Clinical Forum

Intensive glycaemic control in type 2 diabetes mellitus with focus on insulin therapy

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Type 2 diabetes mellitus is a heterogeneous disease and is probably characterised by different pathogenic mechanisms and variable contribution of insulin resistance and insulin deficiency.[1-4] Moreover, the mix of insulin resistance and insulin deficiency is likely to be different in each patient and in any patient, may vary during the course of the disease.[4,5] In turn, chronic hyperglycaemia can impair both insulin-secretory response to glucose and cellular insulin sensitivity (i.e., glucose toxicity).[4,6-8] Epidemiological and clinical data have unequivocally emphasised the relationship between long-term metabolic control and the incidence and progression of diabetic microvascular complications such as retinopathy, nephropathy and neuropathy in both Type 1 and Type 2 diabetes.[9-10] There are several associations and correlations between hyperglycaemia and macrovascular disease[11-23] and a role for hyperglycaemia in the pathogenesis of atherosclerosis and thrombosis is postulated.[24-34] Epidemiological studies have found that insulin is integral to the management of about 30% to 40% of patients with Type 2 diabetes.[35-36] Insulin is temporarily required to control hyperglycaemia during severe stress (e.g., injury, infection, surgery) or in pregnancy, but in majority insulin therapy is aimed at reducing long-term complications. Data from long-term interventional studies[37-39] and others from short-term interventional studies[40-51] have shown that intensive glycaemic control is feasible and beneficial in reducing microvascular complications among patients with Type 2 diabetes. The aim of this review is to provide evidence for the importance of good glycaemic control in Type 2 diabetes, with a focus on insulin therapy.

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The effects of intensive insulin therapy on insulin secretion and insulin action

Several studies have considered the influence of short-term intensive insulin therapy on insulin secretion in Type 2 diabetic patients. The results of these clamping studies are variable but there seems to be a consensus on the concept that induction of a short period of normal blood glucose by insulin therapy

improves insulin secretion and reduces insulin resistance.[46-50] In support of this consensus, the result of a recent study has shown that temporary intensive insulin treatment in insulin-requiring Type 2 diabetics decreases insulin requirement and improves sensitivity to insulin.[51] More recently short-term continuous subcutaneous insulin infusion treatment has been found to improve insulin resistance, and increase insulin secretion in overweight Type 2 diabetic patients with oral antidiabetic treatment failure.[34] Similarly, in Type 1 diabetes, intensive insulin therapy helps to sustain endogenous insulin secretion which, in turn, is associated with better metabolic control.[52] In cases of Type 2 diabetic patients who are at high risk for slowly progressive β-cell failure due to the development of pancreatic auto-immunity, treatment with subcutaneous small doses of insulin may result in improvement of serum c-peptide.[44] Moreover, the results of a recent study suggest that in a significant proportion of newly diagnosed Type 2 diabetic patients who fail to respond to dietary measures, short-term intensive insulin therapy effectively establishes responsiveness.[45]

Micro-vascular disease and intensive insulin therapy in Type 2 diabetes

According to the results of the landmark Diabetes Control and Complication Trial (DCCT),[53] the significance of intensive glycaemic control to retard the onset and the progression of diabetic micro-vascular complications in Type 1 diabetes has been firmly established. There are recent large-scale clinical trials that bear on the issue of intensive glycaemic control in Type 2 diabetes. Previously, the results of the University Group Diabetes Program trial (UGDP)[54] showed that intensive insulin therapy was neither beneficial nor harmful. However, critics suggested the UGDP trial lacked power to assess this issue.[55-56] The results of the recently concluded landmark United Kingdom Prospective Diabetes Study 33 (UKPDS 33)[39] have emphasized that intensive glycaemic control has substantially decreased the risks of microvascular complications in newly diagnosed Type 2 diabetic patients. Moreover, epidemiological analysis of the data of this study has shown a continuous relationship between the risk of microvascular complications and glycaemia, such that for every percentage point decrease in HbA_{1c} (e.g., 9 to 8%) there is a 35% reduction in the risk of microvascular complications. Similar results have been observed in the Japanese Kumamoto Study,[37] but were in patients with Type 2 diabetes of recent onset and who were being treated with conventional insulin therapy. The recently started long-term prospective Veterans Affairs Cooperative Study on Glycaemic control and complications in Type 2 Diabetes Mellitus [39,57] (VACSDM) is likely to yield more data in this regard.

