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Beneficial and Detrimental Effects of Intensive Glycaemic Control, with Emphasis on Type 2 Diabetes Mellitus

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Abstract

Diabetes mellitus is a major health problem in the world. Several clinical trials have shown that some of the major complications of diabetes mellitus can be partially prevented or delayed by intensive glycaemic control. However, there are benefits and risks in aiming for near normal blood glucose levels.

Intensive glycaemic control delays the onset and progression of retinopathy, nephropathy and neuropathy. Epidemiological and observational studies have shown that cardiovascular events may be correlated with the severity and duration of diabetes mellitus, but major randomised trials have only shown weak and nonsignificant benefits of intensive glycaemic management in decreasing event rates. A modest improvement in lipid profile results from blood glucose control although, in the majority of cases, not enough to reach current targets.

Detrimental effects of intensive glycaemic control include bodyweight gain and hypoglycaemia. Controversial issues in the management of patients with diabetes mellitus include the unproven increase in cardiovascular morbidity from

sulphonylureas and hyperinsulinaemia, and the still unknown long term effects of newer oral antihyperglycaemic agents alone or in combination with traditional therapies (such as sulphonylureas and metformin).

It is important to individualise management in setting glycaemic goals. Control of cardiovascular risk factors through blood pressure and lipid control and treatment with aspirin (acetylsalicylic acid) and ACE inhibitors have consistently shown benefits in the prevention of both macro- and microvascular complications in patients with diabetes mellitus; these measures deserve priority.

Diabetes mellitus is a major health problem in the world. In 1995, 135 million adults were diagnosed as having diabetes mellitus and this is projected to rise to 300 million by the year 2025.[1] The overwhelming majority of patients with diabetes mellitus have type 2 diabetes mellitus; previously known as non–insulin-dependent diabetes mellitus or adult-onset diabetes. The incidence of type 2 diabetes mellitus increases linearly with advancing age, with the majority of people with the disease ≥65 years of age.[1] Diabetes mellitus ranks as the seventh most prevalent cause of death in the US, with cardiovascular complications accounting for almost 70% of diabetes-related hospitalisations.[2]

Serious complications such as end-stage renal disease (ESRD) from diabetic nephropathy, blindness from retinopathy and nontraumatic amputations may be caused by the disease. The incidence of strokes and coronary events is 2- to 4-fold higher in patients with diabetes mellitus compared with the nondiabetic population.[3-9] Because of these complications, the yearly mortality rate of patients with diabetes mellitus is 2- to 3-fold higher than that of age-matched controls.[6] The healthcare cost of diabetes mellitus is thus astounding, approaching $US100 billion in the US during 1997.[10]

1. Intensive Glycaemic Control

The results of major randomised prospective trials have shown that intensive glycaemic control toward near-normal blood sugar levels can delay the onset and progression of several indicators of microvascular and neurological diabetic complications.[11-13] However, the question of whether cardiovascular mortality may be improved, unchanged or worsened as a result of intensive therapy remains unsettled,[13-15] and trials addressing this issue are currently in the planning stage in the US.

The American Diabetes Association (ADA) currently recommends a preprandial goal of whole blood serum glucose levels of 80 to 120 mg/dl (4.4 to 6.7 mmol/L), premeal or bedtime serum glucose of 100 to 140 mg/dl (5.6 to 7.8 mmol/L) and a glycosylated haemoglobin (HbA_{1c}) of <7% (normal 4 to 6%), with intensification or change of pharmacological strategy when HbA_{1c} exceeds 8%.[16] These are general guidelines for all persons with diabetes mellitus, but some individuals may warrant different treatment goals. The presence of comorbid diseases, such as pre-existing cardiovascular complications, evidence of advanced microvascular complications, advanced age and the patient's inability to carry out the advised treatment, attenuate the ADA goals and lessen the intensity of treatment,[16] indicating the need to tailor therapy for specific patients with diabetes mellitus. The overall prevalence of glycaemic control is still falling short of the above goals, with reported mean HbA_{1c} values of 8.5 to 10%.[17,18] Perhaps due to the widespread use of the newer oral antihyperglycaemic agents however, there has been improvement in the overall glycaemic control. Veterans Affairs' (VA) data from the US show that almost half of patients diagnosed as having diabetes mellitus, regardless of treatment, have mean HbA_{1c} values below 8% and relatively few patients exceed 9%. However, insulin-treated patients still have mean levels of 8.7%.[19]

In type 1 diabetes mellitus, intensive glycaemic control to near normal HbA_{1c} levels may be achieved by using continuous insulin infusion via

insulin pumps, or multiple daily injections of insulin along with bedtime long-acting insulin.[20] In patients with type 2 diabetes mellitus, double or triple therapy with various oral agents, and ultimately insulin, may frequently be needed to achieve the blood glucose and HbA_{1c} goals.[21]

1.1 Insulin Preparations

A wide variety of insulin types are available that have different durations of action (table I).

