Pharmacotherapy of Diabetes: New Developments

Improving Life and Prognosis for Diabetic Patients

Pharmacotherapy of Diabetes: New Developments

Improving Life and Prognosis for Diabetic Patients

edited by

Carl Erik Mogensen

Medical Department M
Diabetes and Endocrinology
Aarhus University Hospital
Denmark

Springer

Carl Erik Mogensen, MD
Professor of Medicine
Medical Department M
Diabetes and Endocrinology
Aarhus University Hospital
DK-8000 Aarhus C
Denmark

Library of Congress Control Number: 2006939509

ISBN- 978-0-387-69736-9 e-ISBN- 978-0-387-69737-6

Printed on acid-free paper.

9 8 7 6 5 4 3 2 1

springer.com

Dedication

This book is dedicated to my teacher and mentor and my very good friend, Knud Lundbæk (1912–1995). He was a dedicated physician taking care of diabetic patients as well a researcher and teacher for many young physicians. After his retirement, he explored new areas, namely the interrelationship between different cultures. He was really a foresighted man.

Carl Erik Mogensen, Aarhus, March 2007

Introduction

In 1991, I wrote with Eberhard Standl in a book on pharmacology of diabetes: "Treatment of diabetes has become an increasing challenge to the clinicians in recent years. A rapid development has taken place within a number of pharmalogical areas, both with respect to insulin-dependent and non-insulin-dependent diabetes, and also within the prevention and treatment of complications of both types of diabetes."

This is even more true today. Since then we have observed a rapid development in the area with new drugs for treatment of hyperglycemia – both oral agents and new insulin preparations. Indeed, within the area of complications, there are also many new perspectives in the treatment strategy. Combination treatment with agents that treat hyperglycemia is more and more important, also in combination with several agents controlling the complications has become more and more common. It is not unusual that patients receive four or five or six or even more drugs.

Problems within diabetes treatment can usually be divided into two phases, namely (i) acute and short-term treatment of patients and related to well-being and near-perfect physical abilities for professional and leisure activities, most often related to good metabolic control. (ii) On the other hand, the long-term perspective is preventive treatment of complications, both microvascular and vascular complications. Under special situations such as pregnancy, treatment is critical. A number of co-morbid situations are important: heart disease (although not always specifically related to diabetes), obesity (an increasingly important problem), and lipid management (very common). Since 1991, we have seen a rapid development in the treatment of one important issue, namely treatment of erectile dysfunction, which is even more important in diabetic than in nondiabetic individuals.

The so-called metabolic syndrome is also becoming more and more pertinent and an increasing number of patients fulfill that criterion (although it may not be a true syndrome); therefore, multifactorial intervention is important. Indeed, this book is meant as a working guide and a source for more basic knowledge regarding pharmacological treatment, for the practising diabetologist, the internist, and the general physician.

It has been a great pleasure for me to work with many colleagues, most of them personal and/or professional friends that I have known for many years. They represent, I believe, the clinical excellence in diabetes treatment, and it has been possible to collect all the chapters within a few months, which is quite remarkable when you have some experience in editing books.

Finally, I would like to thank the publishers – Springer, who are very much involved in diabetes treatment in general. It has been a pleasure to work with them throughout the whole process – from creating the idea to seeing the book on the street.

References

1. Pharmacology of diabetes. Present practice and future perspectives. Eds C.E. Mogensen and E. Standl. Walter de Gruyter, Berlin/New York, 1991.

Editorial assistant: Birgitte Josefine Henriksen

Aperitif

Edwin Gale, Bristol, UK

Why should anyone bother to put a textbook together? I have often wondered about this, even while doing the job myself. All those who have engaged in this activity will tell you that the work will be harder than you can imagine, that chasing reluctant authors is a depressing business, and that there are easier ways of making money. Worse still, the book you produce will typically have many competitors, and is destined to suffer from built-in obsolescence. All these are questions for those who create a textbook. For you, the reader, the question is: should you consider looking further into this one?

I think you should. The reason, I suggest, is that physicians treat patients, and that this is a book about treatment. Therapy for diabetes is life-long, monotonous, demanding, and has benefits that are mostly deferred into a distant future. Pleasing though it is for patients to learn that their cholesterol, blood pressure, or glycated haemoglobin have fallen within the target range, the fact is that they often feel no better in consequence, and may sometimes actually feel worse. The main argument we can offer them in defence of a demanding diabetes regimen is that—as Maurice Chevalier said of old age – it is so very preferable to the alternative.

A celebrated physician once remarked that it is not the disease that has the patient, but the patient that has the disease, that matters. Nowhere is this more true than for diabetes, for which no treatment will work unless the patient is committed to its success. Insulin is often its own argument, since patients feel so much better for it that they are often reluctant to stop. This is not the case when it comes to pills: people like to ask for them, but are less enthusiastic when it comes to swallowing them on a regular basis—and no medication will work if the patient is not taking it.

Doctors are, or should be, passionate advocates for the benefits of the treatment they offer. Their passion and their advocacy provide the core element in therapy. However, how do we know which treatment is best? Guidelines are necessary and useful, but choosing the right set of treatments, with the help of the person who will have to take them, is the essence of good medicine. And here the choices become ever more complex. Since diabetes is so intimately involved with lifestyle, especially in the overweight, behaviour change is the necessary prelude to any other intervention. Beyond this point, the options proliferate. There are currently nine classes of glucose lowering medication in development or on the pharmacist's shelf, each with its advantages and disadvantages. Further choices as to lipid-lowering and antihypertensive agents will have to be made, with the possible addition of anti-obesity medication. And behind these routine elements of therapy come all the special situations, pregnancy, foot ulcers, erectile dysfunction, and so forth. The diabetes physician must be equipped to deal with all of these, and this is a book which covers them all, which is refreshingly up to date, and currently seems to have no competitors.

It might seem that there is no lack of good advice about medication for diabetes. Specialist associations issue an unending stream of guidelines, and government agencies are increasingly guided by advisory bodies such as the National Institute for Clinical Excellence (NICE) in the UK, bodies which review the

evidence and advice as to how money for health care should be spent. Meanwhile, big Pharma continues to generate new therapies, at ever-increasing cost to the consumer. According to one analysis, global drug costs of US$3.8 billion dollars for diabetes in 1995 expanded to an estimated US$17.8 billion in 2005, and are projected to hit US$27.9 billion by 2010 [1]. As these estimates reveal, we have entered a realm of unsustainable costs and diminishing returns. And it is here, at the cutting edge of pharmacological intervention, that evidence-based medicine lets us down, for the sources of information are controlled by those who wish us to invest in their therapy.

How then do we make the best choice for the patient sitting in front of us? At the end of the day, the wisest advice will usually come from experienced, impartial, and critical clinicians, which is what this book has to offer.

Reference

Hauber A, Gale EAM. The market in diabetes. Diabetologia 2006;49:247–252.

