB and VLDL have both been linked to increased risk of CVD.[15-18] Hyperglycemia is associated with low levels of high-density lipoprotein (HDL).[19] Hyperglycemia may also negatively impact lipoproteins through increased glycosylation and oxidation, decreasing vascular compliance and facilitating the development of aggressive atherosclerosis.[20]

Flow chart 1: Interactions of traditional and nontraditional risk factors in diabetes mellitus



HYPERTENSION

Hypertension among diabetic patients is closely tied to the development of diabetic nephropathy (DN).[13,18,21] In DN, renal cells are stimulated by hyperglycemia, leading to the production of humoral mediators, cytokines, and growth factors. The production of these factors is responsible for structural alterations seen in the glomeruli of diabetic patients including hyaline arteriolosclerosis—primarily of the efferent arteriole, increased collagen deposition in the extracellular matrix, and increased permeability of the glomerular basement membrane.[22] These structural changes increase filtration pressure and lead to MA with a compensatory activation of the renin-angiotensin system (RAAS). If left untreated, DN can progress to a frank nephrotic syndrome, characterized by proteinuria, a hypercoagulable state (due to loss of antithrombin III) and hyperlipidemia.[23,24]

OBESITY AND ABDOMINAL OBESITY

Cardiodiabesity is a hybrid term used to define and describe the relationship between T2DM, obesity, metabolic syndrome, and CVD.[25] Generalized obesity assessed by the body mass index (BMI), and abdominal obesity determined by the waist circumference (WC), are related to a variety of CVD risk factors.[8,26,27] The impact of obesity on both atherogenesis and procoagulant and prothrombotic cardiovascular risk factors is of particular interest in diabetics, as they contribute to increased CVD mortality.[28-32] One possible mechanism linking DM and obesity with subsequent CVD is low-grade inflammation.[33] DM and IR are associated with overexpression of many cytokines by adipose tissue, which contributes to increased inflammation and lipid accumulation, causing endothelial dysfunction, MI, and cardiomyopathy.[11,34] Diabetic patients also have increased C-reactive protein (CRP) and decreased adiponectin levels, which also contribute to endothelial dysfunction.

PHYSICAL EXERCISE

Regular physical exercise correlates with a lower risk of cardiovascular morbidity and mortality, both in primary and secondary prevention. Exercise improves insulin sensitivity in diabetic patients.[35-37] Patients with diabetes have greater IR, which can be mediated by different defects in glucose metabolism, which include decreased number of insulin receptors and glucose transporters, reduction in the intracellular enzyme activity, and reduced oxygenation during exercise; some of which would improve with physical exercise. Aerobic exercises only or combined with resistance exercise improve glycemic control, blood pressure, and TG levels. But resistance exercise alone does not have a clear impact on cardiovascular risk factors.

CIGARETTE SMOKING

Smoking is linked with deterioration in metabolic control in diabetic patients, which is associated with an increased risk for development of macrovascular and microvascular complications and mortality in DM.[38,39] Administration of nicotine raises the circulating levels of insulin antagonistic hormones (growth hormone, catecholamines, and cortisol),[40-42] and affects the autonomic nervous system (ANS)[43] and decreases insulin sensitivity. Also, smoking increases circulating FFA levels,[41] which decrease insulin-mediated glucose uptake.[44] Smoking is an independent and significant risk factor for stroke[45] and peripheral vascular disease.[46]

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INSULIN RESISTANCE AND HYPERINSULINEMIA

Insulin resistance is a principal characteristic of T2DM and it develops in multiple organs including skeletal muscles, liver, adipose tissue, and heart. IR is also associated with an elevation of plasma FFA's, leading to increase in muscle TG stores, hepatic glucose production, and hyperinsulinemia in patients with T2DM.[47] Although molecular mechanisms of IR are not yet entirely understood, abnormalities in insulin signaling have been postulated. Hyperinsulinemia can lead to a disproportionate proliferative signal, while the normal transport of glucose and glucose homeostasis are conserved. This stimulates an increased production of endothelin, plasminogen activator inhibitor-1 (PAI-1), proinflammatory cytokines, and augmented surface expression of adhesion molecules in vascular smooth muscle and endothelial cells.[48] There is endothelial dysfunction with a rise in the interaction between endothelial cells and leukocytes, increase in vascular tone and blood pressure and a prothrombotic state.[49] IR has also been linked to cardiomyopathy in diabetics via cardiomyocyte hypertrophy and contractile dysfunction.[47,50]