Insulin lispro is a relatively new short-acting insulin that is rapidly replacing regular insulin in use. It is shorter acting than regular insulin, mimicking the physiological surge of insulin with meals, and has less of the hypoglycaemic reactions that are associated with the peaks that occur with regular insulin.[23] The newer insulin aspart, another short-acting analogue, has similar properties.

Newer insulins that are currently being marketed include a long acting insulin, insulin glargine, and inhaled insulins. Insulin glargine is a modified human insulin in which glycine is substituted for asparagine at the A21 position, and two arginines are added to the B30 position of the molecule. These alterations shift the isoelectric point to a slightly acidic pH, resulting in low solubility at neutral pH.[24] Its advantage is the flat, peakless, nearly 24-hour action.[25]

Inhaled powder insulin is another insulin analogue that will be marketed soon. It has a rapid onset and short duration of action, which should provide coverage of meals.[26]

Table I. Available insulin preparations (adapted from American Diabetes Association[22])

Insulin preparation	Onset of action	Peak action	Duration of action
Rapid acting (e.g. insulin lispro)	Minutes	45 min	4-5h
Short acting (regular)	30 min	2-5h	5-8h
Intermediate acting (NPH, Lente)	1-3h	6-12h	16-24h
Long acting (Ultralente)	4-6h	8-20h	24-28h
Mixtures (70/30, 50/50)	30 min	7-12h	16-24h

h = hours; **NPH** = neutral protamine Hagedorn (insulin suspension isophane).

1.2 Oral Antihyperglycaemic Agents

The choices for oral diabetic agents have been recently expanded with the appearance of new drug classes. The following are currently available in the US for type 2 diabetes mellitus:

- sulphonylureas [glimepiride, glipizide, glibenclamide (glyburide)]
- meglitinide analogue (repaglinide)
- biguanide (metformin)
- thiazolidinediones (rosiglitazone, pioglitazone)
- α-glucosidase inhibitors (acarbose, miglitol).

The earliest and better documented agents are the sulphonylureas, which lower glucose levels by acting on ATP-sensitive potassium channels, increasing cytosolic calcium and thus enhancing insulin secretion by the β cells in the pancreas. Although the majority of patients may be initially controlled with these agents, the vast majority eventually require the addition of another oral agent and/or insulin for good glucose control. Many factors may participate in the loss of responsiveness (tachyphylaxis, diet, physical activity, concomitant medications) but the results of the United Kingdom Prospective Diabetes Study (UKPDS) clearly document that there is progressive loss of β cell function in type 2 diabetes mellitus, regardless of the therapy used.[13]

The meglitinide agent, repaglinide, acts similarly to the sulphonylureas, stimulating insulin release by the pancreas, but through different β cell receptors. The drug should be taken with meals, since the insulin-releasing effect is short-acting and stimulated by a glucose load. Repaglinide may be more effective in lowering postprandial blood glucose levels than sulphonylureas and may cause fewer hypoglycaemic episodes than the latter agents,[27] but it has to be given in multiple daily doses.

In the biguanide class, only metformin is used. The primary effect is on the liver, decreasing hepatic glucose output. There is also a minor secondary effect of enhancing glucose uptake and utilisation by peripheral tissues. The effect on glycaemic control is comparable to that of sulphonylureas, and it confers an additional effect when added to

sulphonylureas. Metformin does not cause bodyweight gain, which is a common adverse effect of sulphonylureas. When used as monotherapy, metformin does not cause hypoglycaemia; however, when combined with sulphonylureas, it confers at least as high a risk, or possibly a higher risk, than sulphonylureas alone. Metformin has a consistent antihypertriglyceridaemic effect and lowers levels of plasminogen activator inhibitor 1 (PAI-1),[28,29] a circulating atherogenic factor, independent of glycaemic control. Metformin is contraindicated in patients with renal insufficiency (serum creatinine level >1.5 mg/dl) because it has a rare but often fatal adverse effect of lactic acidosis if used in such patients. For the same reason, patients with congestive heart failure, liver disease, risk of hypotension, or other diseases that can predispose to hypoxaemia should not use metformin. It is recommended that the drug be withheld for 48 hours after administration of dye for angiographic procedures.