Contents

Contributors

Henning Beck-Nielsen
Department of Endocrinology, Odense University Hospital, Kloevervaenget 6, 4, 5000 Odense C, Denmark, henning.beck-nielsen@ouh.regionsyddanmark.dk

Toke Bek
Department of Ophthalmology, Århus University Hospital, DK-8000 Århus C, Denmark, toke.bek@mail.tele.dk

D. John Betteridge
Department of Medicine, University College London Medical School, 5 University Street, WC1 6JJ London, UK, rmhajbe@ucl.ac.uk

Andrew J.M. Boulton
Universities of Manchester, UK, Miami, FL, USA Consultant Physician, Manchester Royal Infirmary, Manchester, UK, ABoulton@med.miami.edu

Knut Borch-Johnsen
Director Steno Diabetes Center, Niels Steensensvej 2, DK 2820 Gentofte, Denmark, kbjo@steno.dk

Mark Cooper
Baker Heart Research Institute, P.O. Box 6492 St Kilda Road Central, Melbourne VIC 8008, Australia, mark.cooper@baker.edu.au

Anders Dejgaard
Novo Nordisk A/S, Bagsvaerd, Denmark, ade@novonordisk.com

Niels Ejskjaer
Department of Medicine M (Endocrinology and Diabetes), Aarhus University Hospital, DK 8000 Aarhus C, Denmark, niels.ejskjaer@as.aaa.dk

Markolf Hanefeld
Science and Technology Transfer\NGWT TU Dresden, Centre for Clinical Studies, Fiedler Str. 34 Dresden 01307, Germany, hanefeld@gwtonline-zks.de

Jan Erik Henriksen
Odense University Hospital, Kloevervaenget 6, 4, 5000 Odense C, Denmark,
jan.erik.henriksen@ouh.regionsyddanmark.dk

Kjeld Hermansen
Department of Endocrinology and Metabolism C, Aarhus University Hospital, Tage-Hansens Gade 2, DK-8000 Aarhus, Denmark, kjeld.hermansen@as.aaa.dk

Jannik Hilsted
Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, jhilsted@rh.dk

Serge Jabbour
211 South Ninth Street, Ste 600, Philadelphia, PA 19107, Serge.jabbour@jefferson.edu

Sten Madsbad
Department of Endocrinology, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark, sten.madsbad@hh.hosp.dk

Elisabeth R Mathiesen
Department of Endocrinology 2132, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, DK 2100, Copenhagen Ø, Denmark, em@rh.dk

Carl Erik Mogensen
Medical Department M, Aarhus University Hospital, Nørrebrogade 44, DK-8000 Aarhus C, Denmark, carl.erik.mogensen@ki.au.dk

Niels Møller
Medical Research Laboratories, Aarhus University Hospital, Nørrebrogade 44, Dk-8000 Aarhus C, Denmark, nielsem@dadlnet.dk

Michael Nauck
Diabeteszentrum Bad Lauterberg, Kirchberg 21, D-37431 Bad Lauterberg im Harz
Germany, M.Nauck@diabeteszentrum.de

Torsten Toftegård Nielsen
Aarhus University Hospital, Skejby, Brendstrupgaardsvej, DK-8200 Aarhus N, Denmark,
toftegaard@ki.au.dk

Oluf Pedersen
Steno Diabetes Center, Niels Steensens Vej 2, 2820 Gentofte, Denmark, oluf@steno.dk

Johan V. Poulsen
Department of Renal Medicine C, Skejley Sygehus, Aarhus University Hospital, DK-8200
Aarhus N, Denmark. vpj@sks.aaa.dk

Per Løgstrup Poulsen
Medical Department M, Aarhus University Hospital, Nørrebrogade 44, Dk-8000 Aarhus C, Denmark, logstrup@dadlnet.dk

Gerald M. Reaven
Division of Cardiovascular Medicine, Stanford University School of Medicine, Falk Cardiovascular Research Center, Stanford, CA 94305, USA, greven@cvmed.stanford.edu

Lars Rejnmark
Medical Department M, Aarhus University Hospital, Aarhus Sygehus, Nørrebrogade 44, DK-8000 Aarhus C, Denmark, rejnmark@post6.tele.dk

Bjørn Richelsen
Department of Medicine and Endocrinology C, Århus Sygehus, THG, bjoern.richelsen@as.aaa.dk

Jørgen Rungby
Department of Endocrinology C, Aarhus University Hospital, Tage-Hansensgade 2, DK-8000 Aarhus C, Denmark, jr@farm.au.dk

Gerit Holger Schernthaner
Medical University Vienna, University Clinic, Waehringer Guertel 18–20, 1090, Vienna, Austria, gerit.schernthaner@meduniwien.ac.at

Guntram Schernthaner
Rudolfstiftung Hospital-Vienna, Juchgasse 25, A - 1030 Vienna, Austria, guntram.schernthaner@wienkav.at

Monika Shirodkar
Division of Endocrinology, Diabetes & Metabolic Diseases Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA

Aino Soro-Paavonen
Baker Heart Research Institute, Diabetes and Metabolism Division, 75 Commercial Road, 3004, Melbourne, Victoria, Australia, aino.soro-paavonen@baker.edu.au

Harald Stingl
Rudolfstitung Hospital, Department of Medicine 1, Juchgasse 25, Vienna, Austria, harald.stingl@wienkav.at

Krogsgaard Thomsen
CSO of Novo Nordisk, Novo Allé 1, DK-2880 Bagsværd, Denmark, MKT@novonordisk.com

Alberto Zanchetti, MD
Centro Interuniversitario di Fisiologia Clinica e Ipertensione, Università di Milano and Istituto Auxologico Italiano, Ospedale Maggiore, Via F. Sforza 35, 20122 Milan, Italy, alberto.zanchetti@unimi.it

Section: Overview

1
Pharmacoepidemiology of Diabetes

Jørgen Rungby and Andrew J. Krentz

Keywords: Pharmacoepidemiology, Pharmacoeconomics, Pharmacosurveillance.

The Epidemiology of Antidiabetic Drugs

Type 1 Diabetes

Type 1 diabetes requires insulin treatment soon after diagnosis and thereafter insulin must be continued life-long without interruption. By some definitions type 1 diabetes may have shorter or longer periods early in the disease during which insulin is not yet needed. Insulin secretagogues are often used in such cases before the diagnosis becomes clear, but they will eventually fail to control hyperglycaemia as marked insulin deficiency becomes established. Furthermore, as the obesity epidemic also strikes in patients with type 1 diabetes, combinations of classical insulin treatment regimens with insulin sensitizers, metformin, and in some countries, thiazolidinediones, are becoming more common. Nonetheless, for the 5–10% of the world's diagnosed diabetics who have type 1 diabetes, insulin monotherapy remains lifesaving therapy. The prevalence of type 1 diabetes varies enormously with population genetics, a subject that has been thoroughly discussed elsewhere. Within the seven major insulin markets (USA, Japan, France, Germany, Italy, Spain, UK – total sales) the prevalence of type 1 diabetes ranges from 0.2% (Japan) to 0.7% (Germany). In these countries alone, more than 3.1 million (with an expected increase to 3.4 million in 2011) people are affected. Even though insulin treatment is mandatory, a number of issues cause continued concern from a pharmacoepidemiological viewpoint.

Availability of Insulin

Unfortunately insulin, even in standard formulations (porcine, bovine or human insulin in vials for subcutaneous injections), is not necessarily accessible to all patients with type 1 diabetes. In a survey by the International Diabetes Federation (IDF) Task Force on Insulin performed in 2003 [1], only 44 and 40 out of 74 responding countries reported uninterrupted access to insulin for people with type 1 or type 2 diabetes, respectively. Thus, in 30 countries, people with type 1 diabetes were without continuous access to insulin. Cost remains a major cause of lack of access. However, availability, transportation problems and poor quality of insulin were also reported as major issues. There are considerable regional differences with African countries reporting the worst situation. An unfortunate consequence of low access to insulin is pressure on health personnel and authorities to give preference to people with type 1 diabetes over people with type 2 diabetes. However, as highlighted recently by Beran and Yudkin [2] the life expectancy of patients with type 1 diabetes in parts of sub-Saharan Africa remains extremely short. This situation has changed little in some countries over the last decade. On a global basis, the commonest cause of death in a child with diabetes eight decades since the discovery of insulin is lack of access to the drug. The recent decision by

NovoNordisk to make insulin available to 50 of the world's poorest counties at no more than 20% of the average price in Europe, North America and Japan has been applauded [3]. However, the impact of this initiative has so far been limited.

New Insulin Formulations

In many countries, animal insulin in vials remains the cheapest and most accessible form of insulin, although in North America human insulin is now the cheaper option. The paradigms for insulin treatment have changed within the last two decades with the introduction of insulin analogues and, to a certain extent, increasing use of insulin pumps as an alternative to subcutaneous injections. Currently a new change is emerging, namely the use of non-injection insulins, with inhaled insulins becoming available in some countries [4]. In contrast to the situation in type 2 diabetes, there is as yet no convincing evidence for insulin treatment during the pre-diabetes phase of type 1 diabetes. The market therefore reflects the prevalence and availability of insulin and, unfortunately, health economy politics including reimbursement policies.

