Diabetes and heart disease

Edited by

R. J. JARRETT

Diabetes and heart disease

Edited by

R. J. JARRETT

Department of Community Medicine,
Guy's Hospital Medical School,
London, SE1 9RT, U.K.

1984
Elsevier
AMSTERDAM · NEW YORK · OXFORD

Published by:

ELSEVIER SCIENCE PUBLISHERS B.V.
P.O. BOX 211, 1000 AE AMSTERDAM
THE NETHERLANDS

Sole distributors for the U.S.A. and Canada:
ELSEVIER SCIENCE PUBLISHING COMPANY, INC.
52 VANDERBILT AVENUE
NEW YORK, N.Y. 117

ISBN-series: 0-444-80349-1
-volume: 0-444-80536-2

Library of Congress Cataloging in Publication Data
Main entry under title:

Diabetes and heart disease.

(Metabolic aspects of cardiovascular disease; v. 2)
Bibliography: p.
Includes index.
1. Coronary heart disease—Etiology. 2. Diabetes—Complications and sequelae. I. Jarrett, R. J. (Richard John) II. Series. [DNLM: 1. Diabetes mellitus—Complications. 2. Heart diseases—Complications. ME 961KN v. 2/WK 835 D5335]
RC685.C6D5 1984 616.1'2 84-4104
ISBN 0-444-80536-2 (U.S.)

Printed in the Netherlands

List of contributors

D.J. Ewing, M.D., M.R.C.P.
Wellcome Trust Senior Lecturer in Medicine, Department of Medicine, Royal Infirmary, Edinburgh EH3 9YW (U.K.)

O. Gøtzsche, M.D.
Research Fellow, University Institute of Pathology, University of Aarhus, Kommunehospitalet, 8000 – Aarhus C. (Denmark)

M. Greaves, M.D., M.R.C.P., M.R.C. Path.
Senior Lecturer in Haematology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF (U.K.)

L. Heickendorff, M.D.
Research Fellow, University Institute of Pathology, University of Aarhus, Kommunehospitalet, 8000 – Aarhus C. (Denmark)

R. J. Jarrett, M.D.
Professor of Clinical Epidemiology, Guy's Hospital Medical School, and Honorary Consultant, Guy's Hospital, London SE1 9RT (U.K.)

T. Ledet, M.D.
Senior Lecturer, University Institute of Pathology, University of Aarhus, Kommunehospitalet, 8000 – Aarhus C. (Denmark)

E.A. Nikkilä, M.D.
Professor, Third Department of Medicine, University of Helsinki, 00290 Helsinki 29 (Finland)

F.E. Preston, M.D., F.R.C. Path.
Reader in Haematology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF (U.K.)

L.M. Shapiro, B.Sc., M.D., M.R.C.P.
Cardiac Department, Dudley Road Hospital, Birmingham B18 7QH (U.K.)

Introduction

Although coronary heart disease was an uncommon cause of death in the pre-insulin era, commentators began in the late 19th century to suggest an association between CHD and diabetes. Vergely was sufficiently impressed with the frequency of angina pectoris in patients with diabetes that he recommended tests for glycosuria in all patients with angina. Brunton the discoverer of the beneficial effects of nitrites, in 1907 remarked upon the presence of coronary atherosclerosis in diabetics. Since that time, and particularly since insulin dramatically reduced the mortality rate from ketoacidosis, there have been countless publications concerned with the heart in diabetes. Despite all this industry we remain in ignorance of the reasons why diabetics are more likely to develop severe coronary atherosclerosis; we are also uncertain whether the latter is solely responsible for the excess cardiac morbidity and mortality. In the earlier literature, observations by clinicians and morbid pathologists predominated. More recently, as in atherosclerosis research generally, many disciplines have contributed information and speculation. Thus, in this volume, several disciplines are represented in an attempt to provide an up-to-date and critical review of disorders of the heart in diabetics together with some speculation where appropriate. In addition we have attempted to distinguish between the two major types of diabetes, although all too often investigators fail to characterise their subjects adequately in this and other respects. I hope that as well as providing information we will stimulate at least some readers to look for answers to the many questions remaining.

R.J.J.

References

Vergely, P. (1883) De l'angine de poitrine dans ses rapports avec le diabète. Gaz. hebd. de méd. Paris (Series 2), 20: 364–368.

Brunton, L. (1907) On the heart in relation to diabetes, Practitioner, 79: 42–46.