Macrovascular disease and intensive insulin therapy

Regarding the effect of long-term intensive insulin therapy on macro-vascular disease, the UGDP study suggested that improved glycaemic control with insulin was neither harmful nor beneficial. The UKPDS 33 showed that intensive glycaemic control by insulin neither decreases macrovascular disease substantially nor has adverse effect on cardiovascular outcome as suspected in several previous reports.[56,58-60] However, in the UKPDS 33 there was evidence, albeit inconclusive, of a 16% risk reduction for myocardial infarction, which included non-fatal and fatal myocardial infarction and sudden death. Both the UGDP and UKPD 33 studies

were designed to compare the effect of diet, oral drug therapy, and insulin on glycaemic regulation and vascular events in newly diagnosed Type 2 diabetic patients. However, Hellman *et al* observed that a long-term (>11 years) intensive insulin therapy was associated with significantly lower cardiac mortality than a short-term (<1 year) intensive treatment.[61] In the Belfast diet study, a 10 year prospective follow-up of insulin treatment significantly reduced ischaemic heart disease mortality compared with patients treated with diet alone.[62] In the feasibility study of VA CSDM trial, with an average follow up of 27 months, the pooled total and major cardiovascular event rates, were 26% (11.6% per year) and 16.3% (7.3% per year) respectively.[57] The high cardiovascular event rates in the feasibility study of VACSDM trial might be explained by the long duration of Type 2 diabetes in these group of patients together with the contribution of preexisting cardiovascular disease. However, it is anticipated that the end results of the VACSDM trial will determine the risk-benefit ratio of intensive insulin therapy on progression of macrovascular disease in the population with Type 2 diabetes.

In the context of acute myocardial infarction,[63,64] recently, the Diabetes Mellitus Insulin Glucose infusion in Acute Myocardial Infarction (DIGAM1) study showed a major advantage of improved glycaemic control during and after myocardial infarction in diabetic patients. In this study insulin and glucose infusion during the hospital admission, followed by multiple injection therapy thereafter, reduced mortality after myocardial infarction by around one-third, both at 12 months[65] and at around 3½ years.[66] Whether this advantage is due to early or late glycaemic control[39] or direct effect of insulin[67] as opposed to sulfonylurea [54,68-72] is still unclear. Similarly, as diabetic patients have worse survival and recovery prospects after acute stroke than non-diabetic patients, and hyperglycaemia is a predictor of poor outcome in acute phase of stroke,[19-21] a randomised trial of intensive glycaemic control is warranted in patients with stroke complicated by hyperglycaemia.

Effects of intensive insulin therapy on the lipid profile and the parameters of fibrinolysis

Regarding lipid profile, intensive insulin therapy caused sustained and significant reduction in plasma triglyceride levels[73-75] and this reduction is likely to be due to insulin-induced enhancement of triglyceride clearance.[76] Sustained decrease in serum cholesterol has been induced by intensive insulin therapy in Type 2[73,74] and Type 1 diabetes.[75] Also, intensive insulin therapy reduced low density lipoprotein (LDL) cholesterol in Type 2[74] and Type 1 diabetes.[75] But, other studies found no reduction in LDL cholesterol level at any point in the intensive insulin therapy of Type 2 diabetes.[73] However, there are important compositional changes in LDL cholesterol particles depending on serum triglyceride and glucose levels.[76-79] Specifically, when serum triglyceride is maintained below 150 mg/dl, less atherogenic LDL cholesterol particles emerge. Insulin treatment in Type 2 diabetes induces profound metabolic modifications of lipoproteins, resulting in a significant decrease of the intra-vascular residence time of very low density, intermediate density and low density lipoprotein particles. These modifications are likely to make these particles less harmful.[80] It has been assumed that intensively treated diabetic subjects, have lower proportion of glycated LDL cholesterol[79,81] and

consequently less oxidized LDL cholesterol.[82-84] As glycated and oxidized LDL cholesterol may be more atherogenic than unmodified LDL particles, its lowering with tight glycaemic control retards atherogenesis. Similarly, the levels of high density lipoprotein (HDL) cholesterol were preserved in intensive insulin therapy, whereas there was a slight, but significant, reduction with the conventional insulin therapy.[73] But, intensive glycaemic control did not have any effect on lipoprotein (a) level.[73]