POSTPRANDIAL HYPERGLYCEMIA AND GLUCOSE VARIABILITY

Postprandial hyperglycemia leads to an augmented risk of cardiovascular events.[51,52] Postprandial glucose excursions, especially when accompanied by increased TG levels, are pathophysiologically related to systemic inflammation and endothelial dysfunction, which are associated with increase in atherosclerosis and cardiovascular events.[53]

Microalbuminuria

Microalbuminuria identifies people at increased risk of early cardiovascular death and progressive renal disease. MA is an early indicator of vascular damage to the glomerulus. MA is considered to be a renal symptom of generalized endothelial dysfunction.[54] MA also indicates ongoing low-level inflammatory process. Increasing MA is related to augmented levels of inflammatory markers, endothelial dysfunction, and platelet activation.[55] D-dimer is associated with MA in T2DM patients, which suggests that glomerular dysfunction is in part mediated by hypercoagulability.[56] MA is also independently linked with arterial stiffness and vascular inflammation in diabetic individuals. Also, patients with MA have more severe angiographically detected CAD than those without MA.[57]

HEMATOLOGICAL AND THROMBOGENIC FACTORS

Atherothrombosis is defined as the formation of thrombus on a pre-existing atherosclerotic plaque. Its major manifestations are sudden cardiac death, MI, stroke, and peripheral arterial ischemia. Diabetes is related to a hypercoagulable state, which is more pronounced during the postprandial period. Hyperactivated platelets at injured endothelial interfaces act together with an increased availability of thrombotic precursors, decreased coagulation inhibitors, and diminished fibrinolysis.[58] Atherosclerosis develops more quickly and aggressively in diabetes, and leads more frequently to thrombotic events due to the interaction between the vascular wall and hypercoagulability. The increased platelet activity signifies increased adhesion and aggregation in diabetic patients, in vascular smooth muscle and endothelial cells. There may also be a reduction in the tissue plasminogen activator levels, and increase in the PAI-1 and plasma fibrinogen levels, which have been implicated with an increase in cardiovascular morbidity and mortality.[59,60]

INFLAMMATORY CASCADE, ATHEROSCLEROSIS, ENDOTHELIAL DYSFUNCTION

Low-grade inflammation would be the causal common factor between diabetes, IR, obesity, and CVD. Accelerated atherosclerosis in diabetes may be explained by hyperglycemia, increased oxidative stress, advanced glycation end products (AGEs), dyslipidemia, autonomic imbalance, hyperinsulinemia, inflammatory markers excess, and genetic variables.[61,62] Endothelial vasodilation and vascular reactivity are impaired in diabetes,[63] which is associated with reduced action of nitric oxide (NO). Diabetes, obesity, and IR are associated with overexpression of cytokines produced by adipose tissue, activated macrophages, and other cells such as tumor necrosis factor-α, interleukin-1 (IL-1), IL-6, leptin, monocyte chemoattractant protein-1, PAI-1, CRP, fibrinogen, angiotensin, retinol-binding protein-4, and adiponectin.[64] These cytokines are involved in chronic inflammatory process in vessel walls promoting lipid accumulation leading to atherosclerosis and CVD.[65] Adipose tissue initiates obesity-induced inflammation leading to the recruitment of immune cells, which contributes to the maintenance of inflammatory response,[64] leading to endothelial dysfunction with increased expression of adhesion molecules, migration of monocytes,