List of abbreviations

ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
CHD	Coronary heart disease
FFA	Free fatty acids
HDL	High density lipoproteins
IDD	Insulin-dependent diabetic(s)
IDDM	Insulin-dependent diabetes mellitus
IGT	Impaired glucose tolerance
LDL	Low density lipoproteins
LVET	Left ventricular ejection time
NIDD	Non-insulin-dependent diabetic(s)
NIDDM	Non-insulin-dependent diabetes mellitus
PAEF	Platelet aggregation enhancing factor
PAS	Periodic acid-Schiff reagent
PEP	Pre-ejection period
PHLA	Post-heparin lipolytic activity
VLDL	Very low density lipoproteins

Contents

List of contributors v

Introduction vii

Abbreviations ix

1. *The epidemiology of coronary heart disease and related factors in the context of diabetes mellitus and impaired glucose tolerance*
by R. J. Jarrett (London, U.K.) 1

1. Coronary atherosclerosis 1
2. CHD mortality 4
2.1. Sex differences in CHD mortality 7
3. CHD morbidity 8
4. Blood glucose as a risk factor 9
5. Risk factors for CHD in diabetes and impaired glucose tolerance 10
5.1. Diabetes 10
5.2. Glucose intolerance 11
6. Blood pressure, blood glucose and diabetes 13
6.1. Blood glucose and blood pressure relationships 17
7. Conclusions 17
8. References 20

2. *The pathology of diabetic cardiopathy: pathogenetic reflections*
by T. Ledet, O. Gøtzsche and L. Heickendorff (Aarhus, Denmark) 25

1. Introduction 25
2. Macroangiopathy – microangiopathy – myocardiopathy 25
3. The myocardium 27
4. The small vessels 30

5. The extramural coronary arteries 33
6. In vivo studies 35
7. In vitro studies 37
8. Concluding remarks 40
9. References 42

3. *Haemostatic abnormalities in diabetics*
by M. Greaves and F. E. Preston (Sheffield, U.K.) 47

1. Current concepts relating to haemostatic mechanisms 47
1.1. Platelet vessel wall interactions 48
1.1.1. Platelet and endothelial cell prostaglandin production 48
1.2. The coagulation system 49
1.2.1. The extrinsic coagulation system 49
1.2.2. The intrinsic coagulation system 49
1.3. Coagulation inhibitors 50
1.4. The fibrinolytic system 51
1.4.1. Plasminogen activators 51
1.5. Rheological considerations 52
2. Platelets in diabetes mellitus 52
2.1. Blood platelets and the pathogenesis of atheromatous arterial disease 52
2.2. Platelet aggregation in vitro 54
2.2.1. Diabetic retinopathy 54
2.2.2. Diabetic neuropathy 55
2.2.3. Other vascular complications 55
2.3. Platelet reactivity in vivo 55
2.3.1. Platelet survival 55
2.3.2. Increased platelet reactivity in diabetes mellitus 56
2.4. The mechanisms underlying altered platelet reactivity 58
2.4.1. Platelet aggregation enhancing factor 58
2.4.2. Altered prostaglandin metabolism 59
2.4.3. Other observations 61
2.5. Platelet adhesion 62
2.6. Platelet abnormalities and diabetic vascular disease: cause or effect? 63
2.6.1. The relationship between platelet abnormalities and glycaemic control 64
2.7. Platelets and diabetes: concluding remarks 64
3. Blood coagulation in diabetes mellitus 65
3.1. Coagulation factor abnormalities in diabetes 65
3.1.1. Altered fibrinogen kinetics in diabetes mellitus 66
3.1.2. The factor VIII complex in diabetes 67
3.1.3. Other coagulation factors in diabetes 68
3.2. Coagulation inhibitors in diabetes 69

3.3. Disturbances in the fibrinolytic mechanism in diabetes mellitus 70
3.4. Summary 71
4. Rheological changes in diabetes mellitus 71
5. Concluding remarks 73
6. References 73

4. *Functional aspects of diabetic heart disease*
by L. M. Shapiro (London, U.K.) 81

1. Introduction 81
2. Pathological evidence for functional heart disease 82
3. Methods for studying cardiac structure and function 82
3.1. Invasive techniques 82
3.2. Non-invasive techniques 83
3.2.1. Systolic time intervals 83
3.2.2. Echocardiography 84
3.2.3. Electrocardiography 86
4. Functional cardiac disorders in diabetes mellitus 86
4.1. Invasive investigations 87
4.2. Non-invasive investigations 88
5. Pathogenesis of impaired left ventricular function 93
6. Prevention and management 94
7. Synthesis 95
8. References 95