Thiazolidinediones are insulin-sensitising agents, lowering glucose levels by potentiating the effect of insulin in the muscle, liver and adipose tissues. This class of drug may be very effective in controlling blood glucose levels, resulting in lowered insulin requirements, but causes bodyweight gain and some blood volume expansion. However, the thiazolidinedione troglitazone has been associated with a rare idiosyncratic hepatocellular injury that is reversible with discontinuation of the drug, but that may lead to irreversible liver failure or death.[30] Thus, pretreatment liver function testing and liver enzyme monitoring (alanine aminotransferase determination once monthly for troglitazone and once every other month for rosiglitazone and pioglitazone for the first year) are recommended whenever the thiazolidinediones are used. The incidence of abnormal liver function tests with rosiglitazone and pioglitazone is about 5 to 10 times lower than the 0.2% seen with troglitazone, and it is hoped that this will make them much less likely to cause irreversible damage. The liver toxicity that has been reported can be very rapid in onset, and thus patients should be properly cautioned to immediately inform their physician if they become ill during the first few weeks of treatment with a thiazolidinedione. Troglitazone has been discontinued because of its association with liver toxicity.

Finally, the α-glucosidase inhibitors cause blood glucose lowering by inhibiting the enzyme in the small intestine, slowing the digestion and absorption of glucose. The reduction in HbA_{1c} is small, and the drugs, especially acarbose, are often poorly tolerated because of their gastrointestinal adverse effects.[31]

2. Benefits of Intensive Glycaemic Control

The benefits of tight blood glucose control in preventing diabetic complications have been supported by numerous observational studies and several randomised controlled trials.

2.1 Microvascular and Neuropathic Complications

Microvascular complications include retinopathy, nephropathy and neuropathy; the latter also has other biochemical and structural pathogenesis. Major randomised controlled trials have proven that tight glycaemic control is beneficial in reducing microvascular complications of diabetes mellitus. The Diabetes Control and Complications Trial (DCCT) was a landmark trial that aimed to determine whether intensive glucose control in type 1 diabetes mellitus reduced diabetic complications.[11,12] The mean HbA_{1c} reached was 7.2%, and mean blood glucose level was 155 mg/dl in the intensive group, with a separation from the standard treatment group of 1.9% of HbA_{1c}. After an average follow-up of 7 years, there was an approximately 60% reduction in risk of development or progression of indicators of diabetic retinopathy, nephropathy and neuropathy.

The Kumamoto Study[32] was a trial that randomised 110 Japanese patients with type 2 diabetes mellitus into intensive and conventional groups and followed them for a mean of 6 years. The mean HbA_{1c} was 7.1% in the former group compared to 9.4% in the conventional group. After a 6-year follow up, intensive glycaemic control with multiple

insulin injections was found to decrease the progression of retinopathy, (7.7 *vs* 32%, p = 0.039) and nephropathy (7.7 *vs* 28%, p = 0.049). Significant differences in nerve conduction velocities were also seen between the two groups. It should be noted that the patient population in the study was different from what is usually encountered in the US. They were younger (40 to 50 years, compared with the sixth and seventh decade peak prevalence in the US), leaner [mean body mass index (BMI) 20 kg/m^2], more insulin sensitive (about 20 to 25 units/day), and had no hyperlipidaemia, hypertension or electrocardiogram abnormalities. The number of cardiovascular events in both groups was very small (only 5 events or <1%/year), making it difficult to reach a conclusion from the lack of differences in the rate of combined cardiovascular events in the study.

The results of the Veterans Affairs Cooperative Study on Diabetes Mellitus (VACSDM) Feasibility Trial[33] further supported earlier findings that long term glycaemic control provides a significant protection against progression of microalbuminuria. 153 patients with poorly controlled type 2 diabetes mellitus were randomised into an intensive arm (HbA_{1c} goal of 4 to 6.1%) and standard arm (HbA_{1c} goal <2 standard deviations above the mean) of insulin treatment and followed for an average of 27 months (range 18 to 35 months). The mean HbA_{1c} difference of 2.1% was larger than in other US or European trials.[15]

The UKPDS[13] is so far the longest and largest study of glycaemic control in individuals with type 2 diabetes mellitus. It included 3867 patients with newly diagnosed diabetes mellitus and with a mean follow-up of 10 years. Patients were randomised into intensive treatment with sulphonylurea or insulin or to conventional diet therapy. The intensive group had a median HbA_{1c} of 7.0% compared to 7.9% in the conventional group. The overall microvascular complication rate was decreased by 25% (p = 0.001) in the intensive group; the most important clinical correlate was a difference of 0.03% in photocoagulation (9/1000 in the intensive *vs* 12/1000 in the conventional group). There was no difference in the deterioration of visual acuity or blindness. Among the different intensive groups, no difference in microvascular complication rate was seen.

