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WorldWIDE
Worldwide Initiative for Diabetes Education

WorldWIDE news

WorldWIDE — Worldwise: A Message From the Chairman

On behalf of the WorldWIDE group, welcome to the first issue of WorldWIDE News.

WorldWIDE — Worldwide Initiative for Diabetes Education — was established in the Autumn of 2000 with the aim of enhancing professional education on diabetes through the provision of practical, clinically relevant information. There is an urgent need for improved care of patients with diabetes: the incidence of diabetes is increasing; care has become complex and there is a need for simple, clear information on best clinical practice. WorldWIDE will identify topics for review that we feel will be of interest to specialist diabetologists, general physicians and diabetes educators. Articles and teaching materials on these topics will be made available in formats such as CD-ROM and newsletters and will be available on our website to be launched in the late Summer of 2001. Through WorldWIDE we hope to engender a desire to find out more about diabetes and its treatment and build a network of professionals willing to share their experiences and practices.

I hope that you will find this newsletter useful and will follow the development of this new education initiative with interest. We would welcome your suggestions on topics for WorldWIDE coverage and look forward to your feedback.

Philip Home

Inaugural WorldWIDE Meeting

The inaugural meeting of the WorldWIDE group, chaired by Professor Philip Home, was held in London on 12 October 2000 and included diabetes healthcare professionals from all over the world (see below) who believe that there is an urgent need for new approaches to professional education in diabetes.

Professor Andrew Boulton
Manchester Royal Infirmary
Manchester, UK

Professor Antonio Chacra
University Federal de São Paulo, São Paulo, Brazil

Dr Juliana C N Chan
The Chinese University of Hong Kong
Shatin, Hong Kong

Dr Tim Dornan
Hope Hospital
Salford, UK

Professor Robert Heine
Vrije Universiteit
Amsterdam
The Netherlands

Professor Philip Home
University of
Newcastle upon Tyne
Newcastle upon Tyne, UK

Professor Jorge Jimenez
National University
of Asunción
Asunción, Paraguay

Professor Ryuzo Kawamori
Juntendo University School
of Medicine, Tokyo, Japan

Professor Massimo Massi-Benedetti
University of Perugia
Perugia, Italy

Professor Carl-Erik Mogensen
Aarhus Kommunehospital
Aarhus, Denmark

Professor Jens Sandahl Christiansen
Aarhus University Hospital
Aarhus, Denmark

Professor Jay Skyler
University of Miami
Miami, Florida, USA

Ms Lea Sorensen
Royal Prince Alfred Hospital
Camperdown, New South Wales, Australia

Dr Luigi Uccioli
University of Rome
Tor Vergata, Rome, Italy

Inaugural WorldWIDE Meeting (Continued)

Professor Philip Home introduced the aims of WorldWIDE. Although several large studies have shown the need for improved glycaemic control in patients with diabetes, goals for glycaemic control are not being met. Part of the explanation is that clinical practice has not changed sufficiently in response to these findings. The WorldWIDE group felt that the most urgently required and effective solution was greater education of professionals dealing with patients with diabetes. Although there is a vast and rapidly expanding resource of information available on diabetes, it may not be of practical use to the busy physician. Concerted and novel approaches to education are needed in order to make the most of this information.

Professor Andrew Boulton (UK) gave an overview of educational activities organised under his chairmanship by the Postgraduate Education Subcommittee of the EASD. Dr Tim Dornan (UK) then presented an analysis of the nature of successful professional education, and modern approaches to harnessing this in educational activities. In the discussion following these presentations, all members of WorldWIDE agreed that the old 'didactic' approach to education was now established as being less successful than methods in which participants actively take part. The desired outcome of medical education is a change in practice, making use of new understandings rather than just absorbing them.

I hear and I forget
I see and I remember
I do and I understand
Chinese proverb

WorldWIDE Facts

HbA_{1c} is a parameter that is used worldwide to monitor diabetes, but do you know the background to its use?

An 'abnormal' haemoglobin in the blood of people with diabetes was first reported in 1968 (Rajbar, Clin Chim Acta 1968;**22**:296–298) and has become a useful tool in monitoring blood glucose levels.

In adults there are two main types of haemoglobin (Hb): HbA_1 and HbA_2. HbA_1 comprises two α subunits and two β subunits and is the predominant form (97%) normally found in adults. HbA_2, which consists of two α and two δ subunits, accounts for approximately 2% of the haemoglobin in adults. A non-enzymatic reaction between the free amino groups of haemoglobin and hexose sugars can form glycated haemoglobin inside red blood cells. Binding of hexoses to HbA produces several different glycated haemoglobin classes including HbA_{1a1}, HbA_{1a2}, HbA_{1b}, HbA_{1c} and HbA_{1d}. Of these, HbA_{1c} is the most useful to measure as it is the main subfraction and is both stable and reflective of blood glucose levels.