The Global Insulin Market

Sales of rapid-acting analogues of insulin now exceed those for human sequence insulin. Humalog and Novolog (Novorapid) had combined sales totalling US$1555.2 million in 2005 compared with US$870.2 million for all other rapid-acting insulins, Humalog being the market leader. The intermediate-acting insulins, Humulin and Novolin (Insulatard) being the dominant examples, sold US$1050.8 million in 2005, which was a small decrease compared with 2004. The market (US$1576.8 million in 2005) for prolonged-duration analogues is dominated by Lantus, with Levemir gaining some ground since its introduction. All insulins, including premixed formulations with a sale of US$2256.1 million in 2005 and dominated by Novolog Mix, Novolin Mix and Humalog Mix, are used for both type 1 and type 2 diabetes (all data from [5]). As a consequence there has been a general increase in the use of insulin. Data from recent years in Denmark (with an estimated 25,000 patients with type 1 diabetes and more than 200,000 patients with type 2 diabetes) are shown in Fig. 1. Data from France [6] showed a tripling of the use of insulin from 1976 to 1989 most likely driven by the increasing burden of type 2 diabetes. In addition, the adjuvant use of novel amylinomimetics has gained some ground in the USA.

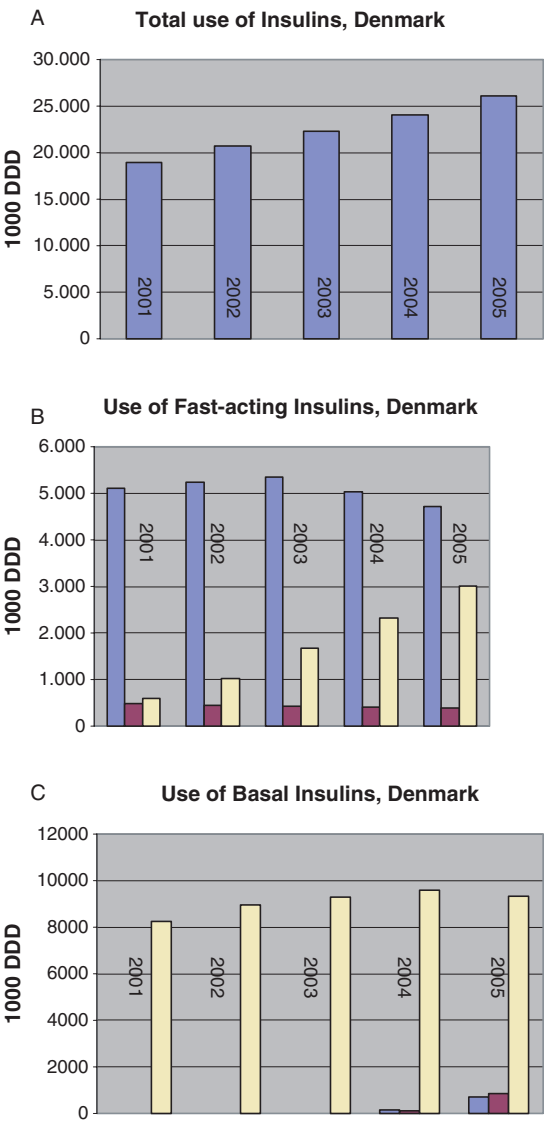

FIG. 1. Trends in the use of insulin in Denmark in the new millennium, all insulins (defined daily doses, DDD) (A), fast-acting insulins (left human insulin, middle lispro, right aspart) (B), basal insulins (left glargine, middle detemir, right human insulin) (C). (From The Danish Medicines Agency at www.dkma.dk.) The numbers reflect the use of insulin in 44,467 patients in 2001, increasing to 56,501 in 2005. Total use of analogues is increasing.

Prescribing of Insulin in Type 1 Diabetes

Internationally, guidelines for the treatment of type 1 diabetes vary little between countries. In essence, the goal remains near-normal glucose levels without inducing severe hypoglycaemia. The options available are legion although the intrinsic limitations of subcutaneous insulin delivery continue to act as a barrier to attainment of this goal in the majority of patients. Although some regimens appear to offer certain advantages over others [7], the choice of treatment remains dependent on the availability of insulin preparations (and delivery systems), local professional expertise and provision of support, and individual preferences of both patients and the diabetes healthcare team. As stated above, while paradigms of care may change, the choice of therapy often reflects the impact of factors other than evidence for treatment efficacy (and safety). For example, in otherwise comparable markets (Denmark and Sweden), the use of continuous subcutaneous infusion systems varies significantly [8] according to reimbursement policies.

Type 2 Diabetes

In the majority of subjects type 2 diabetes is usually not well controlled by lifestyle modifications and so presents major challenges to pharmacotherapy. The increasing number of ways to attack the cardinal metabolic defects of type 2 diabetes – insulin resistance and beta-cell failure – leaves patients and doctors with numerous possibilities for pharmacological interventions. The forecast of increased prevalence of diabetes in the coming years raises enormous ethical and practical questions, which must be resolved to supply patients with the necessary drugs. Data from the IDF suggest that overweight and obesity will affect major proportions of the population in the USA and large European countries, with France at 36% and the USA at 51.9% [1] by 2011, the latter increasing from 45.5% in 2005. Unless this trend is reversed, which at the moment appears unlikely, type 2 diabetes will affect significant proportions of the population. In 2005, Italy registered 6.2% of its population as having type 2 diabetes (increasing from 6.0% in 2004); corresponding figures from the USA were 6.1% and 5.9%. In the USA, diabetes mortality increased form approximately 68,000 deaths in 1999 to 74,000 deaths in 2003. Diabetes is the sixth leading recorded cause of death in the USA [5].

Availability

Varying with socioeconomics and health policies, the availability of oral or injectable antidiabetic agents varies. However, basic drugs for beta-cell stimulation, the sulphonylureas, and for treating insulin resistance and increased hepatic glucose output (the biguanides) remain cheap, effective and widely accessible. Alpha-glucose inhibitors and, in particular, thiazolidinediones, retarding the rates of intestinal glucose absorption and tissue insulin resistance, respectively, are alternatives that have been increasing in use and availability.

The Market for Antidiabetic Agents for Type 2 Diabetes

Including insulin, half of the global diabetes market is accounted for by the USA. Other major markets are Germany (7%), the UK (4%) and France (3%). Highly populated countries with substantial numbers of people with diabetes such as Russia and Brazil each account for approximately 1% of the market. The market is dominated by (54%) original branded drugs; however, generics account for some of the market and unknown numbers of patients are treated with “generics” in countries such as China and India where licensing regulations are less strict [5]. Oral antidiabetic drugs account for 58% of the total market worth US$18.6 billion in 2005, an increase of 11.5% compared with 2004. The market is led by the thiazolidinediones with a pioglitazone turn-over worth US$ 2.544 billion in 2005 (rosiglitazone US$ 2.258 billion, rosiglitazone/metformin combination US$ 382.7 million, metformin US$ 518.7 million, glimepiride US$ 857.9 million, vogiblose US$ 547.1 million). There are few descriptions of regional differences in prescription patterns. It can only be assumed that, as for insulin, availability varies and expectedly even more so since several oral antidiabetics can be used to achieve the same treatment goals in the individual patient. When drugs for associated conditions are included, it is likely that for some

high-prevalence countries, Germany, for example [9], diabetes may account for more than 20% of total pharmacy costs; cardiovascular drugs are the most important cost factor, reflecting the rates of atherosclerotic complications.

