REVIEW ARTICLE

Drug Safety 1999 Jul; 21 (1): 7-22
0114-5916/99/0007-0007/$08.00/0

Benefits and Risks of Transfer from Oral Agents to Insulin in Type 2 Diabetes Mellitus

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Contents

Abstract

The treatment of type 2 diabetes mellitus remains controversial. Since most patients are overweight or obese, regimens based on dietary modification and increased physical exercise are logical and safe treatment approaches. However, the long term impact of these interventions is frequently disappointing and pharmacotherapy is therefore required in the majority of patients. Oral antidiabetic agents, principally the sulphonylureas and biguanides, are often only partially effective, even in combination.

Insulin is the treatment of choice for certain clinical situations, for example, pregnancy. Often insulin will be a temporary measure. Safety considerations will also point to the preferential use of insulin in other circumstances, for example, in patients with pronounced renal impairment. In addition, a significant proportion of patients with type 2 diabetes mellitus will ultimately require insulin therapy in the long term because of failure of oral agents to provide adequate glycaemic control (i.e. secondary failure). Reservations about insulin therapy in patients with type 2 diabetes mellitus, particularly elderly patients with cardiovascular complications, include hypoglycaemia and bodyweight gain. However, severe hypoglycaemia occurs with considerably lower frequency than in patients with type 1 diabetes mellitus. To date, no clear evidence has emerged implicating exogenous insulin therapy in the promotion of cardiovascular disease. On the

contrary, recent clinical and experimental studies suggest anti-atherogenic effects.

Insulin therapy can be successful in type 2 diabetes mellitus if patients are carefully selected. Twice daily isophane (neutral protamine Hagedorn; NPH) or pre-mixed insulin is used routinely in many centres. The role of combinations of insulin and oral agents remains an area of controversy. Combined therapy with sulphonylureas may be more expensive and clear clinical advantages have not been consistently demonstrated. Bodyweight gain may be lessened by the concomitant use of metformin and troglitazone may improve glycaemic control in obese patients.

Procrastination about transfer to insulin is not uncommon. Patient acceptance may be facilitated by a positive attitude from the diabetes care team and discussion of the possibility at a relatively early stage. Adequate support from a multidisciplinary team is important for safe and effective insulin therapy. Even so, in the long term, attainment of glycaemic targets may prove difficult to sustain with present therapeutic strategies.

1. The Syndrome of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is predominantly a disorder affecting middle-aged and elderly people. It is by far the most prevalent form of diabetes accounting for more than 85% of cases worldwide. By definition, insulin therapy is not required to sustain life, compared with type 1 diabetes mellitus.[1] Nonetheless, a significant proportion of patients with type 2 diabetes mellitus will not attain adequate glycaemic control with measures such as dietary manipulation and exercise programmes. Oral antidiabetic agents often prove to be only partially or temporarily effective; in these patients exogenous insulin is used, usually as a last resort.

1.2 Clinical Heterogeneity in Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is a heterogeneous metabolic syndrome. Some of this heterogeneity reflects racial differences.[2,3] Populations with notably high rates of diabetes mellitus include the Pima Indians, who interestingly do not share the increased risk of cardiovascular disease observed in some other diabetic populations, and the Nauruans. These populations have experienced rapid Westernisation during the 20th century. The high prevalence (30 to 40%) of type 2 diabetes mellitus in these groups contrasts dramatically with the low (approximately 1 to 2%) prevalence amongst developing societies; the appearance of affluence-related obesity appears to be largely responsible for the explosive increase in diabetes mellitus which has been described in terms of a developing global epidemic. Higher rates of micro- and macrovascular complications amongst South Asian immigrants to the UK, relative to the indigenous population, may reflect factors such as earlier onset of disease and consequently longer exposure to hyperglycaemia. A higher prevalence of cardiovascular risk factors related to insulin resistance may also be important.[3]

1.2 Metabolic Characteristics

Established type 2 diabetes mellitus is characterised metabolically by abnormalities in the regulation of glucose metabolism. Logical therapy requires an adequate understanding of the pathophysiology of the disorder:

- Impaired insulin action: resistance to the actions of insulin in target tissues, primarily skeletal muscle and adipocytes; excessive rates of endogenous glucose production.
- Relative insulin deficiency: quantitative and qualitative defects in β cell function.

While chronic hyperglycaemia is the metabolic hallmark of all forms of diabetes mellitus, abnormalities also exist in other key aspects of metabo-

lism. Complex interactions exist between these metabolic defects. For example, chronic hyperglycaemia may have adverse effects on insulin action and endogenous insulin secretion. This effect, termed glucose toxicity, has obvious therapeutic implications.[4] Metabolic heterogeneity is manifested as the less common lean (impaired insulin secretion predominating) and more usual obese (insulin resistant) subtypes.[4]

Excessive or inappropriate hepatic glucose production is the principal determinant of fasting hyperglycaemia.[5] Impaired insulin-mediated glucose disposal in skeletal muscle exacerbates postprandial hyperglycaemia; failure of suppression of endogenous glucose production, resulting from a combination of insulin resistance, relative hypoinsulinaemia and hyperglucagonaemia also contributes.[6] It should be noted that suppression of endogenous glucose production by insulin normally occurs at lower plasma insulin levels than those required to stimulate glucose disposal. Impaired regulation by insulin of adipocyte lipolysis, another process sensitive to relatively low plasma insulin levels, may in turn exacerbate hyperinsulinaemia, hepatic glucose production and glucose disposal.[7,8] In addition, increased delivery of non-esterified fatty acids to the liver results in increased production of very low density lipoprotein (VLDL) triglycerides, a prominent component of the dyslipidaemia which is frequently associated with type 2 diabetes mellitus.[7]