The rate at which HbA_{1c} is formed depends only on the concentrations of glucose and haemoglobin in the blood. The reaction is irreversible and the HbA_{1c} formed lasts for the remaining lifetime of the red blood cell. Measuring HbA_{1c} therefore gives a guide to how high the blood glucose level has been over the past 2–3 months. HbA_{1c} is given as a percentage of the total haemoglobin and the DCCT-standardised, non-diabetic range is given as 4.0–6.0%. Measuring HbA_{1c} is not a substitute for measuring plasma glucose levels at different times of the day, but gives an idea of how high (and low) glucose levels have been over the past few weeks. An HbA_{1c} level of 7.0 % is approximately equivalent to an average plasma glucose level of 8.3 mmol/L (150 mg/dL).

Glycated haemoglobin estimation is not reliable when erythrocyte turnover is abnormal, and can be difficult to measure when abnormal haemoglobins are present.

You have probably heard of fructosamine. This measures the level of glycated proteins (mainly albumin) in the blood and reflects blood glucose levels over the previous 2–3 weeks, but again will change if protein turnover is abnormal.

ADA recommendations

The ADA recommends measuring HbA_{1c} twice per year for all people with diabetes, and four times per year for those who require insulin injections or whose blood glucose levels are not well controlled

If you would like to find out more about WorldWIDE and to be added to the mailing list please contact:

worldwide@adelphi.co.uk

Landmark Studies in Diabetes

Several pivotal studies have been published in the last few years which have radically changed the way that we think about managing diabetes. However, despite acknowledging the fact that improved glycaemic control leads to decreased risk of diabetic complications, in general glycaemic control has not improved since the results of the studies were published. Although such studies are criticised as not being reflective of the conditions found in general practice, the messages from the studies remain relevant to all of us involved in treating patients with diabetes — there is a correlation between good glycaemic control and reduced incidence of complications, and any improvement in glycaemic control is highly beneficial. Notably, epidemiological analyses of the two major studies — DCCT and UKPDS — have recently been published. Here we review the main findings of the UKPDS.

UKPDS — the trial and the epidemiology

Study design — a résumé

The UKPDS was a randomised, controlled trial conducted in 23 centres in the UK (references 1–4). Between 1977 and 1991, over 5000 patients with newly diagnosed type 2 diabetes were recruited. Of these, 3867 entered the glucose control arm of the study and were randomised in a ratio of 70:30 to receive 'intensive' or 'conventional' therapy. Conventional therapy was initially diet alone, with implementation of non-intensive pharmacological therapy if marked hyperglycaemia ensued. The goal of conventional therapy was to maintain the fasting plasma glucose (FPG) level below 15.0 mmol/L (270 mg/dL). In contrast, intensive therapy aimed to keep the FPG level below 6.0 mmol/L (110 mg/dL). The treatment used in this group was metformin (in a subset of overweight patients), sulphonylurea or insulin. If treatment with sulphonylurea did not achieve the treatment goal, then metformin or insulin was added.

Findings

Patients were followed for a median 10 years.
The results are summarised below (see reference 1 for full results):

- The median HbA_{1c} levels were significantly lower in the intensively treated group, compared with the conventionally treated group. All therapies in the intensive treatment arm were equally effective in reducing HbA_{1c}.
- There was no evidence of a harmful cardiovascular effect with sulphonylurea or insulin treatment.
- Complications were reduced in the intensively treated group compared with the conventionally treated group:

Endpoint	Reduction
Any diabetes-related endpoint	12%*
Microvascular endpoints	25%*
Myocardial infarction	16%
Cataract extraction	24%*
Retinopathy (at 12 years of follow up)	21%*
Albuminuria (at 12 years of follow up)	33%*

*Statistically significant

- The study also showed a progressive deterioration in β-cell function. When this was extrapolated back to determine when β-cell function had started to deteriorate, the results showed that by the time patients are diagnosed, their β-cell function may have deteriorated by 50%, a process that could have started up to 12 years prior to diagnosis.

In addition, an epidemiological analysis of the results (reference 3) has demonstrated a clear linear relationship between the risk of complications and HbA_{1c} level.

For each 1.0% decrease in HbA_{1c}, the following risk reductions occur:

Amputation or death from peripheral vascular disease	43%
Microvascular complications‡	37%
Any diabetes-related endpoint	21%
Diabetes-related deaths	21%
Cataract extraction	19%
Heart failure	16%
All-cause mortality	14%
Fatal and non-fatal myocardial infarction	14%
Fatal and non-fatal stroke	12%

‡Retinopathy requiring photocoagulation, vitreous haemorrhage, and fatal or non-fatal renal failure

No lower threshold was observed to exist for any of the clinical endpoints.

Conclusion

There is a clear association between hyperglycaemia and the risk of diabetic complications in people with type 2 diabetes. The lower the HbA_{1c} level, the lower the risk. Any reduction in HbA_{1c} is beneficial in people with type 2 diabetes.

