Diagnosis and Management of Endocrine Diseases

ANTHONY D. TOFT
BSc MD FRCPE
Senior Lecturer in Medicine, University of Edinburgh
Honorary Consultant Physician,
Royal Infirmary, Edinburgh

IAN W. CAMPBELL
BSc MB ChB FRCPE
Consultant Physician, Victoria Hospital, Kirkcaldy
Honorary Senior Lecturer in Medicine,
University of Edinburgh

JOHN SETH
MSc PhD MCB
Top Grade Biochemist, Department of Clinical Chemistry,
Royal Infirmary, Edinburgh
Honorary Senior Lecturer in Clinical Chemistry,
University of Edinburgh

BLACKWELL SCIENTIFIC PUBLICATIONS
OXFORD LONDON EDINBURGH
BOSTON MELBOURNE

Diagnosis and Management of Endocrine Diseases

ANTHONY D. TOFT
BSc MD FRCPE
Senior Lecturer in Medicine, University of Edinburgh
Honorary Consultant Physician,
Royal Infirmary, Edinburgh

IAN W. CAMPBELL
BSc MB ChB FRCPE
Consultant Physician, Victoria Hospital, Kirkcaldy
Honorary Senior Lecturer in Medicine,
University of Edinburgh

JOHN SETH
MSc PhD MCB
Top Grade Biochemist, Department of Clinical Chemistry,
Royal Infirmary, Edinburgh
Honorary Senior Lecturer in Clinical Chemistry,
University of Edinburgh

BLACKWELL SCIENTIFIC PUBLICATIONS
OXFORD LONDON EDINBURGH
BOSTON MELBOURNE

Editorial offices:
Osney Mead, Oxford, OX2 0EL
8 John Street, London, WC1N 2ES
9 Forrest Road, Edinburgh, EH1 2QH
52 Beacon Street, Boston
Massachusetts 02108, USA
99 Barry Street, Carlton,
Victoria 3053, Australia

First published 1981

Set by
Scottish Studios & Engravers Ltd,
Glasgow
Printed and bound in Great Britain by
Butler & Tanner Ltd,
Frome and London

DISTRIBUTORS

USA
Blackwell Mosby Book
Distributors,
11830 Westline Industrial Drive,
St. Louis, Missouri 63141

Canada
Blackwell Mosby Book
Distributors,
120 Melford Drive, Scarborough,
Ontario M1B 2X4

Australia
Blackwell Scientific Book
Distributors,
214 Berkeley Street, Carlton,
Victoria 3053

British Library
Cataloguing in Publication Data
Toft, Anthony D.
Diagnosis and management of
endocrine diseases.
1. Endocrine glands - Diseases -
Diagnosis
I. Title II. Campbell, Ian
III. Seth, John
616.4'07'5 RC649

ISBN 0-632-00553-X

Preface

The last decade has witnessed rapid advances in endocrinology. As a result of measurement of hormones by radioimmunoassay, synthesis of thyrotrophin-releasing hormone, photocoagulation for diabetic retinopathy, low-dose insulin regimes for ketoacidosis and drugs such as bromocriptine which affect neuroendocrine control of pituitary hormone secretion, the management of endocrine diseases has been simplified. Equally important have been those discoveries which have increased knowledge of the pathogenesis of the endocrine disease such as stimulating TSH-receptor antibodies, pancreatic islet cell antibodies and the relationship of certain HLA types with autoimmune endocrine disorders. We have been fortunate to practise during this period of exciting development and this book reflects our combined clinical and biochemical experience. We are very much aware that this experience has been enriched by the generosity of many colleagues who have referred us their more interesting patients.

We have attempted to produce a practical textbook. As such it does not dwell on aetiology or physiology, other than those aspects necessary for understanding the basis of rational investigation and treatment. The omission of paediatric and gynaecological endocrinology is intentional as specialized texts are available. We hope that this book is of value to all students of medicine, whether established physicians, postgraduates attempting examinations or more interested undergraduates.

We should like to acknowledge the help and encouragement of Dr John Munro and of Mr Nigel Palmer and Mr Richard Zorab of Blackwell Scientific Publications Ltd, and the patience and secretarial skills of Mrs Sallie Sandison who latterly must have

known the text by heart. Finally, we are immeasurably indebted to our wives and children who have sacrificed many family weekend pursuits during the last eighteen months.