While it is widely accepted that defects exist in both insulin action and insulin secretion there is controversy about the primacy of these factors to the metabolic disturbance in type 2 diabetes mellitus.[9] It is, however, recognised that overt type 2 diabetes mellitus represents a late stage in a process that has its origins in either genetic predisposition or an adverse intrauterine environment.[4] This predisposition can be modified by other factors, notably the development of obesity-related insulin resistance in adult life.[10] Initially, insulin resistance is countered by increased rates of endogenous insulin secretion; glucose tolerance is normal and circulating insulin levels are elevated.[10] However, even during this compensated phase, defects in the dynamics of insulin secretion and processing of its precursor molecule, proinsulin, are demonstrable.[9] As hyperglycaemia proceeds beyond the intermediate stage of impaired glucose tolerance, type 2 diabetes mellitus becomes established and the exaggerated insulin response to glucose challenge starts to decline; when fasting plasma glucose levels exceed 9 to 10 mmol/L the response is reduced when compared with matched control participants without diabetes mellitus, that is, absolute insulinopenia is present.

2. Treatment of Type 2 Diabetes Mellitus

2.1 Objectives of Treatment

The principal aims of treatment of patients with type 2 diabetes mellitus include:

- alleviation of diabetic symptoms
- avoidance of major metabolic decompensation
- minimisation of the risk of microvascular and neurological complications
- reduction in the risk of macrovascular disease
- avoidance of iatrogenic disease.

The first 2 objectives are readily accomplished in the majority of patients with current therapeutic strategies. In contrast, reducing the risk of micro- and macrovascular complications presents a more formidable challenge, not least since tissue complications are often established by the time of diagnosis. This reflects the long asymptomatic period of hyperglycaemia which precedes the diagnosis in the majority of patients with type 2 diabetes mellitus.[1]

2.2 Diet and Exercise

Dietary measures and regular aerobic exercise are the nonpharmacological cornerstones of managing type 2 diabetes mellitus. Calorie restriction in the overweight and obese, with the emphasis on limited fat consumption, is the principal component of dietary manipulation. Physical exercise has a number of potential benefits for patients with type 2 diabetes mellitus. These include improved insulin sensitivity, assistance with bodyweight

control, enhanced cardiovascular fitness, lower blood pressure, improved lipoprotein profiles and enhanced fibrinolysis. Unfortunately, only a minority of patients are able to achieve and maintain good glycaemic control without resort to pharmacotherapy with oral antidiabetic agents; moreover, the maintenance of control in the longer term is problematic whatever therapy is employed with polypharmacy, that is, 2 or more agents from different classes, often being required to attain glycaemic targets.

2.3 Oral Antidiabetic Agents

2.3.1 General Principles

The use of drugs for the treatment of type 2 diabetes mellitus aims to counter the cardinal metabolic disturbances of relative insulin deficiency and insulin resistance. However, currently available agents are at best only partially effective in the majority of patients.[11] The principal actions and adverse effects of the major classes of oral antidiabetic agents are presented in table I. In general, sulphonylureas are used in patients with less marked degrees of obesity since bodyweight gain is a frequent feature of their use. These drugs are thought to be most suitable for patients in whom relative insulin deficiency is prominent.[11-13] However, more severe degrees of insulin deficiency, which will limit a therapeutic response to sulphonylureas, are an indication for insulin. Non-sulphonylurea secretagogues are entering the clinical arena, for example, the meglitinide drug, repaglinide. Biguanides are a more logical choice for the obese patient in whom insulin resistance is thought to be a major factor since significant bodyweight gain is not a feature of their use.[14] Biguanides can be usefully combined with sulphonylureas. The effect is synergistic and this is a frequently-employed strategy. Drugs in this class include metformin, which is the only biguanide available in the UK and US. Phenformin, which carries a considerably higher risk of lactic acidosis, is also still available in some countries.[12] Troglitazone, the first in a new class of insulin-sensitising drugs – the thiazolidinediones[15] – was withdrawn a few months after its launch in the UK following reports of severe hepatotoxicity. The drug remains available in a number of other countries; other agents in this class (rosiglitazone, pioglitazone) are under development. To date, no evidence of hepatotoxicity has emerged for these particular drugs.

2.3.2 Contraindications to Oral Agents

There are a number of clinical situations in which oral agents are contraindicated; these are presented in table II. In most of these circumstances insulin is preferred, either as a temporary measure or as long term therapy. With resolution of the contraindication any subsequent decision to use oral agents requires careful consideration; good glycaemic control with a relatively small insulin dose and absence of a propensity to ketosis are suggestive, if not entirely reliable, pointers to successful transfer to oral agents. However, in the absence of major problems such as hypoglycaemia insulin would be preferred, particularly in younger pa-

Table I. Principal modes of action and adverse effects of currently available oral antidiabetic agents

Oral agent	Principal mode of action	Principal adverse effects
Sulphonylureas	Stimulation of endogenous insulin secretion	Bodyweight gain
		Risk of hypoglycaemia: uncommon, but potentially fatal if severe
Biguanides	Inhibition of hepatic glucose production	Gastrointestinal symptoms
		Lactic acidosis: rare, but associated with high mortality; risk is significantly higher with phenformin
Acarbose	Reduction in intestinal carbohydrate absorption	Gastrointestinal symptoms: caution in bowel disease
		Rare reports of hepatotoxicity
Troglitazone	Enhanced insulin action	Severe hepatotoxicity: careful monitoring of liver function required

Table II. Cautions and contraindications to oral antidiabetic agents in patients with type 2 diabetes mellitus