Prescribing of Antidiabetic Drugs for Type 2 Diabetes

Although hard end-point studies are somewhat sparse in diabetology, little doubt exists that near-normal blood glucose levels are beneficial, relieving symptoms and preventing long-term vascular complications. Guidelines are legion, and treatment goals are becoming increasingly ambitious. For example, the latest IDF guidelines for the treatment of type 2 diabetes [10] aim for HbA_{1c} levels lower than 6.5%. Since this goal is rarely achieved through lifestyle measures alone, oral antidiabetic agents are usually required. Initially, monotherapy is commenced with the most appropriate drug, based on the clinical and biochemical profile of the patient, and in the light of safety considerations. For most patients, drugs from different classes are required in varying combinations, insulin being ultimately necessary in many patients. Current guidelines recommend metformin and sulphonylureas as first-line therapy. Other regimens may be equally effective or even more so. However, comparative studies are sparse. With very prevalent diseases such as type 2 diabetes, pharmacoeconomics become extremely important. Thus, both the economy of society at large and the economy of the individual patient must be taken into account when choosing drug therapy. Safety issues remain important since treatment will often be continued for many years or even life-long, during which time complications, for example, nephropathy or cardiovascular disease, that may alter the safety profile of certain drugs may develop.

Trends in the Use of Antidiabetic Drugs

A recent survey [11] of antihyperglycaemic drugs in ten European countries showed that their use increased in all countries but with very different treatment patterns. The use of insulin doubled from 1994 to 2003 in some countries (England and Germany) but remained stable in others (Belgium, Portugal, Italy). The use of biguanides increased substantially, whereas the use of sulphonylureas increased more moderately in most countries. Insulin accounted for more than 50% of the daily antidiabetic doses in Sweden, the corresponding number in Portugal was <20% (Fig. 2). In an

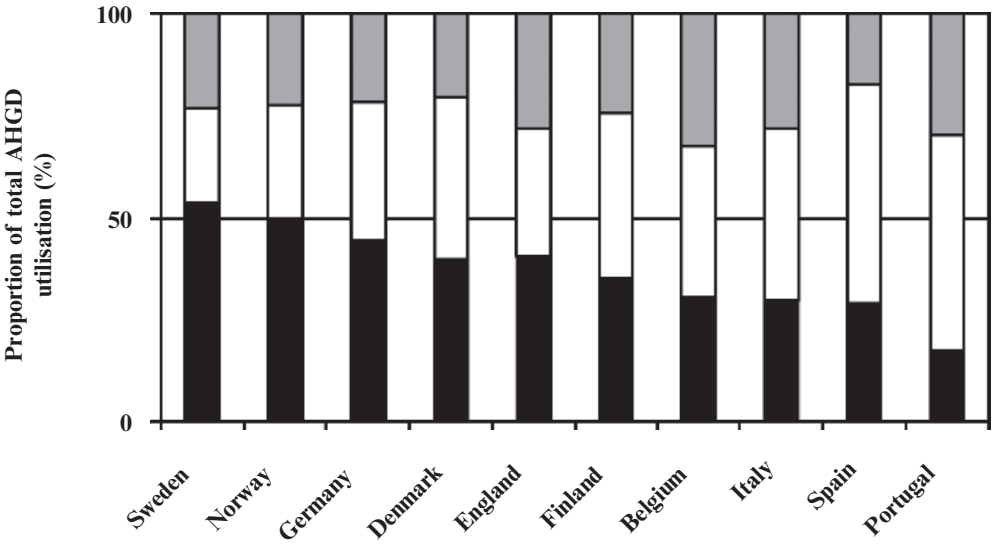

FIG. 2. Use of insulins (black), sulphonylureas (white) and biguanides (grey) as proportions of the total use of antidiabetics drugs in ten European countries (2003). Regional variation is substantial. Reproduced with permission from [11].

interesting comparison between Finland and Denmark (with the expected prevalence of diabetes being 7.2% and 6.9% in 2003, respectively) it was found that in 2000, 3.15% of the population in Finland (insulin 1.76%, oral agents 2.40%) was treated with antidiabetic drugs, the corresponding numbers for Denmark was 1.96% for any antidiabetic treatment (insulin 0.78%, oral agents 1.31%) [11]. It is unlikely that differences in detection levels of diabetes or different diabetic phenotypes, let alone drug availability, can explain such a difference. Local therapeutic convention is a plausible explanation. As described in a comparison of two neighbouring communities in Sweden [12] tradition (specialized diabetes clinician compared with non-specialist clinicians) may have major influences on both drug type and dose. Along with progressively more aggressive treatment of glycaemia, the use of cardiovascular and lipid-lowering drugs also increases with time in patients with diabetes [13]. Although the result is improvements in a number of biochemical risk factors, the relation between prescriptions and improved survival remains somewhat elusive since time-related changes are severely confounded by improved diagnostic awareness and, particularly in the case of diabetes, of recent changes in diagnostic levels of blood glucose [14].

The impact of recommendations or guidelines (more similar between countries for cardiovascular diseases) has been studied in the Euroaspire programme [15]. Among patients with coronary heart disease there appears to be room for improvement in aspects of cardiovascular prescribing if international guidelines were to be rigorously applied. For antidiabetic drugs, however, it has been shown that changes in recommendations coincide with substantial changes in drug prescription [16].

Use of drugs to prevent diabetes or to treat related diagnoses (e.g. polycystic ovary syndrome) may result in changes in prescription patterns in the future. Such changes may confound the interpretation of data on drug use. At present there is some evidence for the efficacy of metformin, troglitazone (now withdrawn), orlistat, rosiglitazone and rimonabant [17–19] on delaying the development from impaired glucose tolerance to diabetes. However, use of these drugs to prevent diabetes is not currently recommended.

Pharmacoepidemiology of Diabetes: Safety Considerations

While phase 1 and 2 trials are necessary for the demonstration of early safety in humans, phase 3 trials (randomized controlled trials) are unsurpassed in design for the demonstration of the effects of a drug on the disease course (efficacy). Post-marketing phase 4 trials vary in design; however, they are often not suited to evaluate therapeutic effects (effectiveness) in the population as a whole and long-term safety in non-selected groups of patients. Pharmacoepidemiology offers methods, retrospective but often including prospective follow-up designs, that allow for the surveillance of larger populations for longer periods. In many cases, as has recently been described for glargine, a long-acting insulin analogue, efficacy and effectiveness measurements are comparable in type and magnitude [20]. Unfortunately, safety issues have in some cases been undetected, and to some extent overlooked, as was the case for troglitazone in the late 1990s [21,22]. It should be borne in mind that well-established antidiabetic drugs such as metformin, sulphonylureas and insulin, even when used appropriately, are associated with appreciable rates of morbidity and, less frequently, mortality [23].

Diabetes-related pharmacoepidemiological research, applying state-of- the-art methodologies, may prove to be a helpful tool in choosing which drugs to prescribe. Recently we [24, 25] and others [26] have evaluated the safety of sulphonylureas by epidemiological methods. Based on preclinical evidence it was suspected that some sulphonylureas were preferable to others with respect to the main cause of mortality in type 2 diabetes, myocardial infarction. In population-based studies from Italy and Denmark similar results have shown a significantly reduced risk of myocardial infarction and mortality (relative risks being approximately 0.8) for gliclazide and glimiperide when compared with other sulphonylureas. This applies for monotherapy as well as for combination therapy when sulphonylureas are used together with antidiabetic agents from other classes. The results were unchanged by corrections for a large number of potential confounding factors, a key issue in epidemiological research that can now be met with an increasing use of detailed databases that allow simultaneous registrations of treatment, disease and

mortality data and a large number of socioeconomic parameters. The estimated number of participants in a prospective controlled trial designed to test this hypothesis would be >60,000 for a 5-year period making the performance of such a study less than likely on economic and practical grounds.

Thus, structured epidemiological surveillance of established diabetes treatments can powerfully complement more established methods used during the development of new drugs.