ADT
IWC
JS August 1981

Abbreviations

Abbreviation	Full name	Other name*
ACTH	Adrenocorticotrophin	Corticotropin
ADH	Antidiuretic hormone	Vasopressin
CG	Chorionic gonadotrophin	Choriogonadotropin
CRF	Corticotrophin-releasing factor	Corticoliberin
FSH	Follicle-stimulating hormone	Follitropin
GH	Growth hormone	Somatotropin
Gn-RH	Gonadotrophin-releasing hormone	Gonadoliberin
LH	Luteinising hormone	Lutropin
LPH	Lipotrophin	Lipotropin
PTH	Parathyroid hormone	Parathyrin
PRL	Prolactin	Prolactin
TRH	Thyrotrophin-releasing hormone	Thyroliberin
TSH	Thyroid-stimulating hormone	Thyrotropin
T_4	L-Thyroxine	L3,5,3′,5′-tetraiodothyronine
T_3	L-Tri-iodothyronine	L-3,5,3′-tri-iodothyronine
r-T_3	Reverse-L-tri-iodothyronine	L-3,3′,5′-tri-iodothyronine

*The names shown in this column are those recommended by the IUPAC–IUB Commission on Biochemical Nomenclature.

Contents

Contributors

HILARY A. KELLETT
MA MB ChB MRCP
Lecturer in Medicine
University of Edinburgh

FREDERICK C. W. WU
BSc MB ChB MRCP
Senior Registrar in Medicine and Endocrinology,
Royal Infirmary, Edinburgh

CHAPTER 1

Classification, presentation and diagnosis of diabetes mellitus

Diabetes mellitus is a clinical syndrome, characterized primarily by chronic hyperglycaemia and glycosuria. It is caused by a heterogeneous group of disorders which have in common either a deficiency or diminished effectiveness of endogenous insulin, resulting in a disturbance of carbohydrate, protein and lipid metabolism. As the routine laboratory investigation of diabetes mellitus and its classification are based on the disturbance of carbohydrate metabolism, this aspect will be briefly reviewed.

Carbohydrate metabolism in health and in diabetes mellitus

Carbohydrate metabolism in man is normally regulated so as to store glucose in the form of metabolic fuels during feeding, and to provide during fasting a continuous supply of glucose to those tissues, such as the brain and erythrocytes, that have an essential requirement for it. Regulation depends on changes in carbohydrate, lipid and protein metabolism to provide alternative sources of energy, these changes being largely controlled by the anabolic effects of insulin on the one hand, and the catabolic effects of cortisol, adrenaline, glucagon and growth hormone on the other.

Response to feeding

The rise in plasma glucose which occurs on digestion and absorption of carbohydrate is a potent stimulus to insulin release from the β-cells of the pancreas. The increase in plasma insulin results in the following changes:

1. Uptake of glucose by liver, adipose tissue and muscle is increased, and synthesis of storage forms of glucose is enhanced. In liver and muscle the polysaccharide glycogen is laid down, while in liver and adipose tissue triglycerides are synthesized and stored.
2. These storage processes are reinforced by the effects of insulin in inhibiting glycogen breakdown (glycogenolysis) and triglyceride breakdown (lipolysis) thereby reducing hepatic production of glucose, and adipose tissue production of free fatty acids.
3. Hepatic production of glucose is further reduced by the insulin-induced suppression of gluconeogenesis, a process in which pyruvate, lactate and amino acids such as alanine are converted into glucose.

The overall effect of insulin release in response to feeding is to move glucose from the extracellular pool (plasma and interstitial fluid) to intracellular storage sites, the liver being the single most important organ in the uptake of an acute glucose load. Insulin plays a vital role therefore in 'smoothing out' the potentially marked increase in plasma glucose that would occur on feeding if absorbed glucose were to remain extracellularly.

Response to fasting

The fall in plasma glucose reduces insulin secretion to low levels, bringing into play a concerted series of mechanisms which maintain plasma glucose levels at the expense of glycogen, triglyceride and protein catabolism. The hormones cortisol, adrenaline, glucagon and growth hormone have specific effects in combination with low insulin levels to stimulate utilisation of these metabolic fuels. The important responses to fasting, mediated by decreased insulin levels, are:

1. Glucose uptake by muscle, liver and adipose tissue is decreased, with reduced formation of storage forms of glucose (glycogen, triglyceride).
2. Glycogenolysis in liver and muscle is stimulated. However, only the liver can contribute to the extracellular glucose pool, as unlike muscle, the liver possesses the enzyme necessary to convert intracellular glucose phosphate to free glucose. Hepatic glycogenolysis contributes to the maintenance of plasma glucose levels principally during the early stages of fasting as glycogen stores in the liver are relatively limited.

