DIABETES

A Clinical Guide

by

JEANNE R. BONAR, M.D.

DIABETES

A Clinical Guide

by

JEANNE R. BONAR, M.D.

Assistant Professor, Endocrinology

Department of Medicine

University of Mississippi

School of Medicine

Jackson, Mississippi

TOPPAN COMPANY (S) Pte. Ltd.

NO.38, LIU FANG ROAD, BOX 22 JURONG TOWN POST OFFICE,

JURONG, SINGAPORE 22

1977

Library of Congress Card Number
76-20078

ISBN 0-87488-710-0

January, 1977

Printed in the United States of America

DIABETES
A CLINICAL GUIDE

CONTENTS

CONTENTS (Continued)

DIABETES

A Clinical Guide

by

JEANNE R. BONAR, M.D.

Assistant Professor, Endocrinology

Department of Medicine

University of Mississippi

School of Medicine

Jackson, Mississippi

TOPPAN PUBLISHING

TOPPAN COMPANY (S) Pte. Ltd.

NO.38, LIU FANG ROAD, BOX 22 JURONG TOWN POST OFFICE,

JURONG, SINGAPORE 22

1977

Library of Congress Card Number
76-20078

ISBN 0-87488-710-0

January, 1977

Printed in the United States of America

PREFACE

During the past decade, there has been an intensified interest in diabetes accompanied by broadening the knowledge in this field. Although we have passed the fiftieth anniversary of the "discovery" of insulin, there are still many controversies even on the question of "Exactly what is diabetes?" Along with increased interest in diabetes, has come an expanding market of literature, diabetes books and symposiums. Each publication presents different views with emphasis on various areas. This volume is intended to present facts rather than the author's opinion, leaving much of the interpretation to the clinician who has the ultimate responsibility of caring for the diabetic patient.

The association of diabetes with many other common diseases, and the ubiquity of the pathological changes in the body, makes the "specialty of diabetes" an extensive subject. Sir William Osler made the statement: "There are in truth no specialties in medicine, since to know fully many of the most important diseases a man must be familiar with their manifestations in many organs." Diabetes mellitus exemplifies this philosophy precisely; perhaps that is why there is a vast source of knowledge in this field and yet a great amount as yet uncovered.

In addition to increasing the knowledge of the physician who treats diabetes (and all physicians must be in contact with some diabetics, no matter what specialty they practice), the physician in turn has the responsibility of teaching the patient all she or he is capable of learning about diabetes. There is still controversy over the question of whether better carbohydrate control will decrease long-term complications. I personally believe that normoglycemia will help avert complications. This is almost impossible to achieve, but in the well-educated patient, normoglycemia is more closely approximated. The diabetic who has the knowledge and the patience, incentive and ability to exercise this knowledge, will survive longer with fewer complications. Thus, physicians have the responsibility of self education and patient education more with diabetes mellitus than most major diseases.

When arguments arise over whether better carbohydrate control really does delay complications, two points are pertinent in support of good control: 1) The poorly controlled diabetic rarely fares better, and 2) the well controlled diabetic usually does not have increased problems.

Writing this volume has been an education for me and has increased my understanding of the many fields touched by diabetes or overlapping with carbohydrate intolerance. I am greatly indebted to a few individuals who helped me with the preparation of this manuscript and to the many authors and researchers who so aptly explored this field so that I could summarize some of their findings.

Ms. Barbara Buckley has labored long hours, typing and organizing the copy, and deserves my sincerest appreciation. Ms. Leslie Ann Glasgow, my daughter, contributed greatly by the skillful preparation of charts, graphs and illustrations. I am also very indebted for the technical assistance of Ms. Sadie R. Buchanan and Capt. Patrick J. Tustain in determining insulin by radioimmunoassay and accumulating data for insulin graphs reported in these chapters. Ms. Hayne H. Mesick and Ms. Kayte Summerlin have continued the technical work with insulin assays keeping the laboratory in operation while I was involved with this manuscript, for which I express my thanks. My very special gratitude goes to my husband, Joseph L. Glasgow, M.D. and children, Leslie Ann, David L. and John Bonar Glasgow for their forebearance and loyal support during the preparation of this volume. I also wish to express my appreciation for the careful proofreading done by Edrie H. Bonar and the tedious indexing done by Sara Edwards.