Drawbacks of the UKPDS study include the narrow median HbA_{1c} separation (0.9%) between the intensive and conventional groups and the considerable overlap of treatments given to the 2 groups. 702 out of the 1138 patients in the conventional group were eventually given sulphonylurea, insulin or metformin.

Table II summarises the major randomised studies comparing intensive versus standard glycaemic control.

2.2 Macrovascular Complications

Cardiovascular disease is the leading cause of death in patients with diabetes mellitus, and most of this is from coronary disease. The lifetime risk of dying of cardiovascular causes is far higher than that from end-stage renal disease (fig. 1); in the UKPDS, it was 70-fold higher.[13] Mechanisms that have been proposed to cause the worse prognosis in patients with diabetes mellitus include more severe and diffuse coronary disease,[35-38] decreased vasodilatory reserve,[39-41] decreased fibrinolytic activity,[42,43] elevated platelet aggregation[44,45] and coagulation factor levels.[46,47] Independent risk factors for cardiovascular disease such as hypertension, hyperlipidaemia and obesity are also more frequent in patients with diabetes mellitus and may contribute to the increased cardiovascular event rate.[48] However, further investigation is needed because randomised controlled trials of intensive glycaemic control have failed to reduce macrovascular complications,[11-14] and observational and epidemiological studies correlating the duration of diabetes mellitus and the severity of hyperglycaemia with cardiovascular morbidity have shown conflicting results.[3-5,7,15,49,50]

In the setting of an acute myocardial infarct (MI), the presence of diabetes mellitus is an independent correlate of early and late mortality, with patients with diabetes mellitus having a relative risk that is double that of the nondiabetic co-

Table II. Major randomised studies comparing intensive versus standard glycaemic control in diabetes mellitus

Study	No. of patients	Average follow-up (y)	HbA_{1c} separation (%)	Microvascular complications	Macrovascular complications
Type 1 diabetes mellitus					
DCCT[11]	1441	6.5	1.9	Occurrence of retinopathy ↓ 76% (CI 62-85%) Progression of retinopathy ↓ 54% (CI 39-66%) Occurrence of microalbuminuria ↓ 39% (CI 21-52%) Albuminuria ↓ 54% (CI 19-74%) Clinical neuropathy ↓ 60% (CI 38-74%)	Reduction in pooled major cardiovascular and peripheral vascular events by 41% (not statistically significant)
Type 2 diabetes mellitus					
Kumamoto Study[32]	110	6	2.3	Occurrence of retinopathy ↓ 76% Progression of retinopathy ↓ 56% Microalbuminuria ↓ 57% Albuminuria ↓ 100% Improved nerve conduction velocity	Number of patients too small to be statistically significant
UKPDS[13]	3867	10	0.9	Aggregate microvascular end-points ↓ 25% (CI 7-40%) Any diabetes-related end-point risk ↓ 12% (CI 1-21%)	Trend for reduction in MI (p = 0.052) in intensive group
VACSDM[15,33]	153	2.25	2.1	Decrease in nephropathy	Trend for increase in major cardiovascular events (p = 0.1) in intensive group

CI = confidence interval; **DCCT** = Diabetes Control and Complications Trial; **HbA_{1c}** = glycosylated haemoglobin; **MI** = myocardial infarction; **UKPDS** = United Kingdom Prospective Diabetes Study; **VACSDM** = Veterans Affairs Cooperative Study on Diabetes Mellitus; ↓ indicates decrease.

hort.[51-64] The Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) study showed that the 30-day mortality rate for insulin-treated patients with diabetes mellitus was 12.5%, for non–insulin-treated patients with diabetes mellitus was 9.7% and for patients without diabetes mellitus was 6.2% ($p < 0.001$).[65] Likewise, the mortality rate for patients admitted with unstable angina is twice as high in patients with diabetes mellitus compared with patients without diabetes mellitus.[66]

A recently published meta-analysis of randomised studies comparing intensive and conventional therapies in type 1 diabetes mellitus showed a decrease in the number of macrovascular events (odds ratio 0.55, 95% confidence interval –0.35 to 0.88, $p = 0.015$) in the intensively treated patients. However, no significant difference was demonstrated in the macrovascular mortality rate or the number of patients who developed macrovascular disease.[67]

The Swedish Diabetes Mellitus and Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study was an interesting trial that randomised 620 patients with diabetes mellitus into a placebo group and a group that received insulin-glucose infusions during an acute MI.[68-70] The patients in the latter group were also administered more intensive insulin treatment for at least 3 months after discharge, with a resulting HbA_{1c} difference of only 0.5% (both groups had near normal HbA_{1c}). The treatment effect was most pronounced in the subgroup of patients who had not had prior insulin medication and were at lower cardiovascular risk. The in-hospital mortality was reduced by 58% ($p < 0.05$) and the 1-year mortality by 52% ($p < 0.02$). There was a 28% reduction in the long term mortality rate in the intensively managed group; it appears likely that these results, if confirmed, are perhaps due to myocardial protection and reduction of injury in the peri-infarction period by the subacute insulin-glucose infusion.[68-70]