3. Lipolysis is stimulated in liver and adipose tissue, releasing fatty acids which provide a major source of energy for many tissues. This conserves glucose for those tissues that specifically require it. In the liver the two carbon fragments resulting from fatty acid oxidation can be converted to the ketoacids, acetoacetate and β-hydroxybutyrate, which also serve as metabolic fuels in extrahepatic tissue. The quantity of ketoacids formed increases as carbohydrate metabolism is suppressed with increasing duration of fasting.

4. As glycogen stores become depleted gluconeogenesis in the liver becomes an increasingly important source of extracellular glucose. Renal gluconeogenesis also contributes during prolonged fasting. Fatty acid metabolism, outlined above, provides energy for gluconeogenesis, while important precursors for glucose synthesis by this route include pyruvate, lactate and amino acids from muscle, with glycerol from adipose tissue lypolysis making a relatively minor contribution.

The overall response to fasting therefore is an adjustment to the use of free fatty acids as the major source of energy, conserving the relatively scarce supplies of glucose. An equilibrium is reached in fasting at which glucose production, mainly by hepatic gluconeogenesis, equals the rate of glucose utilization, principally by neural tissue and erythrocytes. The fasting plasma glucose reflects the extracellular glucose level at this equilibrium.

Metabolic disturbance in diabetes mellitus

Failure of insulin secretion or action is the characteristic feature of all forms of diabetes mellitus. The consequences of this insulin deficiency can be summarized as follows:

1. With modest degrees of insulin deficiency tissue uptake of glucose from the extracellular fluid is decreased, although basal insulin production may be adequate to maintain otherwise normal carbohydrate, lipid and protein metabolism. Thus a dietary glucose load is less rapidly cleared from the plasma space and post-prandial hyperglycaemia is observed even though the fasting plasma glucose is normal.

2. With a greater degree of insulin deficiency, not only is glucose uptake impaired, but there is in addition excessive breakdown of

stored metabolic fuels. As in fasting, triglyceride breakdown is enhanced and free fatty acid levels in plasma are increased providing a major source of energy for many tissues.

3. The rate of metabolism of free fatty acids in the liver appears to be directly related to their plasma concentration. A consequence of the increased rate of fatty acid metabolism is that acetoacetate and β-hydroxybutyrate are formed in greater amounts than normal. Although these ketoacids can be metabolized by extrahepatic tissues, this process is decreased by insulin deficiency, so that ketoacid levels in plasma rise until a new equilibrium is reached at which the rates of excretion and tissue utilization equal the accelerated rate of production.

4. In addition to the abnormally high rate of fatty acid metabolism resulting from insulin deficiency, gluconeogenesis in the liver is increased, and may be more than doubled. This makes an important contribution to the fasting hyperglycaemia of diabetes mellitus. Where the elevation in plasma glucose is sufficient to exceed the renal tubular transport maximum for glucose reabsorption, glycosuria ensues.

5. Decreased amino acid uptake and protein synthesis resulting from insulin lack contributes to the availability of amino acid precursors for gluconeogenesis. Decreased protein synthesis is evident as a negative nitrogen balance and tissue wasting.

Many of the clinical and biochemical features of diabetes mellitus that will be described can therefore be accounted for by failure of insulin secretion or action. It is important to recognize however that insulin deficiency will often only be unmasked by acute disturbances such as trauma or infection, which can increase secretion of cortisol, adrenaline, glucagon and growth hormone that oppose the actions of insulin. More rarely, chronic hypersecretion of these hormones, as, for example, in Cushing's syndrome, phaeochromocytoma or acromegaly, causes relative insulin deficiency and diabetes mellitus.

Biochemical tests in diabetes mellitus

The definitive diagnosis of diabetes mellitus depends on the finding of an abnormally high plasma glucose concentration. Semiquantitative assessment of blood glucose, and glucose and ketones in urine using side-room tests can also be useful in the initial

assessment of the patient. Practical aspects of these tests relevant to their application and interpretation will be outlined here.

Plasma glucose

Type of laboratory method

The methods fall into two broad categories, (a) chemical, which commonly measure glucose according to its reducing properties, and (b) enzymatic, which commonly use glucose oxidase in combination with peroxidase and a suitable substrate to generate a coloured reaction product. Chemical reduction methods are the less specific as other reducing substances in plasma, such as creatinine, uric acid, some drug metabolites, and other reducing sugars such as lactose can contribute to overestimation of the true glucose concentration. Glucose oxidase methods are widely considered to provide the more accurate measurement of plasma glucose concentration and, as a general guide, levels determined by chemical reduction are 0·2–0·6 mmol/l higher than those determined using glucose oxidase. Larger differences have been observed in cases of renal failure with elevated plasma levels of creatinine and uric acid. However, it should be recognized that the lower glucose levels measured using glucose oxidase may be due to negative interference, and such effects have been described with some drugs, e.g. ascorbic acid.