Jeanne R. Bonar, M.D.

DIABETES
A CLINICAL GUIDE

CONTENTS

CONTENTS (Continued)

I. DEFINITION AND CLASSIFICATION OF DIABETES MELLITUS

INTRODUCTION: The metabolic disorder which characterizes clinical diabetes mellitus by hyperglycemia and relative or absolute lack of insulin may be either a reflection of a complex and chronic systemic disease or a causative factor. Early recognition of diabetes is based on hyperglycemia and abnormal carbohydrate metabolism while microvascular and macrovascular abnormalities are recognized as late "complications". The debate over whether the microvascular manifestations are concomitant defects, precursors to metabolic derangements, or consequences of long standing carbohydrate intolerance has not been resolved. Furthermore, the different clinical presentations of diabetes may be associated with different etiologies. The carbohydrate intolerance could represent multiple causes, the same as pneumonia is created by viral, chemical, bacterial and multiple etiologies. It may not seem of practical importance to define or classify various stages of diabetes, but if certain questions are answered then early detection of potential carbohydrate intolerance could prevent the irreversible microvascular defects.

First, is it possible to identify the disease prior to carbohydrate intolerance? With the knowledge of true "prediabetes" can anything be done to avoid progression to clinical disease? If the genetic potential is there, what can be done to reverse the possibility of an inevitable disease? Are certain diabetics destined to develop complications or is intense therapy the answer to delay or abort systemic involvement of micro and macrovascular pathology?

There are two major categories of diabetes mellitus based on etiological considerations. The first is genetic or primary diabetes. The basic defect is an absolute or relative lack of insulin which leads to abnormalities of metabolism, not only carbohydrate but also of protein and fat. There are two subdivisions of genetic diabetes (a) ketosis prone type (b) ketosis resistant type. Several stages of diabetes are described and classified (Table I).

TABLE I. CATEGORIES OF DIABETES MELLITUS

I Primary or Genetic Diabetes Mellitus
- A. Prediabetes
- B. Suspected Diabetes
- C. Chemical or Latent Diabetes
- D. Overt Diabetes
  1. Ketosis prone
  2. Ketosis resistant

II Secondary Diabetes Mellitus

III Glucose intolerance with aging
(Diabetes or a metabolic phenomenon?)

The second major category of diabetes mellitus is that of secondary diabetes which results from: (a) ablation of the majority of functional pancreatic tissue by disease or surgery (b) insulin antagonism from iatrogenic administration of drugs, steroids, or thiazides, or insulin antagonism produced by endocrine disorders with excess secretion of any of the following hormones: hydrocortisone, aldosterone, catecholamines, glucagon or thyroxine.

There are well-defined criteria for the diagnosis of diabetes resting on hyperglycemia and glycosuria and it seems paradoxical that there is widespread argument and disagreement as to when diabetes actually is present. As long as the precise etiology of genetic diabetes has not been clearly defined then there will continue to be many diverse opinions about this subject.

Genetic diabetes mellitus may be more than one inherited disorder characterized by inheritance of pathological processes involving small blood vessels and disorders of glucose metabolism with variable degree of penetrance of either or both of these disorders.

It may also be an inherited propensity to develop certain viral infections leading to destruction of the beta cell.

The accepted classification of genetic diabetes mellitus based on a special report in "Diabetes" is summarized in Table II. There is generally no question as to the presence or absence of overt diabetes mellitus. Symptoms are usually easily elicited in the adult onset type and may be very marked in the juvenile onset diabetic.

Prediabetes: Particular attention should be paid to the state classified as prediabetes. It must be assumed that prediabetes may proceed at any time to overt diabetes or under stress overt diabetes may be precipitated. However, since the number of prediabetic individuals in the population is unknown, proof of this is difficult. The practical reason for thoroughly considering the prediabetic state is that the development of preventative agents which would correct any metabolic deficiency of pancreatic beta cell response to glucose, or for regulation of hepatic glucose output is possible in the future.