Condition[a]	Drugs to avoid	Reason
Ketosis and/or hyperosmolar state	All	Severe insulin deficiency mandates insulin treatment
Pregnancy	All	Considerations of direct effects on fetus and limited capacity of oral agents to attain excellent glycaemic control
Severe sepsis, acute myocardial cardiac failure	Sulphonylureas, biguanides	Stress hormone response may necessitate insulin; infarction, risk of lactic acidosis with metformin
Renal impairment	Biguanides, chlorpropamide, glibenclamide	Risk of severe hypoglycaemia – short-acting sulphonylureas are safer but should be avoided if creatinine level is >200 μmol/L; risk of lactic acidosis with biguanides
Radiological contrast studies	Biguanides	Risk of lactic acidosis (rare)
Hepatic impairment	Biguanides	Risk of lactic acidosis
	Troglitazone	Risk of severe hepatotoxicity
Alcoholism	Biguanides	Risk of lactic acidosis
Surgery, major trauma	Biguanides, chlorpropamide, glibenclamide	Risk of lactic acidosis Risk of hypoglycaemia with long-acting agents
Chronic pulmonary disease	Biguanides	Risk of lactic acidosis

a Insulin is usually the treatment of choice in all of these circumstances, either as a temporary or permanent measure.

tients, if better long term metabolic control could be attained.

2.3.3 Therapeutic Failure of Oral Agents

In a proportion of patients their diabetes will fail to respond to oral antidiabetic agents. It has recently been recognised that in some of these primary therapeutic failures, patients have humoral autoimmune markers directed against islet cell cytoplasm and glutamic acid decarboxylase.[16] In a report from the United Kingdom Prospective Diabetes Study (UKPDS), patients with positive antibodies were at higher risk of requiring insulin treatment by 6 years compared with those who were antibody-negative.[16] Prediction of primary failure in routine clinical practice remains problematic but the patient with marked fasting hyperglycaemia who is either normal bodyweight or underweight is unlikely to show a satisfactory response to oral agents. Assuming adherence to diet, it should be clear within a week or 2 whether sulphonylurea treatment has been successful. Partial therapeutic responses are common. However, doses of sulphonylureas are often escalated beyond the point where any further benefit will be gained. Metformin or another oral agent may be added or oral agents abandoned and insulin commenced in recognition of therapeutic failure.

By convention, the principal indication for insulin in type 2 diabetes mellitus remains the failure of oral agents, usually in combination, to sustain glycaemic control. Failure of oral therapy after a period of apparently satisfactory control affects approximately 5 to 10% of patients per annum.[12,13] There is no universal agreement on how secondary failure should be defined nor does a consensus exist concerning its management. The reasons for secondary failure are incompletely understood and may be multifactorial; dietary noncompliance with continuing obesity and progressive deterioration of β-cell secretion have both been implicated.[11] Since sulphonylureas act by stimulating insulin secretion[12,13] and metformin requires the presence of adequate insulin for its antihyperglycaemic effect[12,13] the re-emergence of significant fasting hyperglycaemia usually marks the point where insulin is required.

2.3.4 Glycaemic Targets in Type 2 Diabetes Mellitus

Expert reports[17,18] have suggested broad therapeutic targets for type 2 diabetes mellitus. However, decisions should be made in the light of individual circumstances which may modify risk-to-benefit relationships of therapy. In the younger, fitter patient at risk of long term microvascular complications, tight glycaemic control will usually

be indicated. On the other hand, for elderly patients with cognitive impairment, major diabetic complications or concomitant life-limiting illness, the principal therapeutic target might reasonably be limited to the avoidance of osmotic symptoms; minimising the risk of severe hypoglycaemia is often regarded as being paramount in such circumstances. When the decision to use insulin has been taken – and accepted by the patient – the improvement in glycaemia will be influenced by factors such as the degree of obesity and compliance with continuing dietary measures. Psychiatric problems, ranging from temporary anxiety or depression to major psychoses or chronic drug-dependence are relatively common in clinical practice; these may impose limitations on the level of glycaemic control that can be attained in the long term.

2.4 Prevention of Long Term Complications

Patients with type 2 diabetes mellitus are, in common with other forms of diabetes mellitus, at risk of developing long term tissue complications; the duration and degree of chronic hyperglycaemia are very important, but not sole, determinants. Blood pressure is an important modifier and other factors may also be operative in some ethnic groups who appear to be at higher risk of tissue complications. For the purposes of discussion, the complications may be subdivided into microvascular and macrovascular, or atheromatous, complications.

2.4.1 Microvascular Complications

Retinopathy and nephropathy, together with diverse neurological complications, constitute the specific microvascular complications of diabetes mellitus. Leading ultimately to visual impairment, renal failure and limb-threatening foot disease, respectively, these complications are a major cause of morbidity and premature mortality. The high prevalence of complications at diagnosis together with the development of new therapeutic agents[12,13,15] has rekindled interest in postponing the transition from impaired glucose tolerance to type 2 diabetes mellitus through pharmacological intervention.[10,19]