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neutrophils, and T lymphocytes. IL-1 modulates vessel wall inflammation, leukocyte chemotaxis and adhesion, angiogenesis, upregulation of matrix metalloproteinases, and destabilization of atheromatous plaques that can lead to plaque rupture and thrombosis.[65] CRP is an acute-phase protein produced in the liver whose release is stimulated by IL-6 and TNF-α. Increased levels of CRP are related with the presence and severity of CAD.[66] CRP causes impaired endothelial production of NO and prostacyclin, increased production of endothelin-1 and other cell adhesion molecules, promotion of cell proliferation in vascular smooth muscle cells (VSMC) due to upregulation of the angiotensin type 1 receptor. CRP also increases the uptake of oxidized low-density lipoprotein (LDL) in coronary vasculature walls, contributing to endothelial dysfunction and development of atherosclerotic plaques.[8]

Adiponectin has many protective actions on the atherosclerotic process due to inhibition of LDL oxidation, reduction of adhesion molecules, inhibition of proliferation and migration of VSMC, and increased production of NO in endothelial cells. Hypoadiponectinemia is associated with an increase in CVD rates.[67] Leptin is secreted by adipose tissue and involved in the regulation of energy expenditure and food intake. It induces oxidative stress; cardiomyocyte hypertrophy; promoting migration, proliferation, hypertrophy of VSMC, and vascular cell wall calcification; stimulating platelet aggregation; attenuating cardiomyocyte contractility reduction of intracellular calcium, and decreased β-adrenergic response.[11,68]

HOMOCYSTEINE AND VITAMIN D

In T2DM subjects, elevated homocysteine (HC) levels have been associated with a rise in the CVD risk independent of other risk factors.[69] HC could play an etiologic role in the pathogenesis of T2DM, systemic inflammation, and endothelial dysfunction. HHC is considered as a risk factor for the development of peripheral arterial disease in T2DM individuals over 65 years of age.[70] Studies have shown that lower levels of vitamin D are related with a high incidence of cardiovascular events and mortality.[71] Vitamin D might protect against CVD, as the vitamin D receptor is also expressed in the vasculature. Increased production of NO, the inhibition of macrophage to foam-cell formation, or decreased expression of adhesion molecules in endothelial cells, might mediate the vascular-protective actions of vitamin D.[72]

CARDIOVASCULAR AUTONOMIC NEUROPATHY

Cardiovascular autonomic neuropathy is common among patients with diabetes and is correlated with increased mortality from CVD. The clinical manifestations of CAN are resting tachycardia, postural hypotension, exercise intolerance, abnormal coronary vasomotor regulation, increased QT interval, and perioperative instability. These are related to increased risk of renal disease, stroke, CVD, and sudden death.[73] The development and progression of CAN are likely related to dysregulation of the ANS with increased sympathetic activity and elevated inflammatory markers. ANS dysfunction can lead to arterial stiffness, left ventricular hypertrophy, and ventricular diastolic dysfunction.[13]

ERECTILE DYSFUNCTION

Men with DM have a higher prevalence of ED compared to the general population. ED might serve as a clinical marker for coronary, peripheral, or cerebrovascular diseases in these people. Several studies have found a positive correlation between ED and the risk of CVD.[8,74]

GENETICS AND EPIGENETICS

Epigenetic reactions could be an important mediator between diabetes, CVD, and chronic inflammatory response. Epigenetic factors could mediate the interplay between genes and environment resulting in activation or repression of genetic transcription. The most important epigenetic reactions affecting genetic transcription are acetylation and methylation, occurring mainly in the tail of histones.[11] Some comorbidities associated with diabetes have also been associated with epigenetics like hypertension and obesity.[75,76]

CONCLUSION

The term cardiodiabetes acknowledges the inter-relationship between diabetes and CVD, and creates a meaningful label for both physicians and patients. It also denotes a need to consider beyond traditional cardiovascular risk factors, glycemic control, and weight management.

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Contents

Section 1: Clinical Spectrum

Section 2: Diagnosis

Section 3: Management Strategies

Section 4: Nutraceutical and Obesity Care

Section 5: Arrhythmia Management

Section 6: Intervention

Section 7: Cardiac Surgery

Section 8: Rehabilitation

Section 9: Future Directions

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