Prediabetes is more than just a concept of a strong hereditary predisposition to development of diabetes mellitus. It is now recognized that although standard glucose tolerance curves and even stress glucose tolerance curves are normal in the prediabetic state, there may be a delay or diminished secretion of insulin after glucose stimulation.

The prediabetic state is characterized by:

(a) Normal glucose levels following an oral glucose load
(b) Low insulin response to oral glucose
(c) The disappearance rate of intravenously administered glucose is significantly lower than normal

TABLE II. STAGES IN THE NATURAL HISTORY OF DIABETES MELLITUS

Terminology by the American Diabetes Association	Prediabetes	Suspected Diabetes	Chemical or Latent Diabetes	Overt Diabetes
Fasting blood sugar	Normal	Normal	Normal or increased	Increased
Glucose tolerance test	Normal	Normal; abnormal during pregnancy, stress	Abnormal	Not necessary for diagnosis
Cortisone-glucose tolerance test	Normal	Abnormal	Not necessary	Not necessary
Delayed and/or decreased insulin response to glucose	+	++	+++	++++
Clinical manifestations	None	Asymptomatic except stress precipitated	Asymptomatic Chemical	Clinical diabetes symptoms

(d) An increased lipolytic response to physical exercise similar to that found in manifest diabetes may occur
(e) Prediabetic mothers potentially may give birth to children with diabetic fetopathy

It has been postulated that low insulin responders constitute the majority of patients who will eventually develop overt diabetes mellitus. There is no way to predict the number of these individuals in the population without a massive survey of the population analyzing insulin levels after glucose administration, then there must be long term follow-up or perhaps lifetime follow-up of these individuals and controls.

Cerasi and Luft have followed 113 patients including 23 prediabetics and 90 controls over a period of three to eight years with repeated intravenous glucose tolerance tests and have found none with overt diabetes. They have predicted that among prediabetics, probably 30% will develop chemical diabetes and only 10% of the total prediabetic population will become overt diabetics.

The beta cell is primarly stimulated by glucose although it is stimulated by certain amino acids, leucine and arginine, also glucagon is insulinogenic. There is evidence that the poor insulin response in the prediabetic and mild diabetic is related to a decrease in sensitivity of the beta cell by glucose. Prediabetics respond to exogenous insulin with greater sensitivity.

The insulin release to tolbutamide in prediabetics has been noted to be normal. If a prediabetic individual were subject to metabolic consequences of diabetes thus developing angiopathy, then pretreatment with a hypoglycemic agent could be considered in these individuals. However, with the question of long-term problems with oral hypoglycemic agents, to be discussed in another chapter, this would still be a debatable approach. With newer development of insulinogenic agents, there is still potential for treatment of the prediabetic state. If there is a viral etiology, vaccination would be a preventative measure.

In respect to the insulin secretion in the genetic prediabetic with normal glucose tolerance there is not complete agreement. For example, Simpson found in a group of non-obese individuals with diabetic heritage, some had impaired early release of insulin but the main response was normal. Others have noted the diminished insulin secretory response to glucose in prediabetics but found no delay in the rise of serum insulin after glucose stimulation.

Suspected Diabetes Mellitus: The other classes of genetic diabetes are not as puzzling as that of prediabetes. Suspected diabetes occurs in an individual who has a temporary carbohydrate intolerance which may revert to normal after a period of stress has subsided. After relief of the precipitating factors, then it is necessary to reevaluate the abnormal glucose tolerance. These individuals generally are asymptomatic from the diabetes mellitus.

There may be insufficient functional reserve of the islet cells in this disorder..

Some examples of stress diabetes would be associated with: (a) pregnancy (b) obesity, with the return of normal glucose tolerance after weight loss, (c) physical or emotional stress, such as trauma, burns and infections, (d) iatrogenic use of steroids or thiazides, (e) endogenous production of hormones which induce an insulin resistance, such as Cushing's syndrome. These would overlap with the category of secondary diabetes also.