References

1. The IDF E-atlas. Issued at www.eatlas.idf.org by International Diabetes Federation (IDF), Avenue Emile De Mot 19, B-1000 Brussels, Belgium.
2. Beran D, Yudkin JS. Diabetes care in sub-Saharan Africa. Lancet 2006;368:1689–1695.
3. Gale EA. Dying of diabetes. Lancet 2006; 368:1626–1628.
4. Rungby J, Brock B, Schmitz O. New strategies in insulin treatment: analogues and noninvasive routes of administration. Fundam. Clin. Pharmacol. 2005; 19(2):127–132.
5. Riley S. The Diabetes Market Outlook to 2011. Business Insights Reports, 2006.
6. Papoz L. Utilization of drug sales data for the epidemiology of chronic diseases: the example of diabetes. The EURODIAB Subarea C Study Group. Epidemiology 1993;4(5):421–427.
7. Hermansen K, Fontaine P, Kukolja KK et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia. 2004;47(4):622–629.
8. Hermansen K, Bendtson I, Borch-Johnsen K et al. [Insulin pump treatment in Denmark] Ugeskr Laeger 2004;166(42):3685–3689.
9. Rathmann W, Haastert B, Roseman JM et al. Prescription drug use and costs among diabetic patients in primary health care practices in Germany. Diabetes Care. 1998;21(3):389–397.
10. IDF Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2005.
11. Melander A, Folino-Gallo P, Walley T et al. Utilisation of antihyperglycaemic drugs in ten European countries: different developments and different levels. Diabetologia 2006;49(9):2024–2029.
12. Olsson J, Lindberg G, Gottsater M et al. Differences in pharmacotherapy and in glucose control of type 2 diabetes patients in two neighbouring towns: a longitudinal population-based study. Diabetes Obes Metab. 2001;3(4):249–253.
13. Wandell PE, Brorsson B, Aberg H. Drug prescription in diabetic patients in Stockholm in 1992 and 1995 – change over time. Eur J Clin Pharmacol. 1997; 52(4):249–254.
14. Wandell PE, Gafvels C. Drug prescription in men and women with type 2 diabetes in Stockholm in 1995 and 2001: change over time. Eur J Clin Pharmacol. 2002;58(8):547–553.
15. Euroaspire II study group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries. Eur Heart J. 2001;22 554–572.
16. Stalhammar J, Berne C, Svardsudd K. Do guidelines matter? A population-based study of diabetes drug use during 20 years. Scand J Prim Health Care. 2001; 19(3):163–169.
17. Padwal R, Majumdar SR, Johnson JA et al. A systematic review of drug therapy to delay or prevent type 2 diabetes. Diabetes Care. 2005;28(3):736–744.
18. Kahn SE, Haffner SM, Heise MA et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355(23):2427–2443.
19. Scheen AJ, Finer N, Hollander P et al. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet 2006;368(9548):1660–1672.
20. Thisted H, Johnsen SP, Rungby J. An update on the long-acting insulin analogue glargine. Basic Clin Pharmacol Toxicol. 2006;99(1):1–11.
21. Gale EA. Troglitazone: the lesson that nobody learned? Diabetologia 2006;49:1–6.
22. Gale EA. Lessons from the glitazones: a story of drug development. Lancet 2001;357(9271):1870–1875.
23. Krentz AJ. Comparative safety of oral antidiabetic drugs. Expert Opinion in Drug Safety 2006; 5:827–834.
24. Thisted H, Jacobsen J, Thomsen RW et al. Use of sulphonylureas and mortality after myocardial infarction in diabetic patients: a Danish nationwide population-based study. Diabetologia 2006;490(091 Suppl. 1):57–58.
25. Johnsen SP, Monster TB, Olsen ML, Thisted H, McLaughlin JK, Sorensen HT, Lervang HH, Rungby J. Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. Am J Ther. 2006;13(2):134–40.
26. Monami M, Luzzi C, Lamanna C et al. Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. Diabetes Metab Res Rev. 2006; 22(6): 477–82.

2
New Definitions of Diabetes: Consequences

Knut Borch-Johnsen

Keywords: Diagnosis, IFG, IGT, classification, definitions.

In 1980, the World Health Organisation (WHO) ended a long phase of confusion by providing international standards for diagnosis and classification of diabetes [1]. Before this, confusion existed with respect to the glucose threshold for diagnosis of diabetes and other categories of glucose intolerance as well as the glucose load used for the oral glucose tolerance test. As always, however, new scientific data and insight combined with health political issues have led to several revisions of the diagnostic criteria and classification of patients with diabetes as well as with other categories of glucose intolerance. The first revision was made in 1985 [2], the second in 1999 [3] and most recently the third revision came out in 2006 [4] based on a collaborative effort between WHO and the International Diabetes Federation (IDF). In addition to these global definitions, national agencies like the American Diabetes Association (ADA) [5,6] as well as international organizations such as the IDF [7] have provided definitions that are not fully in accordance with the WHO definitions of diabetes, glucose intolerance and the metabolic syndrome (Table 1). This lack of concordance has not only created confusion among researchers but also among clinicians. As a consequence of the use of different diagnostic criteria, studies and trials may no longer be directly comparable as "diabetes" "IGT" or "IFG" no longer represents the same population in different studies. Finally, the fact that leading personalities within the field of diabetes have identified themselves with some definitions and not with others as the "fathers and mothers" of the different definitions has split observers and users into groups of "believers" rather than into scientific orientation.

This chapter focuses on the following questions related to definition and classification of diabetes:

- What are the criteria used to identify diagnostic thresholds for DM and impaired glucose regulation (IFG and IGT together)?
- Redefining diabetes – what are the consequences for prognosis and diagnostic tests?
- Reclassifying diabetes – how to differentiate between type 1 and type 2 diabetes?
- Establishing a third category – IFG – why and what is IFG?
- Lowering the threshold for IFG – what are the consequences?
- Open questions by 2007

What are the Criteria Used to Identify Diagnostic Thresholds for DM and Impaired Glucose Regulation (IFG and IGT Together)?

Diabetes is a disease characterised by abnormal glucose metabolism, a risk of developing microvascular complications specific to diabetes and a markedly increased risk of developing macrovascular complications. Consequently, all three elements have been used in trying to define diagnostic thresholds or cut points for diabetes.

Defining diabetes by glucose distribution: In some populations [8,9] but certainly not in all [10] the glucose distribution is bimodal, suggesting that there are distinctly different glucose distributions

TABLE 1. Changes in diagnostic criteria for diabetes and glucose intolerance (all values are plasma glucose in mmol/L).

Category		WHO 1985	WHO 1999	WHO 2006	ADA 1997	ADA 2003
Diabetes	Fasting	7.8	7.0	7.0	7.0	7.0
	2 h	11.1	11.1	11.1	11.1	11.1
Impaired Glucose Tolerance (IGT)	Fasting	<7.8	<7.0	<7.0	<7.0	<7.0
	2 h	7.8–11.0	7.8–11.0	7.8–11.0	7.8–11.0	7.8–11.0
Impaired Fasting Glycaemia (IFG)	Fasting	Not defined	6.1–6.9	6.1–6.9	6.1–6.9	5.5–6.9
	2 h	Not defined	<7.8	<7.8	Not recommended	<Not recommended
Normal (NGT)	Fasting	<7.8	<6.1	<6.1	<6.1	<5.5
	2 h	<7.8	<7.8	<7.8	<7.8	<7.8

ADA (American Diabetes Association) does not recommend the use of an oral glucose tolerance test. Consequently the use of ADA-criteria will normally not allow for identification of individuals with IGT or diabetic individuals where only the post-challenge value is abnormal.

in individuals with and without diabetes. This bimodality was an essential element in deciding on the 2-h post-OGTT cut-point for diabetes in 1980 and 1985 [1,2] with the final cut-point of 11.1 mmol/l largely based on data from the Pima Indian population in the USA. A recent analysis based on global, epidemiological data shows that bimodality is not a universal phenomenon, but furthermore in population where this is found, the actual cut-point in the bimodal distribution varies between populations. In other words, defining diagnostic threshold values for diabetes based on distributions of glucose values at the population level is not particularly helpful.

