UNIT NO. 3

DIABETES MELLITUS AND OPTIMISING CARDIOVASCULAR OUTCOMES

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ABSTRACT

In the last two decades, data has accumulated to convince the medical community that treating diabetes does not mean treating only glycaemia, but all of the condition's attending cardiovascular risk factors as well. This multi-pronged approach acquires particular urgency in type 2 diabetes, but is no less important in type 1 diabetes as well. Both epidemiological and prospective data show that reducing the risk of myocardial infarction, stroke and peripheral vascular disease requires the treatment of, not only glycemia, but also treating other cardiovascular risk factors.

KEYWORDS: Diabetes Mellitus, Cardiovascular, coronary heart disease, outcomes

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INTRODUCTION

The management of diabetes mellitus as we know it today has come a long way. In 2010, when we recount the recent milestones in the history of diabetes treatment, we would almost certainly include the exciting 1993 discovery of the IDX-1 gene that we now know is a master regulator of pancreas development and a key controller of insulin gene expression as well as, in that same year, the first definitive proof of the benefits of intensive therapy to prevent complications in type 1 diabetes.

But in the last two decades, data has accumulated to convince the medical community that treating diabetes does not mean treating only glycaemia, but all of the condition's attending cardiovascular risk factors as well. This multi-pronged approach acquires particular urgency in type 2 diabetes, but is no less important in type 1 diabetes as well.

Although the diagnosis of type 2 diabetes mellitus is made when blood glucose levels exceed values which increase the risk of microvascular complications, macrovascular disease is the major scourge of type 2 diabetes mellitus. Both epidemiological and prospective data show that reducing the risk of myocardial infarction, stroke and peripheral vascular disease requires the treatment of not only glycaemia, but also treating the other cardiovascular risk factors as well. In recent years, data from intervention trials have suggested that benefits with respect to the prevention of macrovascular disease can be achieved by effective treatment of hypertension and hypercholesterolaemia, and by the use of small doses of aspirin.

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The first diabetic person was treated in 1922 with insulin. From 1955, oral drugs were introduced to help lower blood glucose levels. This was followed in the succeeding decades by a systematization of diabetes care, leading to the formation of diabetes support associations, diabetes care teams involving doctors, dieticians, and diabetes nurse educators. Then came the emergence of home glucose monitoring devices in the 1960s, and the information explosion from evidence-based medicine, clinical trials and basic research that we are familiar with today.

ATHEROSCLEROSIS IN DIABETES

Atherosclerosis-related disease accounts for 80% of all diabetic mortality. 75% of all diabetic mortality is caused by coronary heart disease, while stroke and peripheral vascular disease make up the remaining 25%.

The MRFIT study shows that in the presence of diabetes, the effect of other risk factors on cardiovascular (CV) death rates is amplified. The same study offered the first large scale data to demonstrate that total cholesterol predicts coronary heart disease (CHD) mortality, and that CHD mortality rates in diabetic men are 2 to 3 times those in non-diabetic men.

Additionally, The MRFIT study showed a continuous relationship between risk of coronary artery disease and cholesterol down to at least 3.0 mmol/L and perhaps further. It was also able to show that therapy is perhaps more important in higher risk groups, for example diabetics. For ten years of reduction there was about a 30% reduction in the disease levels.

Cardiovascular mortality is increased in relation to impaired glucose tolerance ("prediabetes") and increases even further once diabetes has developed. The evidence for this is found in the DECODE study, among others.

DYSLIPIDAEMIA IN TYPE 2 DIABETES

In type 2 diabetes, the pathognomonic lipid abnormality is increased serum triglycerides, increased VLDL, increased small dense LDL, increased apo B lipoprotein, and decreased HDL. Apo A-1 is usually diminished. Total LDL is not typically raised in type 2 diabetes, only the small dense LDL moiety is.

However, because LDL is the lipid parameter that shows the strongest association with CV disease, the first priority in lipid management in type 2 diabetes is to ensure LDL is lowered to a defined target. What this target ought to be is shown by many trials to be an LDL level < 2.6 mmol/L (100 mg/dl). There are lobbies that call for the LDL target for diabetes persons to be lowered to 1.8 mmol (70 mg/dl)

DIABETES IS A CHD EQUIVALENT

In the East-West Study, a population-based study conducted in eastern and western Finland, more than 1,000 diabetic subjects and almost 1,400 non diabetic subjects were followed up for 7 years. Subjects were stratified by baseline status for both prior myocardial infarction (MI) and diabetes. Diabetics with prior myocardial infarction had a higher incidence of myocardial infarction than diabetics without prior myocardial infarction, but more importantly, diabetics without prior myocardial infarction had a 20.2% incidence of myocardial infarction at 7-year follow-up, compared with an 18.8% incidence in non diabetics with prior myocardial infarction. These results published in 1998 were important in establishing diabetes as a CHD risk equivalent.