Though the improved glycaemic status with intensive insulin therapy is beneficial, the resultant hyperinsulinaemia may have deleterious effects on atherogenesis. It has been reported that serum fibrinogen is increased in diabetic patients compared with non-diabetic subjects[85-87] and that the fibrinogen level correlate positively with the initial fasting serum insulin level[88] and the insulin dosage during therapy.[89] In the feasibility study of the VA CSDM trial, in a cohort of Type 2 diabetic patients, after 2 years of intensive insulin therapy there was a transient rise in serum fibrinogen level— a possible thrombogenic effect.[73] Moreover, it has been recently reported that a defect in the fibrinolytic system which results from an increase in Type 1 plasminogen activator inhibitor (PAI-1) is more frequent in Type 2 diabetic patients than in normal subjects.[27,30-33] The plasma PAI-1 level strongly correlates with fasting serum insulin in Type 2 diabetic patients and in obese subjects.[30-33,90-91] This suggests that insulin plays a major role in PAI- 1 production. On the contrary, others reported that in Type 2 diabetic patients, acute hyperinsulinaemia does not increase PAI-1 production during euglycaemic clamping[92-96] and insulin therapy suppresses PAI-1 activity and proinsulin like molecules independently of glycaemic control.[67] Elevated serum insulin level in an environment of increased glucose and triglyceride (typical of Type 2 diabetic patients) does elicit an insulin-dependent increase in circulating PAI-1.[97] Also, Anderson *et al* have reported that insulin can stimulate vascular smooth muscle cell production of PAI-1, which attenuates fibrinolysis.[98]

The goals of intensive glycaemic therapy

The goal of intensive glycaemic therapy is to reach the glycaemic targets to prevent the onset and the progression of diabetic long-term complications. The goals of the 6-year period of the Kumamoto study were a fasting blood glucose < 6.1 mmol/1 (110 mg/dl), a 2-h postprandial blood glucose <10 mmol/1 (180 mg/dl), and HbA_{1c} <6.5% (normal range 4.8 to 6.4%). Similarly over the 10 year period of the UKPDS 33, the goals were fasting blood glucose < 6 mmol/1 (108 mg/dl), pre-meal glucose concentrations of 4-7 mmol/1 (72-126 mg/dl) and HA_{1c} <7% (normal range 4.5-6.2%). In the 27 month period of the feasibility study of the ongoing VA CSDM trial, the goal was to achieve an HbA_{1c} as close to the normal range as possible (5.1± 1% [mean±2SD]). It also aimed at fasting blood glucose of 4.44-6.38 mmol/1 (80-115 mg/dl) and other preprandial levels to be < 7.22 mmol/1 (130 mg/dl). The European non-insulin dependent diabetes mellitus policy group[99] has set guideline targets for good glycaemic control in Type 2 diabetes. According to these targets, fasting blood glucose, postprandial glucose, and HbA_{1c}, must be less than 6.1 mmol/1 (109.8 mg/dl), 8 mmol/1 (144 mg/dl) and 6.5% respectively. However, the new goals for glycaemic control of the entire population of individuals with diabetes advocated by the American Diabetes Association (ADA) are

capillary blood glucose of 4.44-6.66 mmol/1 (80-120 mg/dl) before meals and of 5.55-7.77 mmol/1 (100-140 mg/dl) at bedtime and HbA_{1c} < 7% (normal range 4-6% [mean 5%, SD 0. 5%]). Table (1)

Approaches of intensive insulin, therapy in Type 2 diabetes mellitus

In Type 2 diabetes, a few short-term studies have evaluated the feasibility of intensive insulin therapy. Garvey *et al* used continuous subcutaneous insulin infusion therapy over 3 a week period to normalise serum glucose levels in mildly obese patients with uncontrolled Type 2 diabetes.[40] Henry *et al* tried conventional subcutaneous insulin therapy using NPH and regular insulin given before breakfast and supper for 6 months to achieve optimal glycaemic control in obese Type 2 diabetic patients.[41] Yki-Jarvinen *et al* used NPH and regular insulin before breakfast and dinner or NPH insulin at 2100 hour with regular insulin before breakfast, lunch, and dinner.[42] Chow *et al* found that twice daily injection of intermediate-acting insulin was effective and well-tolerated form of therapy in Type 2 diabetic patients with secondary failure of oral hypoglycaemic agents.[102] In the Swin study, bedtime NPH insulin injection has been tried to provide good glycaemic control in Type 2 diabetic patients with secondary failure of oral hypoglycaemic agents.[103]

Regarding the methods of long-term intensive insulin therapy, the feasibility study of the VACSDM trial was started with single evening intermediate- or long-acting insulin.[38] In the UKPDS 33, the patients were started on once daily ultralente insulin or isophane insulin and if the daily dose of insulin was more than 14 units or premeal or bedtime home blood glucose levels were more than 126 mg/dl, a short-acting insulin (regular) was added.[39] In the Kumomato Study patients were treated with short-acting insulin at each meal and intermediate insulin at bedtime.[37]