Epidemiological data from the Wisconsin Epidemiological Study of Diabetic Retinopathy[20] firmly implicate glycaemic control in the development of the microvascular complications associated with type 2 diabetes mellitus.[20,21] In this study, baseline haemoglobin (Hb) A_{1c} level was related to the incidence or progression, or both, of diabetic retinopathy, the incidence of clinical proteinuria and incidence of loss of measures of neural sensory integrity. The Diabetes Control and Complications Trial (DCCT) demonstrated unequivocally that in patients with type 1 diabetes mellitus, improved glycaemic control can reduce the incidence and progression of microvascular complications.[22] However, type 1 diabetes mellitus is characterised by absolute insulin deficiency with insulin resistance being a relatively minor and reversible defect. In addition, and in contrast to most patients with type 2 diabetes mellitus, the participants in the DCCT were young, non-obese, normotensive and largely free from macrovascular disease.[23] Evidence for benefits of glycaemic control on microvascular complications in type 2 diabetes mellitus has come from 2 randomised trials; first, the Kumamoto trial[24] which involved a relatively small sample of 110 lean Japanese patients with type 2 diabetes mellitus randomised to conventional or intensified insulin treatment in a study design analogous to the DCCT. More recently, the results of the larger, longer term UKPDS[25,26] have confirmed that improved glycaemic control is associated with reduced rates of microvascular complications. However, the UKPDS did not confirm such a beneficial effect on macrovascular disease.[26] The UKPDS has the advantage over the Kumamoto trial of including typical overweight and obese patients who may also have had lesser degrees of insulin deficiency.

2.4.2 Macrovascular Complications

Although microvascular complications are a major cause of morbidity, the leading causes of premature mortality amongst patients with type 2 diabetes mellitus are macrovascular complications.[27,28] These include:

- coronary heart disease – the leading cause of death
- cerebrovascular disease – risk of stroke is doubled
- peripheral vascular disease – causing claudication and contributing to diabetic foot disease.

The high rates of cardiovascular events in type 2 diabetes mellitus are illustrated by prospective studies such as the Diabetes Intervention Study.[29] This multicentre trial in Germany recorded myocardial infarctions in 15% of patients over an 11-year period with a 20% mortality rate.[29] Another study of newly-diagnosed patients with type 2 diabetes mellitus documented a 10-year age-standardised cardiovascular mortality of 15% for men and 16.6% for women, both rates being significantly higher than those observed in matched control participants without diabetes (5.2 and 2.2%, respectively).[30] In the UKPDS, 9 years after the diagnosis of diabetes mellitus, 20% of patients had experienced a fatal or nonfatal clinical macrovascular complication, coronary heart disease predominating.[11] Patients in the UKPDS with borderline or mild hypertension were randomly allocated, in a factorial design, to differing levels of blood pressure control. This subgroup study, the Hypertension in Diabetes Study, demonstrated that hypertension at the time of the diagnosis of diabetes mellitus, which was present in 39% of the participants, increased the risk of a diabetes-related death or a major clinical complication.[31] Furthermore, tighter control of hypertension led to significant reductions in both macro- and microvascular complications, including diabetes-related deaths.[32]

The increased risk of cardiovascular disease, which is generally 2- to 4-fold higher in patients with type 2 diabetes mellitus, is partially accounted for by conventional risk factors for atheromatous disease, notably hypertension and dyslipidaemia, which are also operative in individuals without diabetes.[33,34] However, the effects of these factors are magnified by the presence of diabetes. Considerable attention has been directed towards the cosegregation of glucose intolerance and type 2 diabetes mellitus with other major cardiovascular risk factors. This constellation, which is closely associated with insulin resistance and hyperinsulinaemia, is known as Syndrome X or the metabolic syndrome.[7] However, much of the increased risk of cardiovascular disease associated with type 2 diabetes mellitus appears to be attributable to the diabetic state *per se*. Moreover, epidemiological evidence is accumulating which implicates hyperglycaemia as an independent predictor of cardiovascular disease.[27,34] The effects on macrovascular complications of type 2 diabetes mellitus are therefore a major consideration in determining benefits and risks of therapy. However, it is generally accepted that reduction of cardiovascular disease requires attention to multiple potentially modifiable risk factors including hypertension, dyslipidaemia and smoking (table III).[32,35]

2.5 Glycaemic Control and Macrovascular Disease

Several cross-sectional and prospective studies support the existence of a relationship between long term glycaemic control and cardiovascular complications in patients with glucose intolerance or type 2 diabetes mellitus.[20,21,27,34] The putative glycaemic threshold is lower than that for microvascular complications of diabetes mellitus, being only marginally above normal values.[33,34] Evidence for a linear relation between glycaemic control and coronary heart disease risk has come from 2 Finnish studies in middle-aged and elderly patients with type 2 diabetes mellitus.[30,36] However, overall hyperglycaemia emerges as a less potent predictor than dyslipidaemia or hypertension.

Several plausible mechanisms have been proposed by which hyperglycaemia could initiate or promote atherosclerosis (table IV).[37] In the Kumamoto study[24] which, incidentally excluded patients with hypertension or hypercholesterolaemia, intensive insulin therapy was associated with a lower incidence of macrovascular events (0.6 *vs* 1.3 events per 100 patient-years). Although lipid results were not presented, insulin therapy produces potentially beneficial effects on lipoprotein metabolism in other populations with at higher risk of hyperlipidaemia-associated atheroma.[38]

Table III. Potentially modifiable risk factors for cardiovascular disease in type 2 diabetes mellitus

Risk factor[a]	Comments
Hyperglycaemia[b]	Increased risk apparent even with relatively minor degrees of hyperglycaemia
	Long term normalisation of glucose difficult in practice
Hypertension	Major risk factor; part of the insulin resistance or metabolic syndrome
High LDL-cholesterol[b]	Risk magnified by the presence of diabetes mellitus; glycation and decreased clearance implicated
	Small dense LDL particles in insulin resistance and type 2 diabetes mellitus particularly prone to oxidation
Low HDL-cholesterol[b]	Important modifier of risk; a component of the characteristic dyslipidaemia associated with type 2 diabetes mellitus
Hypertriglyceridaemia[b]	Closely associated with low-HDL cholesterol levels; increased delivery of fatty acids results in enhanced hepatic VLDL triglyceride synthesis
Prothrombotic/antifibrinolytic	Evidence for disturbances of fibrinolytic system and platelet function; aspirin (acetylsalicylic acid) recommended for high-risk patients with type 2 diabetes mellitus
Obesity	Present in majority of patients with type 2 diabetes mellitus
	Aggravates disturbances in carbohydrate and lipid metabolism, particularly abdominal obesity
Microalbuminuria[b]	Microalbuminuria is a marker for cardiovascular disease
	Associated with greater insulin resistance

a All these risk factors are components of the insulin resistance or metabolic syndrome.

b Factor with potential for improvement by insulin, either directly or via improved glycaemic control.