Although this study was criticized because it was conducted in a relatively high-risk population for CHD, namely Finland in the early 1980s, a subsequently published analysis of the Organization to Assess Strategies for Ischemic Syndromes (OASIS) Registry, which included prospective data from 6 countries (Australia, Brazil, Canada, Hungary, Poland, and the United States), also found that diabetic patients without prior cardiovascular disease had the same event rates as non diabetic patients with prior cardiovascular disease.

Published in 2000, OASIS lends support to the concept of diabetes as a CHD risk equivalent. This study is more generalizable than the Finnish East-West study since it was based in 6 different countries and has a larger population.

DIABETES IS NOT A CHD EQUIVALENT

But while most experts now accept that diabetes is a CHD equivalent, there is data in the scientific literature that militates against this view. For example, in MRFIT, the risk conferred by diabetes for CV events was not quite 'equivalent', but clearly lower that that conferred by prior CHD. In MRFIT, the Kaplan Meier curves for total mortality show that non-diabetic subjects with prior CHD had worse survival than diabetic subjects without CHD.

Similarly the Nurses Health Study showed that the relative risk (RR) of CHD death over 20 years was 8.7 in diabetes subjects compared to 10.6 in non-diabetic subjects with CHD. In the US Male Physicians study, subjects with diabetes had a relative risk of CHD death of 3.3, which was significantly lower that the RR of 5.6 in subjects with prior CHD but no diabetes.

PREVENTION TRIALS

However whether the risk for future CHD in diabetes is "equivalent" or not to that in persons with prior CHD, primary prevention studies like the Heart Protection Study and CARDS, as well as secondary prevention studies like CARE, LIPID, 4S show a clear correlation between mean LDL level and CHD events.

METABOLIC SYNDROME-USEFUL OR NOT?

For nearly two decades since the term joined the medical vernacular, the cardiovascular risks of "metabolic syndrome" have become widely recognized. The cluster of signs and symptoms – including a large waist circumference, hypertension, insulin resistance, and dyslipidaemia – significantly increase the risk of developing future diabetes or experiencing a cardiovascular event such as heart attack or stroke.

But beyond definitions, opinions are widely divided about what metabolic syndrome means and the role that the diagnosis should serve in primary care. This debate climaxed in 2005 when a joint statement from the American Diabetes Association and European Association for the Study of Diabetes said the value of the designation in primary care is limited. As a predictor of cardiovascular events, the statement charged, the diagnosis is no greater than the sum of its parts.

The statement felt that metabolic syndrome was an elusive concept on which even professional organizations (there are at least 5 slightly different definitions from WHO, NCEP ATP III, IDF and AACE) disagree. It further suggested that metabolic syndrome is an ambiguous entity and should not be a term used in primary care.

In July 2006, ADA and AHA, by way of a 'truce', issued a statement introducing an initiative to encourage a broader approach to health management by adopting the term "cardiometabolic risk" (CMR) to designate the risks of diabetes and cardiovascular events that may result from pre-diabetes, hypertension, dyslipidemia, and obesity.

TREATING GLYCAEMIA – WHAT TARGETS?

It is important to remember that the most appropriate target levels for blood glucose and HbA1C have not been systematically studied. Current targets look to controlled clinical trials, such as the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and the U.K. Prospective Diabetes Study (UKPDS) and Kumamoto Study in type 2 diabetes for data to help us determine the glycemic goals of therapy that result in improved long-term outcomes. Both the DCCT and the UKPDS had as their goals the achievement of glycaemic levels in the non diabetic range. But neither study was able to sustain A1C levels in the non diabetic range in their intensive-treatment groups. The achieved mean levels over time of ~7% were still 4 SDs above the non diabetic mean.

The current glycaemic goal recommended by the American Diabetes Association, selected on the basis of practicality and the projected reduction in complications over time, is "in general" an A1C level <7%. For "the individual patient," the A1C should be "as close to normal (<6%) as possible without significant hypoglycemia." The most recent glycaemic goal set by the European Union–International Diabetes Federation is an A1C level <6.5%. The upper limit of the non diabetic range is 6.1% (mean A1C of 5% + 2 SD) with the DCCT-standardized

assay, which has been promulgated through the National Glycohemoglobin Standardization Program (NGSP) and adopted by the vast majority of commercially available assays.

WHAT ABOUT ACCORD?

Public surprise and later furore erupted in Feb 2008 when a landmark study called ACCORD involving US and Canadian subjects showed that intensive glucose lowering led to increased mortality.

The data analyses showed that over 3.5 years of treatment, 257 participants in the intensive group (aiming to have HbA1c <6.0%) died, compared to 203 in the standard group – a difference of 54 deaths, or an excess of about 3 deaths per 1,000 participants treated for a year. This translates to a statistically significant 22% higher rate of death in the intensive than the standard group.

ACCORD had three arms-glucose-lowering, blood pressure lowering and lipid lowering. All three ACCORD clinical trials have ended.