5. *Cardiac autonomic neuropathy*
by D. J. Ewing (Edinburgh, U.K.) 99

1. Introduction 99
2. Diagnosis 100
2.1. Valsalva manoeuvre 100
2.2. Heart rate (R-R interval) variation 101
2.3. Heart rate response to standing 102
2.4. Blood pressure response to standing 104
2.5. Blood pressure response to sustained handgrip 105
2.6. Practical aspects of cardiovascular reflex testing 106
3. Abnormalities of cardiac autonomic function in diabetes 106
3.1. Prevalence of abnormal cardiovascular reflex tests 106
3.2. Patterns of abnormality 110
3.3. Abnormalities of heart rate control 111
3.3.1. Heart rate 111
3.3.2. Influence of drugs on heart rate 115
3.3.3. Valsalva manoeuvre 115

3.3.4. Heart rate (R-R interval) variation 116
3.3.5. Standing 118
3.3.6. Lying down 118
3.3.7. Baroreflex sensitivity, lower body negative pressure and facial immersion 118
3.3.8. Bicycle exercise 119
3.3.9. Tilt 119
3.3.10 Sustained handgrip 119
3.4. Abnormalities of blood pressure control 119
3.4.1. Postural hypotension 119
3.4.2. Sustained handgrip 121
3.4.3. Bicycle excercise 121
3.4.4. Tilt 121
3.4.5. Lower body negative pressure 122
3.4.6. Nitroglycerin and insulin 122
4. Natural history of autonomic neuropathy 122
4.1. Test abnormalities 122
4.2. Mortality 123
5. Relation to other aspects of diabetes 124
5.1. Type of diabetes 124
5.2. Metabolic control 124
5.3. Duration of diabetes 124
5.4. Retinopathy 125
5.5. Nephropathy 125
5.6. Peripheral somatic neuropathy 125
5.7. Painless myocardial infarction 125
6. Conclusions 126
7. References 127

6. *Plasma lipid and lipoprotein abnormalities in diabetes* by E. A. Nikkilä (Helsinki, Finland) 133

1. Introduction 133
2. Triglycerides and very-low-density lipoproteins (VLDL) 134
2.1. Insulin-dependent (type 1) diabetes mellitus (IDDM) 134
2.1.1. Concentration 134
2.1.2. General aspects of triglyceride and VLDL metabolism 136
2.1.3. Triglyceride and VLDL metabolism in insulin deficiency 137
2.2. Non-insulin-dependent (type 2) diabetes mellitus (NIDDM) 140
2.2.1. Concentrations of serum triglyceride and VLDL 141
2.2.2. Mechanism of hypertriglyceridemia in type 2 diabetes: overproduction or impaired removal? 142
2.2.3. Effect of treatment on triglycerides and VLDL 144

3. Cholesterol and low-density lipoproteins (LDL) 145
3.1. LDL concentration and metabolism 145
3.2. Structural changes of LDL 146
4. High-density lipoproteins (HDL) 148
4.1. HDL in insulin-dependent diabetes 149
4.2. HDL in non-insulin-dependent diabetes 152
4.3. Effect of anti-diabetic treatment on HDL 154
5. Impact of lipoprotein abnormalities on excess atherosclerosis in diabetes 154
6. Summary 156
7. References 157

Subject index 169

Jarrett (ed) Diabetes and heart disease

CHAPTER 1

The epidemiology of coronary heart disease and related factors in the context of diabetes mellitus and impaired glucose tolerance

R.J. JARRETT

Guy's Hospital Medical School, London SE1 9RT, U.K.

1. Coronary atherosclerosis

In the quarter century following the introduction of insulin, there were numerous comparisons – though chiefly from the United States – of the post-mortem appearance of the coronary arteries in diabetics and non-diabetics. The general observation was of more widespread and more severe coronary atherosclerosis in the diabetics. The descriptions were, however, qualitative and said little or nothing about the possible effects of age at onset, type of diabetes or duration of diabetes. Some of these factors have only recently been investigated, either by post-mortem examination or by angiographic techniques during life.

Waller et al. [1] systematically re-examined the hearts of 229 diabetics, whose age at onset was greater than 30 years of age, who had undergone autopsy at the Mayo Clinic between 1945 and 1975. Matched control patients were selected from patients with fatal coronary heart disease from the same population. The authors attempted to answer three questions.