A 37% decrease in the risk of microvascular complications was observed per 1.0% decrease in HbA_{1c}

A full list of publications by the UKPDS group, together with background information on the UKPDS, a summary of the main results and the official slide set, can be found at

www.dtu.ox.ac.uk/ukpds

UKPDS — Some Answers, But More New Questions!

A commentary by Dr Paul Van Crombrugge

The UKPDS (references 1–4) is a landmark study in the field of diabetes. Few studies have provided so many clear conclusions with practical relevance for diabetes care. However, as a clinician, I still have many questions:

- The stepwise therapeutic additive approach used in this study makes it difficult to translate these results into a practical strategy, taking into account the many pharmacological drugs available at present.
- Type 2 diabetes is a very heterogeneous disease (obese/lean, latent autoimmune diabetes in adults [LADA], insulin resistance/insulin underproduction). It is likely that these subgroups will respond differently to treatment. This needs to be studied in future trials.
- It is a pity that the obvious beneficial results of blood pressure intervention observed in this trial on macro- and microvascular complications have led many physicians to conclude that blood glucose control in people with diabetes is only of secondary importance. What these colleagues have not realised is that the blood pressure study was conducted in a subgroup with a markedly higher risk for complications. The observational data (Figure 1) clearly demonstrate that both items are important.
- Metformin is known to lower blood glucose in obese and non-obese subjects. A study arm with metformin as monotherapy in non-obese patients would be very interesting, but was not included in the UKPDS study.
- I am eager to learn the effect of lipid intervention in this trial, a third factor of extreme importance in the development of complications. A relevant study is in progress.
- How should we transpose the findings of this study to other patient groups that we encounter frequently in our practice: children, older patients, patients with a long history of diabetes, patients who already have serious complications...?

As usual, good studies provide many strong answers, but also generate exciting questions.

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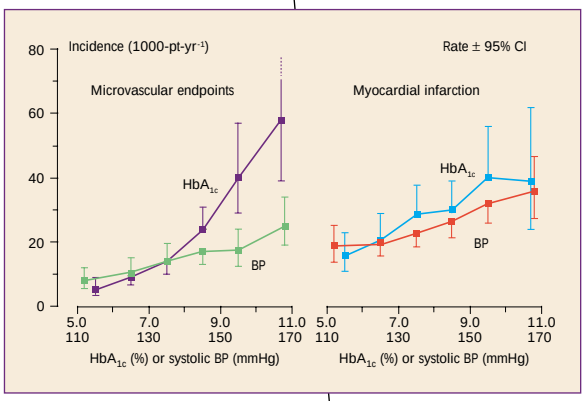

Figure 1. Relationship between endpoints and HbA_{1c} or blood pressure in the UKPDS. (P Home, personal communication; adapted from references 3 and 4).

Response by Dr Amanda Ingham Adler

Dr Van Crombrugge has acknowledged the importance of the UKPDS trial, and wonders whether the UKPDS generated "some answers but more new questions". If true, this is not necessarily bad. Yet more pertinent is whether the UKPDS answered its predefined research questions: whether control of blood glucose and blood pressure lowers the risk of complications in type 2 diabetes, and whether this differs by treatment. In this sense, the UKPDS not only succeeded in answering these questions, but showed that intervention makes a difference. Since trials can incorporate only those treatments which exist at the time of planning, it is only to be expected that the longer the trial — 20 years for the UKPDS — the greater the number of new therapies and unanswered questions that would arise.

Of the questions inspired by the UKPDS, those identified by Dr Van Crombrugge are among the most pertinent. Not only would it be interesting to learn if metformin alters the risk of complications in non-obese individuals with diabetes, but also in individuals with glucose intolerance who are not yet diabetic, particularly since the UKPDS strongly suggested that metformin was associated with a reduction in complications independent of glycaemia. The Diabetes Prevention Program in the USA will help answer this question. The UKPDS did not include randomisation to lipid-lowering therapy, and hence could not report it. To even describe the course of patients was not possible since only a very small percentage of patients in the UKPDS happened to be on lipid-lowering therapy. Conversely, the Lipids in Diabetes Study run by the Diabetes Trials Unit in Oxford is a randomised controlled trial currently enrolling 5000 patients. It aims to address whether patients who are not hypercholesterolaemic, yet — because of type 2 diabetes — have a high cardiovascular risk, may benefit from lipid lowering.

Dr Van Crombrugge has identified the prevailing sentiment among some diabetologists that blood glucose control is of "secondary importance". This would be true if resource permitted only one line of therapy. Indeed, the effects of blood glucose and blood pressure control are additive. Also, while blood glucose intervention, unlike blood pressure control, appears to do little if anything to alter the risk of stroke, it did significantly reduce the risk of microvascular complications. As a physician cannot know which complication(s) a patient will develop, both blood glucose and blood pressure must be treated.

Dr Amanda Ingham Adler
Principal Investigator, UKPDS
Diabetes Trials Unit
Oxford, UK

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