Researchers continue to analyze the ACCORD data to try to understand why these "intensive" interventions did not reduce the rates of cardiovascular outcomes as hypothesized.

Current information suggest that hypoglycaemia does not consistently explain the excess mortality seen in the intensive control group of ACCORD. Data also showed severe hypoglycemia (glucose below 50 mg/dL) in both intensive and standard treatment groups was associated with a higher risk of death but, among those who had severe hypoglycemia in the intensive arm, it was associated with a lower risk of death compared to those who had severe hypoglycemia in the standard group.

WHAT DIABETES DRUGS?

In the published literature there are a fair number of head-to-head comparisons involving oral anti-diabetes medications. Most of these comparisons show equivalent efficacy. But they did not recruit very large subject numbers. A summary of anti-diabetes medications and their impact on HbA1c as monotherapy is shown in Table 1. In Table 2, a summary of combination trials is presented.

Data from the UKPDS suggests that an important intervention that is likely to improve a patient's chance of having better long-term control of diabetes is to make the diagnosis early, when the metabolic abnormalities of diabetes are usually less severe. Lower levels of glycaemia at time of initial therapy are associated with lower A1C over time and decreased long-term complications.

Table 1. Summary of antidiabetic interventions as monotherapy

nterventions	Expected decrease in A1C (%)	Advantages	Disadvantages
Step 1: initial			
Lifestyle to decrease weight and increase activity	1–2	Low cost, many benefits	Fails for most in 1st year
Metformin	1.5	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
Step 2: additional therapy			
Insulin	1.5–2.5	No dose limit, inexpensive, improved lipid profile	Injections, monitoring, hypoglycemia, weight gain
Sulfonylureas	1.5	Inexpensive	Weight gain, hypoglycemia*
TZDs	0.5–1.4	Improved lipid profile	Fluid retention, weight gain, expensive
Other drugs			
α–Glucosidase inhibitors	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Exenatide	0.5–1.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Glinides	1–1.5	Short duration	Three times/day dosing, expensive
Pramlintide	0.5–1.0	Weight loss	Injections, three times/day dosing, frequent GI side effects, expensive, little experience

** Severe hypoglycemia is relatively infrequent with sulfonylurea therapy.The longer-acting agents (e.g. chlorpropamide, glyburide [glibenclamide], and sustained-release glipizide) are more likely to cause hypoglycemia than glipizide, glimepiride, and gliclazide. Repaglinide is more effective at lowering A1C than nateglinide. GI, gastrointestinal.*

Table 2. Antidiabetes oral agent combination therapy: randomized controlled trials

Source	Randomization	n	Duration	HbA1c reduction
Erle et al 1999	Glyburide + metformin vs glyburide + placebo	40	6 mo	1.0
UKPDS 1998	SU + metformin vs SU alone	591	3 yr	0.6
DeFronzo et al 1995	Glyburide + metformin vs glyburide alone	632	29 wk	1.6
Standl et al 2001	Metformin/glyburide + miglitol vs metformin/glyburide + placebo	154	24 wk	0.4
Wilms & Ruge 1999	SU + acarbose vs SU + metformin vs SU + placebo	89	12 wk	1.0 (acarbose), 1.2 (metformin)
Rosenstock 1998	Metformin + acarbose vs metformin + placebo	148	24 wk	0.7
Coniff et al 1995	Tolbutamide + acarbose vs either drug alone	290	24 wk	0.4 (vs tolbutamide), 0.8 (vs acarbose)
Chiasson et al 1994	Metformin or SU + acarbose vs metformin or SU + placebo	354	1 yr	0.8 to 0.9
Fonseca et al 2000	Metformin + rosiglitazone vs metformin + placebo	348	26 wk	1.2%
Horton et al 1998	Glyburide + troglitazone vs either drug alone	552	1 yr	2.7%
Raskin et al 2000	Troglitazone + repaglinide vs either drug alone	256	22 wk	1.3 (vs troglitazone), 0.9 (vs repaglinide)

LEARNING POINTS

- **Atherosclerosis-related disease accounts for 80% of all diabetic mortality. 75% of all diabetic mortality is caused by coronary heart disease, while stroke and peripheral vascular disease make up the remaining 25%.**
- **The first priority in lipid management in type 2 diabetes is to ensure LDL is lowered to a defined target.**
- **The current glycaemic goal recommended by the American Diabetes Association, selected on the basis of practicality and the projected reduction in complications over time, is "in general" an A1C level <7%. For "the individual patient," the A1C should be "as close to normal (<6%) as possible without significant hypoglycemia."**
- **Current information suggest that hypoglycaemia does not consistently explain the excess mortality seen in the intensive control group of ACCORD.**
- **Data from the UKPDS suggests that an important intervention that is likely to improve a patient's chance of having better long-term control of diabetes is to make the diagnosis early, when the metabolic abnormalities of diabetes are usually less severe.**