Defining diabetes by microvascular complications: The microvascular complications in the retina and the kidney are to a large extent specific to diabetes. Based on this observation the ADA expert committee in 1997 [5] was able to define thresholds for fasting and 2-h post-OGTT glucose values based on data from Egypt and the USA. This analysis led to the lowering of the fasting plasma glucose threshold from 7.8 to 7.0 mmol/L. Low numbers in the populations included, however, left this analysis with considerable uncertainty with respect to the optimal cut-point.

Defining diabetes by macrovascular complications: Although microvascular complications are only specific to diabetes, macrovascular complications remain the leading cause of death in diabetic individuals. Consequently, it has been suggested that abnormal glucose values should be defined as the glucose values in fasting and following an OGTT, which are associated with an increased risk of developing or dying from CVD (cardiovascular disease). Several publications from the DECODE-study have tried to follow this track. For fasting glucose values this analysis would support a threshold of 7.0 mmol/L while for the 2-h value there is no threshold but a continuous increase in mortality with increasing glucose value from the normal range, through the IGT range to diabetes as defined at present [11].

In conclusion none of the three approaches described here have proven to be superior in defining diabetes. Nevertheless, the use of microvascular complications still appears to be the most rational way as this is the only approach based on a feature specific to diabetes. This view was also adopted by WHO in the 2006 version of diagnostic criteria for diabetes. Thus, the focus should be on providing additional scientific data that could be helpful by conducting epidemiological surveys in individuals without previously diagnosed diabetes, where standardised screening for retinopathy using methods that can detect the very early stages of retinopathy are included as part of the study.

Redefining Diabetes – What are the Consequences for Prognosis and Diagnostic Tests?

Following the change in diagnostic threshold for diabetes by ADA in 1997, a large range of studies analysed the potential consequences of changing the diagnostic criteria for diabetes. The largest and

most systematic effort was done through the DECODE-study initiated under the European Diabetes Epidemiology Study Group [12]. This collaborative effort used population-based epidemiological studies of diabetes based on the use of a standard 75-g oral glucose tolerance test from a large number of centres in Europe to analyse the effect of revising the diagnostic criteria. Most of the publications are based on data from between 25,000 and up to 50,000 individuals.

The first DECODE-publication [12] clearly showed that there is only a partial overlap between individuals diagnosed based on the revised fasting glucose criteria and those diagnosed on the basis of the 2-h post-challenge value. Approximately 1/3 are diagnosed by the fasting value only, 1/3 by the 2-h value only and the remaining 1/3 are diabetic based on both the fasting and the 2-h value. The same study demonstrated some phenotypic differences between those diagnosed based on the fasting and those diagnosed based on the 2-h value. Those with diabetic fasting values only tended to be younger and more obese than those diagnosed based on the 2-h value.

As the two groups were different in phenotype, the emerging question was whether this had an impact on prognosis [13]. As demonstrated in Table 2 the 2-h post-OGTT glucose value was more strongly associated with prognosis (all cause mortality and death from CVD) than fasting plasma glucose, and individuals with diabetic fasting, but normal post-OGTT values, did not have any excess mortality at all.

These studies were the first to challenge the concept that the more convenient diagnosis based on fasting glucose values equalises the more complicated diagnosis based on the oral glucose tolerance test. The observations were, however, confirmed by others, and this was the rationale for WHO in modifying the diagnostic criteria in 1999, where WHO in contrast to the ADA recommended the use of the oral glucose tolerance test in epidemiological surveys as well as in the diagnosis of diabetes in individuals at high risk based on the fasting plasma glucose.

In conclusion, the revised diagnostic criteria for diabetes, suggested by ADA in 1997 and subsequently confirmed with minor modification by WHO in 1999, increased the number of individuals with diabetes to a moderate extent. They identified a fasting plasma glucose level that statistically (but not necessarily clinically) corresponded better to the diagnostic 2-h value, but initiated studies that clearly demonstrated that the prognostic impact of fasting versus 2-h post-challenge glucose is not identical.

Reclassifying Diabetes – How to Differentiate Between Type 1 and Type 2 Diabetes

So far the focus on the 1997 ADA and 1999 WHO revision of the diagnostic criteria has been on the impact of the revised diagnostic thresholds. Another often neglected but equally (or even more) important revision relates to the classification of patients. In 1985, patients were classified as having insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetes based on the underlying disease, that is, whether beta-cell dysfunction was reduced to a level where insulin was needed to survive without entering ketoacidosis (insulin-dependent diabetes) or whether the patient had diabetes based on insulin resistance (with or without associated beta-cell dysfunction) where the patient would survive without insulin, but where insulin could be necessary to maintain acceptable metabolic

TABLE 2. All cause excess mortality by fasting and 2 hour glucose in the DECODE study (Adopted from ref 11).

		Fasting plasma glucos (mmol/L)			
		≤6.1	6.1–6.9	7.0–7.7	≥7.0
2-h plasma glucose (mmol/L)	≤7.7	1	1.1	1.4	1.4
	7.8–11.0	1.6	1.3	1.7	1.7
	≥11.1	2.1	1.9	2.2	2.3

control. From 1985 and onwards several clinical studies [14] as well as practical clinical experience demonstrated that a large proportion of patients characterised as non-insulin dependent would subsequently need insulin to maintain acceptable metabolic control. This often led to confusion with respect to classification of the individual patient, and increasingly patients were re-classified from NIDDM to IDDM. This clinical observation combined with a wish to establish a classification based on a combination of clinical stages and aetiological types [15] led WHO to abandon the terms IDDM and NIDDM and to reintroduce the terms Type 1 and Type 2 diabetes. This development was helped by the identification of several markers of autoimmunity linked to the destruction of beta cells such as islet cell antibodies (ICA), insulin auto- antibodies (IAA) and auto-antibodies to glutamic acid decarboxylase (anti-GAD). Consequently, the revised classification included as the two main groups

- Type 1 diabetes (beta-cell destruction, usually leading to absolute insulin deficiency). In this group 85–90% are antibody positive for at least one of the antibodies ICA, IAA or GAD, while a smaller group (10–15%) have total beta-cell destruction without any signs of autoimmunity. Within the group of patients with type 1 diabetes there is a smaller group that have antibodies, but are not insulin-requiring for survival at least for several years. These patients are characterised by a slower disease process and very slow loss of beta-cell function and this group is often referred to as latent autoimmune diabetes in adults (LADA).
- Type 2 diabetes (predominantly insulin resistant with relative insulin deficiency or predominantly an insulin-secretory defect with/without insulin resistance). These individuals consequently have a relative not an absolute insulin deficiency. At the same time this group of individuals have no other known specific aetiology. At present this group comprises 70–80% of all cases of diabetes (even more in some parts of the world), but given the fact that molecular biology combined with other scientific disciplines continuously identifies an increasing number of "specific types" this group will gradually diminish. Apart from this the specific types will not be discussed further in this chapter.

One problem related to the change in classification to an aetiological definition is that the diagnosis of a so-called type 1 process is based on measurement of autoimmune markers, which is not a part of routine clinical practice, and markers that currently have none or very limited impact on the treatment regiment for the individual patient. As a consequence of this, a patient with diabetes with considerable residual beta-cell mass and obviously not insulin requiring from a clinical point of view, but with an ongoing autoimmune process, will be diagnosed as having type 2 diabetes unless admitted to a centre where measurement of auto-antibodies for some reason (typical research) is a part of routine clinical practice. In this case, in real life, the classification of the patient would therefore reflect the centre at which the patient is treated, not the underlying disease process. This would clinically be a minor problem, but with 5–15% of patients with type 2 diabetes being antibody positive, and given that treatment guidelines differ and type 1 diabetes patients are treated centrally while type 2 diabetic patients are treated in general practice, this would have tremendous impact on the organisation of the health care system if all patients had antibodies measured and subsequently were remitted accordingly.