In pregnancy, gestational diabetes, the abnormal glucose tolerance may revert to normal following delivery but there is a high risk factor in these individuals. Fetal abnormalities that suggest diabetes of the "stress" or "suspected" variety in the mother may be manifested by large babies, habitual abortion, fetal and neonatal deaths or hydramnios.

The obese individual is metabolically different in many ways from a nonobese person, with respect to carbohydrate metabolism. Glucose utilization are the most frequently found metabolic abnormalities in the obese individual. Insulin levels are elevated in obese individuals who have normoglycemia. Insulin levels are higher than those of normal weight individuals in the diabetic, obese individuals but not as high as their nondiabetic obese counterpart. Comparative insulin levels are charted (Figure 1) for obesity, diabetic obesity, chemical and juvenile diabetes.

There are two views on the endocrine production of diabetes such as that found in Cushing's syndrome and iatrogenically induced by the administration of corticosteroids. The difference of opinion rests on whether or not these individuals are genetic diabetics precipitated by stress or an insulin antagonism or whether or not this should be classified as a secondary diabetes.

Chemical Diabetes (Latent): The next stage in tne development of diabetes would be that of chemical or latent diabetes. This is also asymptomatic but is found in the absence of stress or does not revert to normal after stress situations have been eliminated. The hyperglycemia is found in the postprandial period while fasting blood glucose is normal.

Overt Diabetes: Overt diabetes mellitus needs no explanation and it is not necessary to do a tolerance test for diagnosis. Fasting hyperglycemia and symptoms related to the hyperglycemia and glucosuria are present in these individuals. Overt diabetes mellitus may be again subdivided into the ketosis prone individual or the ketosis resistant type of diabetes mellitus. If classified by age the ketosis prone is known as a juvenile or growth onset diabetic and the ketosis resistant type is the adult or maturity onset type.

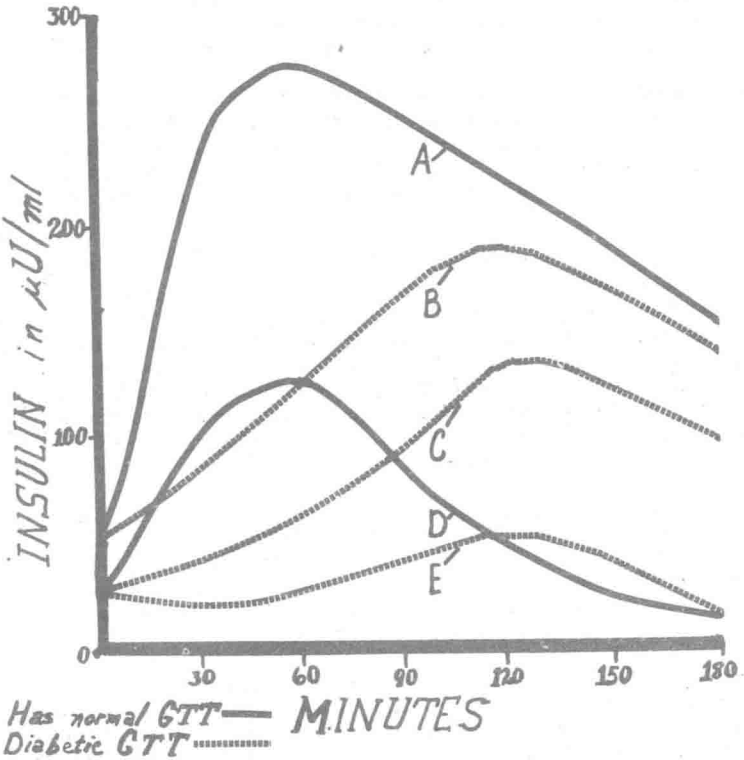

Figure 1. Comparative insulin levels seen in: A.obesity, B.obese diabetic, C.Early or latent diabetic, D.Normal, E.Juvenile, ketosis prone, low insulin diabetic.