The UKPDS study in newly diagnosed patients with type 2 diabetes mellitus found no difference between the intensive and conventional groups in the combined macrovascular endpoints, but there was a nonsignificant trend toward fewer nonfatal myocardial infarctions in the intensive group.[13] In a separate analysis (UKPDS 34), which studied the use of metformin in overweight individuals, the investigators found a 39% lower risk ($p = 0.010$) of MI and 41% lower risk of stroke ($p = 0.032$) in the metformin group versus conventional treatment.[71] Patients/months exposure to metformin (81 and 83%) was similar in both arms. Furthermore, compared with the sulphonylurea alone group, the addition of metformin was associated with a significantly higher number of fatal MIs and twice the diabetes-related death and all-cause mortality. Interestingly, microvascular complications in the metformin substudy were not significantly different from those in controls. However, the addition of metformin to sulphonylurea was not part of the primary randomisation, but rather a late randomisation of a subset who underwent step-up therapy. The issue of the safety of this combination remains an important one, as the largest use of metformin in the US is in combination with sulphonylureas.

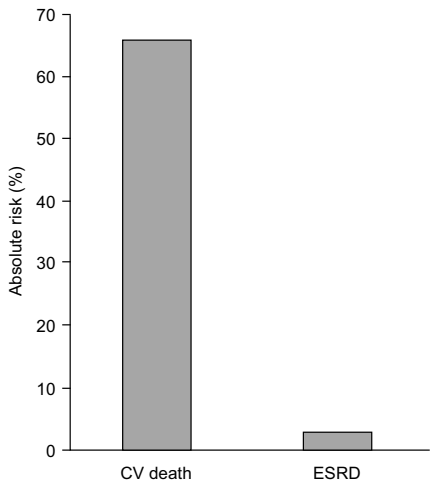

Fig. 1. Comparative risk of end-stage renal disease (ESRD) versus cardiovascular (CV) mortality in type 2 diabetes mellitus. The risk of cardiovascular death represents averages (no effect of glycaemia). The lifetime risk of end-stage renal disease is at age 55 years, glycosylated haemoglobin of 11% (data from Geiss et al.[2] and Vijan et al.[34]).

In the DCCT trial,[11] there was no statistically significant effect on macrovascular complications and this was presumed to be due to the small number of complications observed and the younger population in this study of patients with type 1 diabetes mellitus. The reduction in the macrovascular events was primarily due to peripheral vascular events and not coronary artery events. A follow-up study of the DCCT cohort failed to show a relationship between previous intensive treatment or HbA_{1c} and carotid wall intimal thickness.[72]

The VACSDM Feasibility Trial of obese patients with poorly controlled type 2 diabetes mellitus found a borderline trend towards increased nonfatal cardiovascular events in the intensive treatment arm (35 versus 26 events, $p = 0.10$).[15]

2.3 Lipids

Dyslipidaemia is seen in 40 to 50% of patients with diabetes mellitus. The lipid profile is usually characterised by increased triglycerides, decreased high-density lipoprotein (HDL) and normal to moderately increased low-density lipoprotein (LDL) levels.[73]

The VACSDM study, a feasibility study, prospectively evaluated the effect of intensive insulin therapy on lipid levels. A sustained decrease in serum triglyceride and total cholesterol levels was noted and HDL and LDL levels remained unchanged. However, there was a significant increase in the LDL-cholesterol/apolipoprotein B ratio, which is a less atherogenic profile.[74]

The experience of the VACSDM indicates that the response of the altered lipid profile to intensive glycaemic therapy alone is not sufficient, and lipid-lowering agents are frequently needed to achieve the recommended lipid goals for these patients.[75]

Some of the newer oral antihyperglycaemic agents in the US, such as metformin and the thia-

zolidinediones, are known to improve lipid profile, increasing HDL and decreasing triglyceride levels.