Another problem that has not been solved is that even in the general population with normal glucose tolerance following an OGTT 2–5% are antibody positive [16,17]. This would suggest that some antibody positive individuals with clinical T2DM are truly type 2 diabetic where antibody positivity reflects a "by chance finding" and not necessarily an ongoing autoimmune disease process.

Establishing a Third Category – IFG – Why and What is IFG?

The new category – Impaired Fasting Glycaemia – was introduced by the ADA expert committee in 1997. This was in many ways the logical consequence of their recommendation to stop using the OGTT, as this would make the diagnosis of IGT impossible. The hope was that through establishing the new category IFG it would be possible to identify a group comparable to the IGT with respect to risk of progression to diabetes and risk of developing CVD.

As already discussed, the DECODE-study showed that while IGT is associated with an increased risk of developing CVD this is only the case in IFG-individuals if they also have abnormal 2-h glucose values [11,13]. In other words, isolated IFG is not associated with increased risk of CVD or increased all cause mortality. It has also been shown that while IGT is often associated with other abnormalities associated with the metabolic syndrome as dyslipidemia and hypertension, this is not the case for isolated IFG (at least not to the same extent) [18].

The different phenotypes of individuals with IFG and IGT have led to the question whether these two conditions reflect the same underlying pathogenic mechanisms. An answer to this question is important, as several trials have shown that progression from IGT to diabetes can be prevented by life style intervention (diet and physical activity) [19–22]. These interventions are likely to exhibit their effects through increased insulin sensitivity and modifications in body composition. Consequently, the interventions are only likely to be effective in the case of insulin resistance as the underlying mechanism. If, however, IFG is more linked to beta-cell dysfunction than to insulin resistance (which would be in compliance with the relative absence of metabolic abnormalities in IFG-individuals), then life style intervention would be less likely to have an effect on this group of individuals. It should also be noted that IFG only identifies approximately 25–30% of all individuals with IGT in a given population. In conclusion it should therefore be noted that IFG and IGT are not the same conditions; they are not characterised by the same phenotypic abnormalities; and they are not associated with the same risk of progression to diabetes or risk of developing CVD. Therefore, the clinical relevance of IFG as a clinical category or risk group remains questionable.

Lowering the Threshold for IFG – What are the Consequences?

The most recent revision of the diagnostic criteria for IFG by ADA [6] lowered the diagnostic threshold for IFG 6.1–5.6, so now the diagnostic interval for IFG according to ADA is 5.6–6.9. The major reason for redefining IFG was an attempt to improve the alignment of IFG and the corresponding intermediate category based on the oral glucose tolerance test [impaired glucose tolerance (IGT)] in predicting the future development of type 2 diabetes. The proposed new diagnostic threshold is derived from receiver–operator characteristic curves of the different levels of fasting plasma glucose that predict the development of diabetes. The optimal cut-point (optimising the sum of sensitivity and specificity) was between 5.2 and 5.7 mmol/L [6]. A secondary, but equally important consideration was to increase the proportion of individuals with IGT identified as having IFG. With the previous definition (6.1–6.9) [18] only 29% of individuals with IGT also have IFG. Lowering the diagnostic threshold to 5.5 mmol/L would increase this proportion to 69%. Identification of patients with IGT is important from the perspective of preventive medicine, as this is the group where intervention studies have proven effective in preventing progression to diabetes as discussed above [19–22].

We used the DETECT-2 database [23] to analyse the consequences of change in diagnostic criteria on concordance between IFG and IGT, on the CVD-risk profile in individuals with IFG and on the public-health impact of modifying the diagnostic criteria [24]. We analysed the impact on concordance based on populations from Denmark, France, USA, India and China. In these countries the prevalence of IGT was 12.0, 8.2, 20.3, 11.2 and 10.3%, respectively, and based on the old criteria for IFG only 3.5, 3.5, 4.4, 3.0 and 2.8% were IGT and IFG positive. As indicated above, one aim was to increase the fraction of IGT individuals identified through IFG, and this was a success as the prevalence of combined IGT and IFG positivity based on the new criteria increased to 7.2, 6.1, 9.4, 7.2 and 5.2%, respectively, in the five countries. However, everything comes with a price. The increased probability of identifying individuals with IFG was only possible because the prevalence of IFG increased dramatically from 11% to 16% with the old criteria to 29–46% with the new criteria. Consequently, the probability of an individual with IFG also having IGT decreased from approximately 27% to 20%. As expected, the cardiovascular risk profile is even less atherogenic in individuals classified as IFG based on the new diagnostic criteria from ADA, as illustrated in Table 3 based on data from the Inter99 study from Denmark [24,25].

TABLE 3. The cardiovascular risk profile according to the diagnostic criteria in the Inter99 population [24] (from ref [24]).

	IFG_old (6.1–6.9 mmol/L)	IFG new (5.6–6.0 mmol/L)	*p*-value
N	1,645	788	
% Women	29.6	38.4	<0.0001
Age	49.4(6.8)	47.4(7.4)	<0.0001
SBP (mmHg)	139.5(17.4)	133.1(15.8)	<0.0001
DBP (mmHg)	88.0(11.4)	84.4(10.6)	<0.0001
Total-cholesterol (mmol/L)	5.9(1.2)	5.7(1.1)	<0.0001
HDL-cholesterol (mmol/L)	1.3(0.4)	1.4(0.4)	0.002
Triglyceride[a] (mmol/L)	1.5(0.6)	1.2(0.5)	<0.0001
Fasting insulin (pmol/L)	47.0(0.6)	37.8(0.5)	<0.0001
2-h insulin (pmol/L)	211.2(0.9)	160.1(0.9)	<0.0001
BMI (kg/m^2)	28.4(4.8)	27.0(4.4)	<0.0001
Waist (cm)	94.6(12.3)	90.0(12.1)	<0.0001
% daily smoker	64.4	64.5	N.S

Values are mean (SD), where stated percentage are given.
[a]Values are geometric means and coefficient of variation.

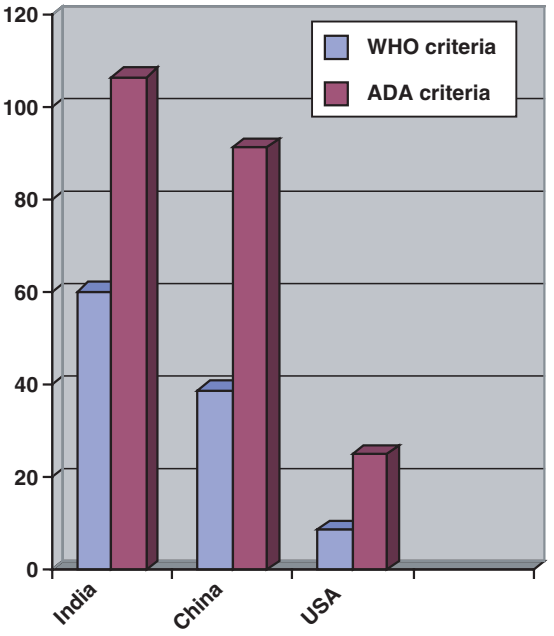

FIG. 1. Number of individuals with IFG in India, China and USA in the age group 45–64 years based on the WHO and ADA diagnostic criteria for IFG by 2005 (based on the DETECT-s study (modified from [24])).

The public health impact of the ADA-revision of the diagnostic criteria is illustrated in Fig. 1. We used population-based studies from India, China and USA and the demographic data from WHO for these three countries to illustrate the effect by calculating the number of individuals in the age group of 45–64 years that would have IFG based on the WHO and ADA criteria, respectively. The effect was dramatic in all three countries leaving the number of individuals characterised as having IFG so high that any possibility of individual-based prevention programme would seem impossible to even think of.