The recent recommendations of ADA[101] to achieve near normal or normal blood glucose levels in all Type 1 diabetic patients and by some Type 2 diabetic patients are multiple daily injections of rapid(lispro), short (regular), intermediate(NPH or lente), or long-acting insulins or by continuous subcutaneous insulin infusion. However, two main strategies of insulin treatment are commonly recommended[104] for insulin-treated Type 2 diabetic patients. The first strategy is the injection of a combination of neutral and intermediate insulin (e.g., 30% regular

Table 1 Glycaemic control for non pregnant adults with diabetes*. (Reference 101)

Biochemical index	Normal	Goal	Additional action suggested
Preprandial blood glucose (mg/dl) +	<110	80-120	<80 >140
Bedtime blood glucose (mg/dl) +	<120	100-140	<100 >160
*HbA_{1c} (%)	<6	<7	>8

* HbA_{1c} referenced to a nondiabetic range of 4.0-6.0% (mean 5.0%, SD 0.5%).
+ Measurement of capillary blood glucose

plus 70% NPH human insulin) before breakfast and before dinner. The second is the injection of regular insulin before main meals along with intermediate insulin in the morning or at bedtime. Interventional studies show that giving intermediate acting insulin at bedtime is either equal or even more effective than giving it in the morning.[102,103,105-106]

Side effects and risks of intensive insulin therapy

The main side effects of intensive insulin therapy in Type 2 diabetes are hypoglycaemia, weight gain, and hyperinsulinaemia. In the Kumamoto study the hypoglycaemic episodes were milder, compared to those seen in the DCCT. This might be due to the difference in insulin dosages between the two studies. Likewise, in the VA CSDM feasibility study hypoglycaemic episodes requiring assistance were rare. Indeed, the rate was at least 20 times lower than in trials on Type 1 diabetes.[53] However, in the UKPDS 33 all intensive treatments increased the risk of hypoglycaemia. The rates of major hypoglycaemic episodes per year were 0.7% with diet control alone, 1.0% with chlorpropamide, 1.4% with glibenclamide and 1.8% with insulin. Regarding weight gain, in patients with Type 2 diabetes it has been shown that improved glycaemia during insulin therapy promotes weight gain by decreasing both basal metabolic rate and glucosuria.[107] There was a slight but not significant increase in body mass index in both Kumamoto study and VA CSDM feasibility study. Indeed a 2% lowering of HbA_{1c} was not associated with weight gain in the VA CSDM feasibility study. In the UKPDS 33 there was a significant weight gain in the intensive treatment with insulin or sulphonylurea (mean 2.9 kg) compared with the conventional treatment with diet alone ($p<0.001$). The patients assigned insulin had a greater weight gain (4.0 kg) than those assigned chlorpropamide (2.6 kg) or glibenclamide (1.7 kg). A major concern about the intensive insulin management of Type 2 diabetes is weight gain leading to increased peripheral insulin resistance, which in turn could result in higher insulin requirement. Also, the resultant hyperinsulinaemia might accelerate atherosclerosis.[56,58] Nevertheless, the evidence for this hypothesis is remarkably thin in the current literature.[112] The results of the prospective UKPDS 33 [39] showed that intensive glycaemic control with insulin or sulfonylurea have no adverse effect on cardiovascular outcome. In fact, the UKPDS observed a 'non-significant' trend toward protection.

It has been known that in patients with Type 1 diabetes, intensive glycaemic control deteriorates pre-proliferative or proliferative retinopathy and nephropathy (in those with albumin excretion of >300 mg/24h).[113-115] However, there are a few studies on intensive insulin therapy and progression of retinopathy in Type 2 diabetic patients.[116-117] Henricsson *et al* pointed to an increased risk of retinopathy progression after start of insulin therapy, and showed that the progression was related to the degree of improvement in glycaemic control. The change of treatment from oral drugs to insulin was associated with a 100% increased risk of retinopathy progression and a 3-fold increased risk of blindness /visual impairment.[116] However, several recent studies failed to reveal morphological deterioration of diabetic retinopathy with intensive

insulin therapy in Type 2 diabetic patients.[37-39] A proper international trial in Type 2 diabetes is needed to resolve this issue. The paradoxical worsening of advanced diabetic retinopathy(known as normoglycaemic re-entry phenomenon) appeared to be more frequent and/or more severe when improvement in control was greater or more rapid. In some reports worsening occurred more frequently in women.[118] Hence, in patients with poor glycaemic control whose retinopathy is already approaching the high-risk stage (very severe non-proliferative diabetic retinopathy or early proliferative diabetic retinopathy), it seems appropriate to do ophthalmologic monitoring during treatment (at 3-month interval for 6 to 12 months) or to delay the initiation of intensive treatment until photo-coagulation is completed. [115,117] There is experimental evidence to support a possible role for insulin like growth factor-1 (IGF-1) in the 'normoglycaemic re-entry phenomenon'. Hence, monitoring of IGF-1 concentrations might be helpful before starting intensive insulin therapy.[115]