HDL = high density lipoprotein; **LDL** = low density lipoprotein; **VLDL** = very low density lipoprotein.

2.5.1 Sulphonylureas or Insulin for the Prevention of Macrovascular Disease in Type 2 Diabetes Mellitus?

Favourable changes in hepatic lipase activity and plasma triglyceride and high density lipoprotein (HDL_2) levels have been observed with insulin therapy even when similar glycaemic control is obtained with a sulphonylurea.[39] Insulin therapy has also been demonstrated to preferentially reduce the activity of plasminogen activator inhibitor-1 and levels of proinsulin-like molecules, which have also been implicated in atherogenesis, when compared with a sulphonylurea.[40] These studies provide theoretical support for the use of insulin in patients at high risk of cardiovascular events.

Evidence favouring insulin therapy comes from a Swedish multicentre randomised trial of insulin therapy following myocardial infarction in patients with diabetes mellitus (the DIGAMI study).[41] Over 600 study participants, more than 80% of whom were considered to have type 2 diabetes mellitus, were randomly assigned to intensive treatment with an intravenous insulin/glucose infusion on the coronary care unit followed by multiple daily insulin injections, or to a control group who received insulin only if clinically indicated. HbA_{1c} levels decreased significantly in both groups during follow-up, the reduction being greater in the intensively-treated group at the 3 and 12 month follow-up.

During the first year of follow-up, a relative reduction in mortality of 30% was observed in the intensively-treated group, mainly after discharge from hospital. After nearly 3.5 years, a significant reduction ($p < 0.05$) in mortality of 11% was still evident. Of particular interest, the reduction in mortality was most pronounced in a pre-defined subgroup who had not previously received insulin treatment and were at lower cardiovascular risk as a consequence of being younger (<70 years) with no prior history of myocardial infarction or congestive cardiac failure. In view of the greater mortality of patients with diabetes mellitus post-myocardial infarction[42] these results have important implications for clinical care. While improved glycaemic control is a plausible explanation for the improvement in survival, insulin-mediated improvements in plasma fatty acid[42] and lipoprotein metabolism are of potential relevance.

Another intriguing possibility that has been raised is that the reduced mortality in the intensively treated patients might, at least in part, have

resulted from withdrawal of sulphonylurea treatment. Concerns about the cardiovascular safety of sulphonylureas were initially raised by the findings of the University Group Diabetes Program (UGDP) in the 1970s.[43] This controversial study reported an increased risk of cardiovascular mortality in patients randomised to tolbutamide.[38] Although the UGDP received much criticism for failings in randomisation procedure, ascertainment and compliance,[37] the possibility of an adverse effect of sulphonylureas on cardiovascular disease finds some support from studies of myocardial ischaemia in experimental animal models.[44] Sulphonylureas stimulate insulin secretion by acting via specific receptors to close ATP-dependent K^+ channels in the islet β cells; this results in calcium entry and depolarisation of the cell with release of insulin. It has been suggested that sulphonylurea-induced closure of similar channels in the vasculature of the acutely ischaemic myocardium might amplify ischaemic damage.[44] However, there are reservations about the validity of extrapolations from animal experiments to clinical diabetes mellitus. Moreover, this disadvantageous effect must be set against evidence of a potentially protective effect of K^+ channel closure on post-infarct arrhythmias and positive effects of sulphonylureas on glycaemia, lipoproteins and other cardiovascular risk factors in diabetes mellitus.[13,44] Clinical studies in participants with lesser degrees of glucose intolerance suggest that early treatment with sulphonylureas may have beneficial cardiovascular effects.[45,46] More recently, the UKPDS investigators found no evidence of a difference ($p = 0.66$) in rates of myocardial infarction between sulphonylurea- and insulin-treated patients on an intention-to-treat analysis.[25] However, a subgroup analysis sulphonylurea-treated patients given metformin at early stage had a significant increase in all-cause mortality.[14] The mechanisms responsible and the interpretation of this observation are uncertain.[26]

2.5.2. Exogenous Insulin and Cardiovascular Risk in Type 2 Diabetes Mellitus

At this juncture it is appropriate to consider the controversy concerning hyperinsulinaemia as a risk marker for cardiovascular disease. A relationship between hyperinsulinaemia and atherogenesis was first postulated in the late 1960s; the issue has remained contentious.[47] Discrepancies between different prospective studies of patients without diabetes mellitus in the nature and consistency of the relationship between plasma insulin levels have undermined this relationship.[48] Reaven[49] has argued that insulin resistance, rather than compensatory hyperinsulinaemia, is the fundamental defect which in any case may increase the risk of cardiovascular disease through its associations with other risk factors. Since elevated plasma insulin levels are a surrogate marker for tissue insulin resistance[10] the cardiovascular risk factors which cosegregate as components of the insulin resistance syndrome[7] are likely to have been operative in studies of patients who do not have diabetes mel-

Table IV. Potential mechanisms by which hyperglycaemia may contribute to accelerated atherogenesis