The *World Health Organisation Expert Committee on Diabetes Mellitus* (WHO, Geneva, 1980) define diagnostic values in terms of results obtained with a glucose oxidase method, and this recommendation will be followed here. Interpretation of values obtained by a chemical reduction method may need to take account of the slightly higher values that such methods provide.

Type of specimen

Venous blood or plasma. Although glucose can be measured in whole blood or plasma, plasma is generally preferable for three reasons.

1. With chemical methods of analysis based on the reducing properties of glucose, there is more non-specific interference with

whole blood than with plasma, largely due to erythrocyte glutathione.

2. Glucose concentration in whole blood is about 15 per cent lower than in plasma, but the degree varies with the haematocrit. This is due to the water content of erythrocytes being lower than that of plasma, while glucose concentrations in erythrocyte and plasma water are equal.

3. Plasma specimens can be frozen and are more suitable for storage than blood.

In some clinics blood specimens are obtained by thumb prick and are therefore capillary blood. These specimens yield values that are similar to arterial levels, and are only 0·1–0·2 mmol/l higher than those in venous blood under fasting conditions. After a glucose load, however, increased glucose uptake by the tissues can result in levels in capillary blood being 1·1–1·7 mmol/l higher. The term 'plasma glucose' used hereafter refers to venous plasma glucose.

Preservation of specimen. In whole blood at room temperature glucose is lost at a rate of about 0·4 mmol/l/h. The major cause of loss is glycolysis by leucocytes and bacterial contaminants, although erythrocytes and platelets also contribute. Blood for glucose analysis must therefore be collected in tubes containing sodium fluoride, to inhibit glycolysis, and potassium oxalate to serve as an anticoagulant. Plasma should be separated within 4 hours and stored at –20°C if glucose is not to be measured immediately.

Side-room tests for glucose and ketones

Semi-quantitative assessment of glucose in blood and urine, and ketones in urine can be valuable in the initial assessment and follow-up of the diabetic patient, and test materials are commercially available that permit these tests to be performed in the clinic. Full instructions on their use are supplied by the manufacturers, and only a general description of the available tests will be given here.

Blood glucose (Dextrostix*, Reflotest† and BM-Test Glycemie 20–800†)

These are based on the specific glucose oxidase enzymatic

*Ames Co. Ltd
†Boehringer Corp. Ltd

technique, the reagents being impregnated in an absorbent pad at the tip of the test strip. The intensity of the colour developed on the reagent pad is visually compared with colour blocks on a standard chart to give a semi-quantitative reading of blood glucose. The range of glucose values covered using Dextrostix and Reflotest is approximately 0 to 14 mmol/l (250 mg/dl). A more objective and precise measurement of blood glucose can be obtained if these test strips are used in conjunction with the appropriate reflectance meter, i.e. Eyetone*, Reflomat†. The BM-Test Glycemie 20-800 has a dual sensitivity test area and provides direct visual readings between 1·1–44·4 mmol/l (20–800 mg/dl).

These test strips are not designed for use with serum or plasma, and should not be used with blood containing fluoride, which can inhibit the enzyme reaction and give spuriously low results.

Urinary glucose

Although glucose is normally excreted in small quantities in the urine (4·0 mmol/24 h) this is insufficient to be detected by the commonly used tests for glycosuria. Two types of test are widely used, which have important differences in sensitivity and specificity.

Clinistix, Diastix**. These strip tests are based on the specific glucose oxidase technique but show some minor differences in interferences, Ketones in excess may depress results with Diastix, while high concentrations of ascorbate may give negative results with Clinistix. Both tests have a detection limit of 5·5 mmol/l and Diastix provides semi-quantitative readings up to 110 mmol/l (2 per cent).

*Clinitest**. This test measures glucose according to its reducing properties, and contains the necessary reagents in tablet form. The limit of detection is 14 mmol/l (0·25 per cent), and semi-quantitative results up to 110 mmol/l (2 per cent) can be obtained. It is non-specific and detects other reducing sugars, e.g. lactose, a common cause of positive results during pregnancy and lactation.

A negative result with Clinitest and positive result with Clinistix or Diastix may be due to the higher sensitivity of the latter two tests. The converse situation, i.e. positive result with Clinitest and negative with Clinistix or Diastix, indicates the presence of non-glucose reducing substances.,

*Ames Co. Ltd.