In conclusion, from this part of the chapter the revised diagnostic criteria for IFG seem to have limited relevance. The additional individuals identified by the revised criteria seem to be at low risk of developing CVD; they have lower probability of also having IGT and meanwhile the overall number of individuals diagnosed as having IFG will be double to triple. All together this explains why WHO did not follow ADA in their 2006 version of diagnostic criteria for diabetes and impaired glucose regulation [4].

Open Questions by 2007

With the recent publication from WHO and IDF on definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia [4], a natural question could be – have we now reached the end of the road? Unfortunately, the only possible answer is a no. Science is progressing, and as part of this, our understanding of the underlying aetiology and pathogenic mechanisms behind abnormalities in

glucose metabolism will improve. Definition and classification of diseases must (or at least should) always be following progress in our understanding of the disease aetiology. When it comes to definition and classification of diabetes there are a number of open questions.

1. Could the diagnosis of diabetes be simplified? This was the intention of the ADA-recommendation in 1997, where they recommended discontinuation of the logistically complicated and time-consuming oral glucose tolerance test and recommended that all diagnostic tests should be based on fasting glucose. Unfortunately, this strategy did not fulfil its aim, and consequently the WHO retained the OGTT. An alternative would be to replace the diagnosis based on fasting plasma glucose or the OGTT with a diagnosis based on HbA_{1c} as it reflects the average plasma glucose over a period of 2–3 months and as it does not require any special preparation such as fasting. HbA_{1c} is associated with the risk of retinopathy in the same manner as fasting or 2-h glucose [5] and is associated with the risk of developing CVD even in the non-diabetic range [26]. There is, however, still a considerable variability dependent on the laboratory method used although standardisation is ongoing [27], and the association between HbA_{1c} and the category of normal or impaired glucose metabolism is not clear-cut [28]. If the diagnosis was to be made on HbA_{1c} and not on glucose, this would clearly lead to the reclassification of individuals and it would require global standardisation of the method. Consequently, this change will not happen in the near future, but it may happen in the more distant future.
2. Should intermediate hyperglycaemia (IFG and IGT) be redefined? As outlined above, the rationale for maintaining IFG as a separate category is somewhat weak. On the other hand, there is a need for identifying individuals at high risk of developing diabetes with the aim of initiating targeted intervention in these. At present little is known with respect to the underlying mechanisms behind IFG and IGT, but several studies are ongoing. These studies will tell us whether we will need this category also in the future.
3. How should patients with auto-antibodies (anti-GAD in particular) be classified? According to the 1999 WHO classification, all these individuals are expected to have an ongoing type 1 process classifying them as having type 1 diabetes independent of the actual glucose levels. From a scientific point of view this seems rational, but in practice this creates confusion. If the principle was followed rigorously then up to 10–15% of all current type 2 diabetic patients should probably be reclassified, almost doubling the pool of patients classified as having type 1 diabetes. Generally, patients with type 1 diabetes are treated in specialised centres but would that be relevant for all patients now classified as having type 1 diabetes and what would be the correct treatment for these patients to preserve their residual beta-cell function. All these answers are presently unanswered and call for further studies leading to clarification and ultimately to new classification guidelines.

References

1. WHO Expert Committee on Diabetes Mellitus. Second Report. Technical Report Series 646. Geneva: WHO, 1980.
2. World Health Organization Study Group. Diabetes Mellitus. WHO Technical Report Series 727. Geneva: WHO, 1985.
3. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: Diagnosis and classification of diabetes mellitus. Geneva: WHO, 1999.
4. World Health Organization. Definition and diagnosis of diabetes mellitus an intermediate hyperglycaemia. Report of a WHO/IDF Consultation. Geneva: WHO, 2006.
5. The Expert Committee on the diagnosis and classification of diabetes mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1997;20:1183–1197.
6. The Expert Committee on the diagnosis and classification of diabetes mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003; 26:3160–3167.
7. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome-a new worldwide definition. *Lancet* 2005; 366:1059–1062.
8. Rusforth NB, Bennett PH, Steinberg AG, nBurch TA, Miller M. Diabetes in the Pima Indians: evidence of bimodality in glucose tolerance distributions. *Diabetes* 1971;20:756–65.

9. Lim T-O, Bakri R, Morad Z, Hamid MA. Bimodality in blood glucose distribution. Is it universal? *Diabetes Care* 2002;25:2212–2217.
10. Borch-Johnsen K, Colagiuri S, Vistisen D on behalf of the DETECT-2 collaboration. Is there a bimodal distribution of plasma glucose. American Diabetes Association Annual Scientific Meeting, 2006, *Diabetes* 2006;55(Suppl. 1):A19, Abstract 77.
11. The DECODE Study Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Archives of Internal Medicine* 2001;161:397–405.
12. DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group. Will new diagnostic criteria for diabetes mellitus change the phenotype of patients with diabetes? British Medical Journal 1998;317:371–375.
13. DECODE-Study Group. Glucose tolerance and mortality. Comparison of the WHO and ADA diagnostic criteria. *Lancet* 1999;354(9179):617–621.
14. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999;281:2005–2012.
15. Kuzuya T, Matsuda A. Classification of diabetes on the basis of etiologies versus the degree of insulin deficiency. *Diabetes Care* 1997;20:219–220.
16. Bosi EP, Garancini MP, Poggiali F, Bonifacio E, Gallus G: Low prevalence of islet autoimmunity in adult diabetes and low predictive value of islet auto antibodies in the general adult population of northern Italy. *Diabetologia* 1999;42:840–844.
17. Ruige JB, Batstra MR, Aanstoot HJ, Bouter LM, Bruining GJ, De Neeling JN, Heine RJ: Low prevalence of antibodies to GAD65 in a 50- to 74-year-old general Dutch population. The Hoorn Study. *Diabetes Care*, 1997;20:1108–1110.
18. DECODE Study Group. Is fasting glucose sufficient to define diabetes? Epidemiological data from 20 European studies. *Diabetologia* 1999;42:647–654.
19. Pan X, Li G, Hu Y-H, Wang J, Yang W, An Z et al. Effects of diet and exercise in preventing NIDDM in people with Impaired Glukose Tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997;20:537–544.
20. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New English Journal of Medicine* 2001;344:1343–1350.
21. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA et al. Reduction of the incidence of type 2 diabetes with lifestyle intervention or metformin. *New English Journal of Medicine* 2002;346;393–403.
22. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. *Lancet* 2002;359:2072–2077.
23. Glümer C, Vistisen D, Borch-Johnsen K, Colagiuri S; DETECT-2 Collaboration. Risk scores for type 2 diabetes can be applied in some populations but not all. *Diabetes Care* 2006(Feb);29(2):410–414.
24. Borch-Johnsen K, Colagiuri S, Balkau B, Glümer C, Carstensen B, Ramachandran A, Dong Y, Gao W. Creating a pandemic of prediabetes: the proposed new diagnostic criteria for impaired fasting glycaemia. *Diabetologia* 2004;47:1396–1402.
25. Glümer C, Jørgensen T, Borch-Johnsen K. Prevalence of diabetes and impaired glucose regulation in a Danish population – The Inter99 study. *Diabetes Care* 2003;26(8):2335–2340.
26. Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N. Glycated haemoglobin, diabetes and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). British Medical Journal 2001;322:15–18.
27. Jeppsson JO, Kobold U, Barr J, Finke A, Hoelzel W, Hoshino T, Miedema K, Mosca A, Mauri P, Paroni R, Thienpont L, Umemoto M, Weykamp C. Approved IFCC reference method for the measurement of HbA1c in human blood. Clinical Chemistry and Laboratory Medicine, 2002;40:78–89.
28. Davidson MB, Schriger DL, Peters AL, Lorber B. Relationship between fasting plasma glucose and glycosylated haemoglobin: Potential for false-positive diagnoses of type 2 diabetes using new diagnostic criteria. *JAMA*, 1999;281:1203–1210.

Section: Pharmacotherapy of Diabetes