3. Detrimental Effects and Limitations of Intensive Glycaemic Control

3.1 Hypoglycaemia

The major limitation of tight glucose management is hypoglycaemia, particularly in patients with type 1 diabetes mellitus. In the DCCT, the risk of hypoglycaemia was 3-fold higher in the intensively treated group.[11] In the UKPDS, the rates of any hypoglycaemia were also significantly higher in the intensive groups (11% in those who received chlorpropramide, 17.7% glibenclamide, 36.5% insulin compared with 1.2% in those who received diet alone). The prevalence of severe hypoglycaemia was much lower: 0.4% for chlorpropramide, 0.6% for glibenclamide, 2.3% for insulin, 0.1% for diet,[13] similar to that in the VACSDM.[15] The feared consequences of hypoglycaemia are numerous, including coma, seizures, strokes and even heart attacks in the elderly. This association is, however, seldom documented; and in the VACSDM, there was no correlation between hypoglycaemic episodes and new cardiovascular events.[15]

Repeated episodes of even mild hypoglycaemic episodes may play a role in the development of hypoglycaemia unawareness.[76] This is a condition where the threshold for the release of counterregulatory hormones and initiation of symptoms is shifted downwards, manifesting as neuroglycopenia and unconsciousness without warning symptoms despite low blood glucose levels. Thus, it is important that the risk of hypoglycaemia be weighed against the goal of maintaining near normal blood sugar levels.

3.2 Cardiovascular Issues with Oral Agents

The University Group Diabetes Program (UGDP) data, which was published in 1970, was the first study that raised concerns of increased cardiovascular mortality with sulphonylureas. The agents used in the study were the sulphonylurea tolbutamide and the biguanide phenformin, and both were associated with increased cardiovascular mortality.[14]

Molecular mechanisms explaining the increased cardiovascular morbidity with sulphonylureas have been proposed. Potential adverse effects include prolonged myocardial refractoriness leading to dysrhythmias, worsening of vascular reactivity and induction of vasoconstriction, increase in infarct size, increase in insulin levels and promotion of bodyweight gain.[77] There have been studies suggesting an adverse effect on coronary angioplasty outcomes.[78] However no definitive results are available and conclusions cannot be made about the cardiovascular safety of sulphonylureas in every situation. In the UKPDS, there was no apparent adverse cardiovascular effect of sulphonylureas compared with insulin.[13] Concerns regarding combination of sulphonylureas and metformin are discussed in section 2.2.

3.3 Hyperinsulinaemia and Ischaemic Heart Disease

The role played by hyperinsulinaemia in the development of ischaemic heart disease, independent of other related risk factors, is still controversial.[79] Studies have shown that insulin has potent vascular effects, characterised by a dose-dependent dilation that is mediated by the endothelium-derived nitric oxide, and that is impaired in insulin-resistant states.[80] Other effects of insulin on the arterial wall that may be atherogenic include stimulation of growth factors, proliferation of smooth muscle cells and interference with plaque regression.[81] Also, there is evidence for a direct atherogenic role of insulin via glycation and glycoxidation of proteins and alteration of haemostatic function.[82]

The results of clinical studies are conflicting. Fontbonne et al.[83,84] reported that hyperinsulinaemia was not associated with an increased risk of ischaemic heart disease unless accompanied by increased triglyceride levels. On the other hand, 5 prospective studies have found that elevated plasma insulin levels are associated with increased risk of ischaemic heart disease.[49,85-88] The level of

fibrinogen, a powerful predictor of cardiovascular events, has been reported to be increased with higher insulin levels.[89] In the VACSDM, the intensive treatment arm showed increased fibrinogen levels at 1 year,[74] but this was not correlated with insulin dose, and the effect reverted by the second year.

3.4 Adverse Effects of Rapid Glycaemic Improvement

Intensive glycaemic control may cause deterioration of pre-existing retinopathy[90] as well as proteinuria[91] in type 1 diabetes mellitus. These phenomena have also been reported in patients with type 2 diabetes mellitus.[92] On the other hand, the VACSDM found no statistically significant deterioration of retinopathy after 2 years of intensive insulin treatment,[93] and in fact showed a reduction of the progression of microalbuminuria.[33] However, the intensive treatment arm displayed a slightly higher reduction of creatinine clearance than the conventional treatment arm. Furthermore, the appearance of combined new cardiovascular events had a borderline statistical correlation ($p = 0.05$) with low attained HbA_{1c} levels at the time of the event.[15] It is not clear what factors affect these potential adverse effects of glycaemic improvement; a possible role of insulin-like growth factor-1 in the aggravation of retinopathy[94] and destabilisation of glycated products in the vascular plaques by glucose lowering in microangiopathy have been proposed.[95]

3.5 Bodyweight Gain

Bodyweight gain is a potential consequence of intensive glycaemic control. In the DCCT, the intensively treated group had a 14% higher prevalence of obesity (BMI >27.8 kg/m^2 for men and >27.3 kg/m^2 for women) than the conventional group.[96] The UKPDS found that bodyweight gain was also significantly higher in the intensive groups (mean of 2.9kg, $p < 0.001$), being highest in those who received insulin (4kg).[13] In patients who were overweight, metformin resulted in less bodyweight gain than insulin and sulphonylureas and this can probably be explained by the combined anorectic effect of the drug and the hyperinsulinaemia that results from sulphonylurea and insulin treatment. In the VACSDM there was no difference in bodyweight gain between the intensive and standard treatment arms.[75]