Urinary ketones (Acetest*, Ketostix*, Keto-Diastix*)

These test materials are based on the colour produced when acetoacetate reacts with nitroprusside and glycine. β-hydroxybutyrate does not react, and the sensitivity to acetone, a breakdown product of acetoacetate, is poor. False positive results are given by large quantities of phenylketones and by bromsulphthalein. L-dopa metabolites give atypical colours.

The oral glucose tolerance test (OGTT)

The OGTT has an important but strictly limited role to play in the investigation of suspected diabetes mellitus. In general it is required to identify only cases of relatively mild insulin deficiency, and to elucidate the cause of glycosuria.

INDICATIONS

The routine clinical indications for the OGTT are:

1. Suspected diabetes mellitus with equivocal raised values for fasting or random plasma glucose (p. 17).
2. Follow-up of patients known to have impaired glucose tolerance (p. 13).
3. Investigation of suspected gestational diabetes mellitus (p. 14).
4. Investigation of other causes of glycosuria, e.g. alimentary glycosuria, renal glycosuria.

PATIENT PREPARATION

The response to the OGTT can differ on repeat testing in the same patient, even when performed under carefully controlled conditions. The following known causes of variability should therefore be controlled in performing the test.

Diet. Severe carbohydrate restriction can decrease glucose tolerance. Carbohydrate intake should be therefore at least 150 g daily for the three days preceding the day of the test, i.e. the patient should be instructed to continue a normal eating pattern.

*Ames Co. Ltd.

The patient should have fasted for 10–16 hours immediately before commencing the test, although water is allowed.

Physical activity. Glucose tolerance is decreased within a few days of absolute bed rest. The test should be performed therefore only on patients who are mobile. Unusual physical activity during the test should be avoided.

Illness and trauma. These decrease glucose tolerance, possibly due to increased secretion of hormones that inhibit the actions of insulin. The test should not be performed until recovery is complete.

Drugs. Some drugs, e.g. corticosteroids, oral contraceptives, diuretics, phenothiazines and antidepressants decrease glucose tolerance and should be discontinued, if possible, before testing.

Timing of OGTT. A diurnal variation exists in glucose tolerance, which is best in the morning, and deteriorates later in the day. However, the conventional time for performing the test is in the morning.

Posture. This affects the rate of gastric emptying. The patient should be seated, as far as possible, throughout the test.

Smoking and beverages. Smoking and any form of caffeine should be avoided prior to and during the test.

TEST PROCEDURE

After preparation of the patient as detailed above, blood is collected for measurement of fasting plasma glucose, and urine for testing for glycosuria. A 75 g dose of glucose in 250–350 ml water is then drunk in about 5 minutes. The time of starting the glucose drink is taken as zero time, and blood specimens are collected at 30, 60, 90 and 120 minutes. Urine specimens are collected at 60 and 120 minutes.

INTERPRETATION

Many different criteria for interpretation of the OGTT have been

offered, but both the National Diabetes Data Group of the National Institute of Health, USA* and the WHO Expert Committee on Diabetes Mellitus regard the two hour value as an important criterion for classification. On the basis of the OGTT three diagnostic classes can now be defined. These are normal, impaired glucose tolerance (IGT) and frank diabetes mellitus (p. 17, Table 1.4).

CLASSIFICATION OF DIABETES MELLITUS AND OTHER CATEGORIES OF GLUCOSE INTOLERANCE

The aetiology of diabetes mellitus is complex, involving the interaction of genetic, immunological, environmental, metabolic and hormonal factors. The following classification is based on recent advances in the understanding of the pathogenic role of these various factors (Table 1.1).

TABLE 1.1 Classification of diabetes mellitus and other categories of glucose intolerance

Diabetes mellitus (DM)
Insulin-dependent (type I DM)
Non-insulin-dependent (type II DM)
DM secondary to certain medical conditions or associated with genetic syndromes
Impaired glucose tolerance (IGT)
Gestational diabetes mellitus
Previous abnormality of glucose tolerance
Potential abnormality of glucose tolerance

Diabetes mellitus (DM)

Insulin-dependent DM (type I DM)

This was previously known as juvenile-onset DM because it usually occurs in the young, but it can occur at any age and there is a second peak of incidence in the 60–70 age group. Type I DM represents approximately 25 per cent of diabetics. There appears to be a seasonal variation in incidence in younger patients, highest in the winter months and lowest in the summer. Cell-mediated immunity may be present against pancreatic antigens and positive pancreatic islet cell antibodies (ICA) occur in over 80 per cent of patients at

* *Diabetes*, (1979) **28**, 1039–1057.