Mechanism	Comments
Glycation of proteins	Glycation of LDL, HDL and platelets may accelerate atherogenesis
	Advanced glycation end-products of collagen may result in loss of vascular compliance
PAI-1	This inhibitor of plasminogen activator is released by vascular endothelium by hyperglycaemia
	Release of PAI-1 from platelets is higher in patients with type 2 diabetes mellitus than control individuals
	Tissue plasminogen activator and plasminogen may also be glycated
Endothelial dysfunction	Implicated in atherogenesis; demonstrable in patients with type 2 diabetes mellitus
	May be associated with microalbuminuria
Oxidative stress	Increased in diabetes mellitus; small, dense LDL particles are more easily oxidised and hence more atherogenic

HDL = high density lipoprotein; **LDL** = low density lipoprotein; **PAI-1** = plasminogen activator inhibitor-1.

litus. Not all studies have taken such factors, notably dyslipidaemia, into account.[47] However, a recent prospective study in Canadian men without diabetes mellitus demonstrated in multivariate analysis that fasting hyperinsulinaemia was an independent risk marker for coronary events.[50] Direct effects of insulin on processes involved in atheroma formation have been demonstrated *in vitro*.[51] However, the relevance of the pharmacological levels of insulin employed in some studies is of dubious relevance to the situation in humans. More recent clinical and experimental data contradict the view that exogenous insulin accelerates atherogenesis.[26,52] Nonetheless, concerns have been expressed about the use of exogenous insulin in type 2 diabetes mellitus for fear of exacerbating atheroma.[37,53] Cross-sectional studies have been reported in which plasma insulin levels and/or insulin dose have correlated with the presence of atheromatous disease.[47] However, these observations have not been confirmed in prospective studies.

Clearly, the nature of the relationship between insulin and atheroma is of relevance to the treatment of type 2 diabetes mellitus and randomised clinical trials have been advocated as the only reliable means of resolving this issue.[27,37,52] The feasibility trial of the Veterans Affairs cooperative study (VA CSDM) involved 153 men, 80% of whom were overweight, average age 60 years with a mean duration of type 2 diabetes mellitus of 7.8 years with suboptimal glycaemic control. The participants were randomly allocated to standard or more intensive insulin treatment.[54] Standard treatment comprised a single daily injection of insulin whereas the intensive treatment arm used a stepped therapy regimen designed to produce near-normoglycaemia. This began with a single evening injection of insulin, escalating to include additional daytime sulphonylurea therapy, followed by 2 and then 3 (or more) injections per day if required. A statistically significant separation between the 2 groups in HbA_{1c} of 2.07% was sustained for a mean follow-up of 27 months. Of note, improved glycaemic control in the intensive insulin therapy groups was attained without causing significant elevations of blood pressure, exacerbation of dyslipidaemia, severe hypoglycaemia or excessive bodyweight gain. However, mild and moderate hypoglycaemia was more common in the intensive treatment group at 16.5 *vs* 1.5 episodes per patient per annum. Mean insulin dose was significantly (23%) lower in the standard treatment arm.[55] Although there was no difference in total and cardiovascular mortality between the groups ($n = 5$ and $n = 3$, for the intensive and standard groups, respectively) there was a non-significant ($p = 0.10$) trend towards more new cardiovascular events in the intensive treatment group (32 *vs* 20%). In Cox regression analysis, the only significant correlate for new cardiovascular events was previous cardiovascular disease. Although no cardiovascular event was temporally associated with hypoglycaemia, an obvious if infrequently encountered concern in clinical practice, there was a trend towards more cardiovascular events in patients with lower HbA_{1c} levels.

The investigators speculate intriguingly about the possibility that intensification of glycaemic control may have had a transient effect on cardiovascular events in a manner analogous to that observed in clinical trials of retinopathy, a microvascular complication, in patients with type 1 diabetes mellitus. For example, in the DCCT secondary prevention group, that is, patients with early retinopathy at baseline, retinopathy worsened transiently during the initial 3 year period of the trial. The conventional and intensive treatment groups then diverged, the subsequent progression of retinopathy being reduced in the latter group providing overall benefit during the remainder of the study.[22] If a similar effect operated in the VA CSDM trial, the implication is that benefit would have ultimately accrued with intensive therapy. This phenomenon, which has been termed normoglycaemic re-entry,[56] has also been implicated in cases of acute symptomatic neuropathy which occasionally follow the initiation of insulin treatment. A recent report from Sweden highlighted the increased risk of deterioration in per-existing retinopathy following improvement in glycaemic control with insulin in patients with type 2 diabetes

mellitus.[57] However, rather than being an argument for therapeutic inaction this report emphasises the need for careful surveillance and timely photocoagulation.[56] Finally, in the UKPDS, intensified therapy with either sulphonylureas or insulin was associated with a borderline ($p = 0.052$) reduction in myocardial infarction over 15 years[25] with no evidence of a deleterious effect of intensified therapy on any of the macrovascular endpoints studied.[25]

2.6 Strategies for the Use of Insulin in Type 2 Diabetes Mellitus

Insulin is used either as monotherapy in patients with type 2 diabetes mellitus, usually as a once or twice daily injection or, less commonly, in combination with oral antidiabetic agents.