(1) Do necropsy patients with diabetes + clinical CHD have more, less or similar amounts of narrowing by atherosclerotic plaques than patients with CHD but no diabetes?

(2) Do necropsy patients with diabetes and clinical CHD have more, less or similar amounts of coronary narrowing by atherosclerotic plaques than patients with diabetes but no clinical CHD?

(3) Among patients with onset of diabetes after 30 years of age, does the age at onset or the duration of diabetes correlate with the amount of coronary narrowing by atherosclerosis?

There were similar degrees of severe narrowing (>75%) by atherosclerotic plaques in the right, left anterior descending and left circumflex coronary arteries in

each of the three groups of patients. The diabetics, however, had a significantly higher frequency of narrowing of the left main coronary artery, and within the diabetic group, a higher frequency was found in those with a clinical history of CHD. When duration groups were constructed: 1–5, 6–10, 11–25 and 26–40 years, no significant differences were observed for either degree of severe narrowing in the three major coronary arteries or the frequency of severe narrowing of the left main coronary artery. There were also no significant differences related to treatment of the diabetes.

An additional point of interest was a significantly different frequency in types of cardiac death between diabetics and controls (see Table 1.1). These findings are in accord with several other reports.

TABLE 1.1

Fatal cardiac events in diabetics and non-diabetics with clinically evident CHD prior to death

Cause of death	Diabetics (%)	Non-diabetics (%)
Acute myocardial infarct	55	43
Sudden death	31	57
Congestive heart failure	14	0

Abstracted from Waller et al. [1].

Vigorita et al. [2] performed a similar study, but used the technique of post-mortem coronary angiography. Both the diabetics and age- and sex-matched controls had undergone autopsy at the Johns Hopkins Hospital, Baltimore, between 1968 and 1978. Twenty-two percent of all patients autopsied were studied, selection being predominantly 'the expectation of cardiac disease', and it can only be assumed that selection was identical for diabetics and non-diabetics. All abnormalities were graded in relation to severity. Compared with controls, the diabetics showed a significantly higher rate of coronary atherosclerosis and of infarcts. Within the diabetic group, there were no significant differences according to treatment (nil, diet, oral agents, insulin), nor was there a significant association with the duration of diabetes, even by univariate analysis.

In addition to these hospital based studies, there are two population based pathological studies. In the International Atherosclerosis Project [3], several diverse population groups were surveyed and standardised observations made upon the aorta and coronary arteries. According to the authors: "with but few exceptions, mean extent of raised lesions ranks the geographic and ethnic groups in the order that would have been predicted from general knowledge of their relative economic status, standard of living, mortality from CHD, or other epidemiological variables

which have long been known to be associated with atherosclerosis and its sequelae". The severity of coronary atherosclerosis in the diabetics varied in parallel with the general severity in the population from which they were sampled, but the effect of diabetes was "superimposed on any level of average severity of atherosclerosis". The authors did not examine possible effects of the type of diabetes or of diabetes duration. In the Five Towns Study [4], standardised comparisons were made on post-mortem material from Prague, Malmö, Tallin, Yalta and Ryazan. The effect of diabetes was much greater in the coronary arteries than in the aorta. Even in non-hypertensive diabetics, both raised and calcified lesions in the coronary arteries were more extensive than in the controls. Indeed, the severity of coronary atherosclerosis in non-hypertensive diabetes was similar to that in hypertensive non-diabetics. The effect of duration was studied by comparing subjects who had been suffering from diabetes for less than and more than 10 years. Coronary atherosclerosis was more frequent in the latter group, but it appears that the comparison was not controlled for age at death or presence of hypertension.

Dortimer et al. [5] compared the extent of coronary artery disease determined by coronary angiography in 37 living diabetics and 79 matched controls. Of the diabetics, only seven were insulin-treated. The controls were matched for age, sex and high or low risk factor status. In both groups the indication for angiography was chest pain; the severity of disease was assessed blind using a grading system. Of the diabetics, 43% had three vessel disease compared with 25% of controls, a difference which escaped conventional statistical significance in these numbers ($0.1 > P > 0.05$). However, 68% of all vessels visualised in the diabetics were diseased compared with 46% in controls ($P < 0.005$). In addition, grade 3 or greater stenoses were significantly more frequent in the diabetics.