More recent analysis of the DCCT results showed that the group that gained the most bodyweight also had the greatest increases in insulin doses, total cholesterol, LDL and apolipoprotein levels and systolic blood pressure.[97] Similarly, a recently published epidemiological study analysed the relationships among bodyweight gain and glycaemic control in patients with type 1 diabetes mellitus and found that there was a correlation between HbA_{1c} improvement and bodyweight gain. ($r = -0.21$, $p < 0.001$).[98] Bodyweight gain still resulted in a favourable effect on the lipid profile, if associated with improved glycaemic control, but adversely affected it in the absence of glycaemic improvement.

3.6 Quality of Life

To achieve intensive glucose control, the use of multiple daily injections and insulin pumps in patients with type 1 diabetes mellitus, and multiple oral agents alone or in combination with insulin in patients with type 2 diabetes mellitus, may be necessary. These require more frequent blood sugar monitoring, and regular blood tests for the thiazolidinediones. Stricter dietary management, to which some patients find difficult to adhere, is also advised to prevent bodyweight gain. Nonetheless, quality of life assessments in prospective studies indicate favourable profiles with intensive treatment in type 1[12] and type 2[99] diabetes mellitus.

4. Who Will Benefit from Intensive Glycaemic Control?

As discussed, the benefits of intensive glycaemic control are always accompanied by potential risks. In elderly individuals with type 2 diabetes mellitus, the question arises as to how aggressive glycaemic management should be. Vijan et al.[34] calculated the lifetime risk of clinical microvascu-

lar end-points, applying to type 2 diabetes mellitus the rate of progression in the patients with type 1 diabetes mellitus who were involved in the DCCT. These calculations are a 'worst case' scenario. They do not take into consideration the 90% visual sparing effects of yearly ophthalmological examinations,[100] now a standard of care. They also do not take in account the highly protective effect of blood pressure control. The risk of developing end-stage outcomes were highest in those who developed diabetes mellitus at a younger age and those who had poor glucose control, and thus the most marked benefit was observed in this group (figures 2 to 4).

For example, figure 2 shows that in patients who develop diabetes mellitus at 45 years of age, a 2% improvement in HbA_{1c} from 9 to 7% results in a 2.3% decrease in lifetime risk of blindness, compared to only a 0.5% decrease in those who developed diabetes mellitus at the age of 65 years.[34] For renal disease, the lifetime risk of end-stage renal disease was decreased by 1.5% in the 45-year-old group compared to 0% in the 75-year-old group when HbA_{1c} was improved from 9 to 7% (fig. 3).

Thus, the management of elderly patients with type 2 diabetes mellitus, particularly those already with multiple complications, may be different from

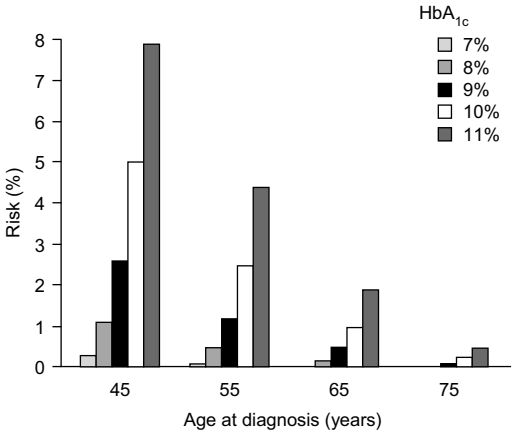

Fig. 2. Estimated lifetime risk of blindness in patients with type 2 diabetes mellitus according to glycosylated haemoglobin (HbA_{1c}) level (data from Vijan et al.[34]).

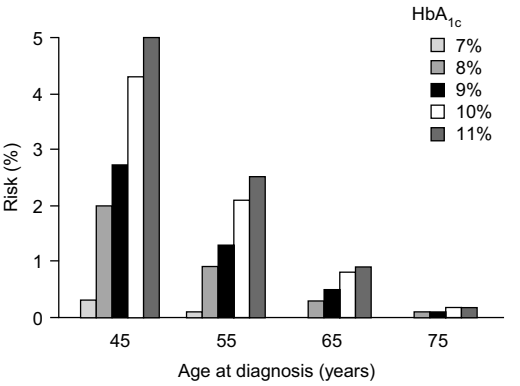

Fig. 3. Estimated lifetime risk of end-stage renal disease in patients with type 2 diabetes mellitus according to glycosylated haemoglobin (HbA_{1c}) level (data from Vijan et al.[34]).

that of younger patients. The potential cardiovascular benefit of glycaemic control remains unproven, but possible, since cardiovascular mortality correlates with glycaemia in the elderly.[50] Poor glycaemic control, i.e. an HbA_{1c} above 8%, is probably undesirable at any age, and the need for at least moderate glycaemic control in the elderly is recommended by the 2000 ADA guidelines.[16]

5. Other Aspects of the Management of Diabetes Mellitus

It is important to remember that the management of diabetes mellitus should go beyond blood glucose control. Other risk factors, such as hypertension and hyperlipidaemia, are possibly more important, and should be as aggressively managed.