2.6.1 Combination Therapy with Insulin and Oral Agents

Both sulphonylureas and metformin are used in conjunction with insulin, albeit with widely varying degrees of enthusiasm. Proponents of combination therapy can point to evidence from clinical trials of reduced insulin requirements and less marked bodyweight gain when sulphonylureas are combined with insulin.[58-60] Daytime sulphonylurea therapy with a morning or evening injection of isophane insulin provides comparable short term glycaemic control to 2 daily injections of premixed insulin.[61,62] However, it is uncertain whether advantages in terms of bodyweight gain described for sulphonylurea plus evening insulin are independent of improvements in glycaemic control.[63] Residual endogenous insulin secretion is regarded as a prerequisite for successful combination therapy;[13,54] evidence from the UKPDS indicates that insulin reserves decline with time.[11] In the relatively short VA CSDM feasibility trial, 64% of patients had advanced to 2 or more injections per day, although the additional benefit in HbA_{1c} was marginal.[54] In their latest report, the authors report that maximal effect of glipizide was observed at a dosage of 10 mg/day; higher doses were associated with a trend towards higher HbA_{1c} levels.[64] Similar incremental progression has been reported in other studies.

It is suggested that combination therapy may be useful in elderly patients who have reservations about transfer to insulin.[13] To some extent, this may reflect an effect of the attitudes, expressed both overtly and tacitly, of the diabetes care team. Many patients are understandably concerned about the inconvenience, discomfort and potential risks of insulin;[65] insulin treatment may be regarded either as a semi-punitive measure or as representing a deterioration in an individual's diabetes which carries adverse prognostic implications. Combination therapy could be regarded as something of a half-way measure and in our experience, insulin therapy can be remarkably well accepted and successful even by elderly patients. A positive approach to the prospect of insulin treatment, raised at an early stage and avoiding any suggestion of culpability on the patients' part, may assist the transfer to insulin when secondary failure of oral agents ensues.[66]

Although detractors of combination therapy voice concerns about polypharmacy, the clinical and biochemical heterogeneity of type 2 diabetes mellitus suggests that there may be merit in tailoring treatment to the individual. With an expanding range of oral agents this approach may become more popular. Combination therapy may be more expensive than insulin as monotherapy and this is not invariably associated with advantages in terms of risk of bodyweight gain.[67] There is some evidence for less marked bodyweight gain when insulin is combined with metformin[68] although the clinical implications of effects on other cardiovascular risk factors remain uncertain.[69] A recent randomised trial showed that in combination with bedtime insulin, metformin was associated with a favourable triad of improved glycaemic control, prevention of bodyweight increase and a relatively low rate of hypoglycaemia.[70] The introduction of troglitazone has added another agent which may be useful in combination with insulin.[71] Studies in the US indicate that glycaemic control may be improved thereby allowing a reduction in insulin

dose. However, the long term gains from this approach are unknown and must be set against the small risk of hepatotoxicity with this particular drug.[72]

2.6.2 Insulin as Monotherapy

Twice-daily insulin, given as isophane or premixed preparations (e.g. 30% short-acting, 70% isophane or in 50 : 50 combination), is often effective in patients with type 2 diabetes mellitus. Pen injectors may improve acceptability and compliance, although elderly patients may experience practical difficulties resulting from limited dexterity or visual impairment. Important issues of supervision and support are raised by patients who are unable to safely self-inject. In addition, home-monitoring of capillary blood glucose levels is regarded as an essential prerequisite to safe insulin therapy[13,58] and if this is not possible therapeutic targets may have to be relaxed. The pharmacokinetics of isophane insulin are such that once-daily injections will rarely produce glycaemic control that is satisfactory throughout the day. In particular, adequate suppression of overnight endogenous glucose production, principally by the liver, is necessary to control of fasting hyperglycaemia. Increasing a single daily dose runs the risk of hypoglycaemia at other times, especially in non-obese patients with less marked insulin resistance. Insulin-mediated suppression of fatty acids may contribute to reductions in hepatic glucose production.[73] Longer-acting insulins, for example, ultralente, have been used as the basis of so-called basal-bolus regimens wherein the long-acting preparation provides background low level insulin upon which pre-meal boluses of short-acting insulin are superimposed.[11,74] Such regimens, which are more demanding and may not result in better control than twice-daily injections,[63] are rarely indicated in patients with type 2 diabetes mellitus. This applies to other strategies such as pump-delivered continuous subcutaneous insulin infusions.[58] Implantable insulin pumps remain experimental[58] as do novel approaches such as insulin-like growth factor-1 therapy.[75] The potential role of shorter-acting insulin analogues such as lispro in patients with type 2 diabetes mellitus is presently uncertain.

2.7 Potential Adverse Effects of Insulin Therapy

2.7.1 Hypoglycaemia

Hypoglycaemia is the most-feared adverse consequence of insulin therapy. Severe hypoglycaemia, which may be associated with incapacity, seizures or injury, is a particularly unwelcome prospect in the elderly patient who has a high probability of significant atherosclerotic disease. Clinical studies generally indicate that the risk of severe hypoglycaemia in patients with type 2 diabetes mellitus is several-fold lower in insulin-treated patients with type 2 diabetes mellitus.[58] This may reflect, at least in part, the setting of less strict glycaemic targets and reserves of endogenous insulin secretion which may result in a lower dose of insulin; insulin resistance may offset the latter effect. However, patient selection may be an important factor in studies comparing type 1 and type 2 diabetes mellitus.

For example, in a study in which 104 patients with type 2 diabetes mellitus were matched for duration of insulin therapy with patients who had type 1 diabetes mellitus, thereby reducing differences attributable to residual endogenous insulin secretion between the groups, the frequency of severe hypoglycaemia was similar.[76] Hypoglycaemia was reported in over 70% of the middle-aged patients assigned to insulin in the UKPDS with major hypoglycaemia requiring third party assistance or hospitalisation occurring in 11% over 6 years.[11] Major hypoglycaemic events occurred at rates of 0.7 and 2.3% per annum for sulphonylureas and insulin, respectively. Despite a relatively low incidence of hypoglycaemia, approximately one-quarter of that for patients with type 1 diabetes mellitus, the UKPDS suggests that this is a limiting factor in sustaining target levels of glycaemia; even adding short-acting insulin pre-meals did not prevent a gradual progressive rise in HbA_{1c} levels from the end of the first year of the study onwards.[11] In part, this may reflect the fact that, un-

like the highly selected and motivated participants in the DCCT, not all of the insulin-treated patients in the UKPDS were willing or able to monitor a multiple injection regimen.