Vigorito et al. [6] performed a similar study in 34 diabetics and 120 controls with CHD. In this study the controls were not individually matched, though on average they were similar in many respects to the diabetics. The major difference between the two groups was the significantly higher frequency of multiple vessel disease in the diabetics. By contrast, Verska and Walker [7] found no difference in severity of CHD as assessed by coronary angiography between 35 diabetic and 77 non-diabetic patients. These patients had, however, all been pre-selected as suitable for coronary by-pass surgery, and so subjects with more extensive disease would have been excluded.

Weitzman et al. [8] noted a substantially increased mortality rate, in diabetics and non-diabetics alike, following a first myocardial infarct when the site of the infarct was anterior. There was some support in this study for a greater frequency of anterior infarcts in diabetics, this contributing to the overall increase in mortality.

To summarise the above studies, it appears that at least in countries where atherosclerosis is common in the general population, in diabetics coronary atherosclerosis is both more extensive and more severe than in appropriately matched controls. There is insufficient evidence to distinguish between NIDD and IDD in this respect. Curiously, at least in older (mainly NIDD) diabetics, there is no good evidence of a positive association between duration and degree of coronary atherosclerosis.

2. CHD mortality

A series of papers from the Joslin Clinic [9–11] has documented the changing pattern of diabetic mortality since the introduction of insulin. The striking feature has been the rise in the proportion of deaths due to cardiovascular-renal disease, in part due to improved survival rates in IDD and in part to the increasing number and proportion of NIDD. The pattern of mortality also differs between these two diagnostic groups, with young-onset IDD having a high risk of renal failure death (or transplantation/dialysis today) and NIDD having a high risk of cardiac death. This is illustrated in Table 1.2, using Joslin Clinic data. The proportion of renal deaths is much higher in patients in whom the age at onset is under 20 years of age. Above 40 years the proportion of renal deaths is less than 3%, irrespective of duration. The proportion of cardiac deaths is similar when age at onset is above 40 years or above 20 years with a duration exceeding 10 years. When age at onset is more than 40 years there is no consistent trend with duration of diabetes.

Also, using Joslin Clinic data, Kessler [11] compared mortality rates in clinic diabetes with those in the general population of Massachusetts. As others have noted [12,13], a relatively higher excess in all-causes mortality rates occurred in the 30–40 year age group. A significant excess in CHD mortality rates occurred in nearly all age and sex groups above the age of 35 years. Mortality from cardiac disease other than CHD was under-represented in the diabetics.

These Joslin Clinic data refer to the situation immediately before and after as well as during World War II. As we shall see, however, the broad picture has not changed subsequently in Western societies.

One of the early and still relatively few studies of morbidity and mortality of diabetics within a defined population was that carried out in Framingham, Massachusetts. It should be kept in mind, however, that the conclusions of this study in relation to diabetes rest upon observations on only 118 men and 121 women [14]. When these groups are sub-divided in various ways, the sub-group size becomes rather small. The mortality and morbidity data from the Framingham Study relate to subjects judged to be free of cardiovascular and rheumatic heart disease on entry into the study. CHD mortality was similarly increased over that in the general population in both male and female diabetics. The latter had a greater excess of cardiovascular mortality, wholly attributable to deaths due to congestive heart failure in insulin-treated women [15]. In fact, 21 deaths were attributed to cardiovascular disease in the diabetic women, and 16 of these occurred in insulin-treated patients. This observation appears to be unique to Framingham. The effects of diabetes duration upon CHD mortality have not been reported from Framingham.

In the Whitehall Survey of male Civil Servants aged 40–64 years, a number of previously known diabetics participated (IDD and NIDD). The age-corrected 10-year mortality rates in these men, both from all-causes and CHD, were approximately double those of the non-diabetics (Table 1.3). In the NIDD, there was no significant relationship between duration and mortality (Table 1.4). Numbers of IDD were too few to analyse seperately.

TABLE 1.2

Renal and cardiac deaths as a proportion of all deaths by age at onset and duration of diabetes: Joslin Clinic, 1956–62

	Age at onset														
	<20 years				20–39 years				40–59 years				60+ years		
Duration of diabetes (years)	<10	10–19	20–29	30+	<10	10–19	20–29	30+	<10	10–19	20–29	30+	<10	10–19	20–29
Cardiac deaths (%)	–	11	21	36	31	44	57	59	50	57	56	47	52	51	48
Renal deaths (%)	6	53	46	23	3	16	8	5	2	3	2	–	1	1	1

Abstracted from Entmacher et al. [9].