In contrast with the marginal clinical outcomes of glycaemic control in the UKPDS, improvement of hypertension in that study, by 10 and 5mm Hg systolic and diastolic, respectively, caused a 34% reduction in risk of deterioration of retinopathy, 47% reduction in risk of deterioration of visual acuity, 44% reduction in risk of stroke and 32% reduction in cardiovascular mortality.[101] A target blood pressure of <130/85mm Hg and systolic blood pressure of <160mm Hg is recommended by the ADA, although this may not be easily achievable.[16] Combination antihypertensive therapy is

frequently utilised to try to achieve or maintain these goals. Dyslipidaemia in patients with diabetes mellitus has been proven to increase the risk of complications, and the results of management of lipid disorders in diabetic subsets have shown a significant reduction of macrovascular events.[102-104] It is recommended that LDL should be lowered to <100 mg/dl and triglycerides to <200 mg/dl.[17]

Screening for nephropathy should be performed annually, and if there is evidence of microalbuminuria (>30 mg/g of creatinine) in type 1 diabetes mellitus, or clinical proteinuria in type 2 diabetes mellitus, ACE inhibitor therapy should be initiated.[16] This class of antihypertensives is known to delay the progression of diabetic nephropathy and is usually the first choice for hypertension in the diabetic population, even if microalbuminuria is not present. However the UKPDS showed no advantages in using captopril over atenolol, implying that blood pressure lowering in itself may be more important than the treatment used.[105]

Studies have proven the benefit of aspirin (acetylsalicylic acid) therapy,[72,106] and the ADA advises those persons with diabetes melllitus who are above the age of 30 years to take an aspirin a day.[16]

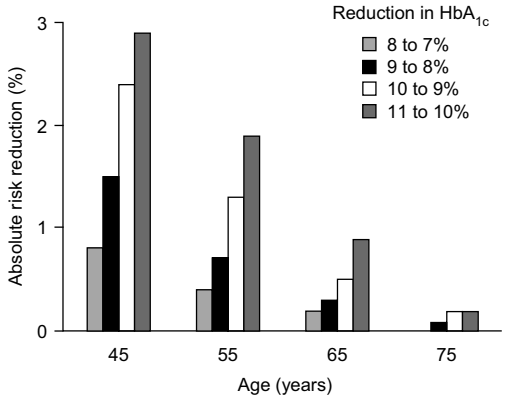

Fig. 4. Absolute reduction in risk of blindness with 1% reduction in glycosylated haemoglobin (HbA_{1c}) level (data from Vijan et al.[34]).

Lastly, preventive care, such as annual eye examinations, foot care and immunisations, are equally important in the management of the patient with diabetes mellitus.

6. Conclusion

Intensive glycaemic control has been shown to decrease the microvascular complications of diabetes mellitus. The effect on macrovascular disease is not established, although there is some supporting preliminary evidence for a favourable effect of intensive glycaemic control in the literature. Additional beneficial effects of intensive glycaemic control include modest improvement of lipid profiles. Detrimental effects include bodyweight gain, the risk of hypoglycaemia and the unproven risk of cardiovascular morbidity and mortality from hyperinsulinaemia and sulphonylureas. It is thus recommended that the benefits of intensive glycaemic control be weighed against the risks, and appropriate therapy to meet specific goals be tailored to the needs of the individual patient.

In the US, a Department of Veterans Affairs' 7-year prospective study of glycaemic control and complications in type 2 diabetes mellitus began in July 2000. This study aims to clarify whether the benefits of glycaemic control outweigh the risks in a population already poorly responsive to conventional therapy and who have an expected high prevalence of pre-existing cardiovascular disease, obesity and insulin resistance.[107,108] A separate trial is being proposed by the Heart, Lung and Blood Institute of the National Institutes of Health to investigate the benefits of intensification of blood pressure and lipid control beyond current recommendations; in a factorial design, these will be compared to the benefits of intensification of glycaemic control alone in patients not yet treated with insulin. Both North American studies complement each other and are likely to answer therapeutic questions not yet resolved.

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