Interestingly, in the Kumamoto study, intensive insulin therapy did not result in any episodes of severe hypoglycaemia over 6 years; mean HbA_{1c} level was 7.1% in this group, higher than that of the UKPDS intensive therapy group.[24] In a randomised study of elderly patients, mean age 68 years, no episodes of severe hypoglycaemia were observed during 6 months in patients assigned to twice-daily insulin.[67] Nonetheless, factors such as social isolation and cognitive impairment are important considerations in elderly patients.

2.7.2 Bodyweight Gain

Bodyweight gain is a predictable effect of insulin therapy; increases in both adipose tissue and lean body mass contribute. Although this may be disadvantageous in patients who are already overweight or obese insulin treatment should not be withheld for this reason; control of hyperglycaemia must take precedent in the long term. During the first 9 years of the UKPDS, mean bodyweight increased by 5 and 7kg, respectively, in patients assigned to sulphonylureas or insulin, compared with 3kg in those who continued with diet. Fasting plasma insulin levels were higher in the insulin- and sulphonylurea-treated groups. Obese patients assigned to metformin and to conventional therapy had increases of only 1kg.[11]

In a randomised study, Yki-Järvinen et al.[63] reported a mean increase of 2.9kg in a multiple injection group although follow-up continued for only 3 months. This was associated with a 39% increase in diurnal serum free insulin levels. In the most recent publication from these investigators, combining metformin with bedtime insulin in patients poorly controlled with sulphonylureas resulted in bodyweight gain at 1 year of only 0.9kg.[70] In the aforementioned trial in which 34 elderly patients were treated with twice-daily insulin, mean bodyweight increased significantly over 6 months from 67.4 to 71.4kg.[67]

In a 6 month trial of insulin in 14 patients with a mean body mass index of 31 kg/m^2 and secondary failure of oral agents, Henry et al.,[77] aiming for tight glycaemic control using twice-daily mixtures of insulin, found that bodyweight gain was inversely related to the pre-treatment glucose disposal rate as determined using the glucose clamp technique. Thus, on average, the more insulin-resistant the patient at baseline, the greater the gain in bodyweight. In addition, bodyweight gain, which averaged 9% of initial bodyweight, was directly correlated with both mean day-long serum insulin levels and total insulin dose. In another study, Shank et al.[78] found that bodyweight gain following the initiation of insulin treatment was almost entirely accounted for by the reduction in glycosuria.

The morbidly obese patient inadequately controlled with oral agents remains a particularly difficult problem; there is a paucity of clinical trial data to guide clinicians.[79] Such patients may require substantial doses of insulin which may prove daunting for doctor and patient alike; even so, glycaemic targets may not be attained. There is emerging evidence suggesting that the thiazolidinediones may be particularly useful in such circumstances.[72] In such patients the reduction of glycaemia should be the primary goal, rather than reduction of insulin dose.

2.7.3 Effects on Quality of Life

Improvement in glycaemic control in patients with type 2 diabetes mellitus who have osmotic symptoms can be expected to bring rapid symptomatic benefit. However, many patients with type 2 diabetes mellitus have elevated renal thresholds for glucose which protect them from osmotic symptoms. Nonetheless, hyperglycaemia in patients with type 2 diabetes mellitus may be associated with other vague symptoms of chronic ill-health that improve with the institution of insulin therapy. This hyperglycaemia-associated malaise[80] may be multifactorial; unwanted effects of oral antidiabetic agents, notably metformin, may contribute. There is evidence from cross-sectional studies that higher HBA_{1c} levels in patients with

type 2 diabetes mellitus are associated with higher negative scores for physical symptoms, mood and wellbeing.[81] Despite the perceived inconvenience associated with insulin therapy transfer from oral agents, with improved glycaemic control, does not necessarily result in reduced treatment satisfaction.[82] Insulin treatment may have potentially serious consequences for employment prospects. The implications of transfer to insulin for holders of vocational driving licences and patients whose occupations preclude insulin therapy must be borne in mind. These restrictions reflect concerns about risks posed by insulin-induced hypoglycaemia.

3. Conclusion

Insulin therapy improves the major disturbances in glucose metabolism which characterise type 2 diabetes mellitus. Furthermore, insulin has potentially beneficial effects on other risk factors for atheroma (table III). However, the inconvenience of delivering and monitoring insulin therapy together with concerns about severe iatrogenic hypoglycaemia and bodyweight gain have led to underutilisation of this treatment. Certain clinical situations demand insulin as the treatment of choice, but for many patients insulin is regarded as a last resort, not infrequently after years of inadequate metabolic control. The benefits of insulin therapy should prompt consideration of insulin earlier in the course of type 2 diabetes mellitus. This approach would seem particularly applicable to patients with early onset of disease and a high propensity for chronic complications.[3,83]

The evidence that good glycaemic control is important is now overwhelming; improvements in control are particularly beneficial for individuals with higher HbA_{1c} levels. Moreover, recent studies suggest that intensive treatment of type 2 diabetes mellitus appears to be a well tolerated and effective option for many patients. The potential health benefits are large. However, careful patient selection and provision of high quality multidisciplinary care are required; therapy should be tailored to the individual if the benefit-to-risk ratio is to be maximised.[84,85] Further studies comparing different insulin regimens and combinations of insulin and oral agents are indicated.

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