Conclusion

As the association between tight glycaemic control and prevention/amelioration of micro-vascular complications in Type 2 diabetes has been proved, intensive glycaemic control should be instituted early. Medical nutrition therapy, exercise and diabetes education are essential components of tight glycaemic control. In obese patients, the need for weight loss and prevention of weight regain should be stressed. Though, oral hypoglycaemic drugs are effective for a variable period, most patients with Type 2 diabetes will ultimately require insulin therapy. In the UKPDS, 22% of patients randomised to metformin and 30% of patients randomised to suphonylurea were switched to insulin therapy by 6 years.[119] The results of Kumamoto study [37] and more recently the landmark UKPDS 33,[39] suggest that starting insulin earlier in the course of type 2 diabetes, substantially decreases the risk of microvascular complications. It is hypothesised that earlier in the natural history of Type 2 diabetes insulin treatment is started, the more endogenous reserve will be available.[104]

Hypoglycaemia, hyperinsulinaemia and weight gain are the important side effects of intensive insulin therapy. Self home blood glucose monitoring is generally considered necessary for prevention and early detection of hypoglycaemia. To prevent hyperinsulinaemia and weight gain, every effort should be made to achieve the best possible glycaemic control using the lowest dose of insulin. The fear that intensive insulin therapy will affect the quality of life [120] is alleviated in the UKPDS, [121] which showed that quality of life was more affected by diabetic complications than by intensive therapy. However, intensive glycaemic control of Type 2 diabetes may increase economic cost, but these costs must be weighed against the expected long term benefit of reducing microvascular complications. The treatment goals of intensive insulin therapy should be individually quantified, taking into consideration of the age, life expectancy and co-morbid conditions of the patient.

References

1. Olefsky JM. Introduction: Pathogenesis of insulin resistance and hyperglycaemia in NIDDM. Am J Med 1985; 97 (Suppl 3 B): 1-7.

2. De Franzo RA. The triumvirate : beta cell, muscle, liver: a collusion responsible for NIDDM. Diabetes 1988; 31:667-687.

3. Taylor SI, Accili D, Lmai Y. Insulin resistance or insulin deficiency. Which is the primary cause of NIDDM? Diabetes 1994; 43:735-740.

4. Ferrannini E. Insulin resistance versus insulin deficiency in non-insulin dependent diabetes mellitus: problems and prospects. Endocr Rev 1998; 19(4): 477-490.

5. Lev-Ran A, Hwang DL. C-peptide in NIDDM. Diabetes Care 1993; 16: 76-81.

6. Roneti L, Schulman GJ, Zawalich W, De Franzo RA. Effect of chronic hyperglycaemia on in vivo insulin secretion in partially pancreatomized rats. J Clin Invest 1987; 80: 1037-1064.

7. Yki-Jarvinen H. Glucose toxicity. Endocr Rev 1992; 13: 415-431.

8. Unger RH, Grundy S. Hyperglycaemia as an inducer as well as consequence of impaired islet cell function and insulin resistance: implications for management of diabetes. Diabetelogia 1985; 28: 119-125.

9. Pirart J. Diabetes mellitus and its degenerative complications: a prospective Study of 4400 patients observed between 1947 and 1973. Diabetes Care 1978; 1: 168-88: 252-61.

10. Engerman R, Bloodworth JM Jr, Nelson S. Relation of microvascular disease in diabetes to metabolic control. Diabetes 1977; 26:760-769.

11. Nathan DM, Mechanisms of diabetic complication. the glucose hypothesis: the pathophysiology of diabetes complications. How much does the glucose hypothesis explain ? Ann Intern Med 1996; 124 (1 pt 2): 86-89.

12. Klein R, Klein BE, Moss SE. Relation of glycaemic control to diabetic microvascular complications in diabetes mellitus. Ann Inter Med 1996; 124(1 pt 2): 90-6.

13. Kuusisto J. Mykkanen L, Pyorala K, Laakso M. NIDDM and its metabolic control predict coronary heart disease in elderly subject. Diabetes 1994; 43: 960-967.

14. Laakso M. Glycaemic control and the risk for coronary heart disease in patients with NIDDM The Finnish Study. Ann Intern Med 1996; 124: 127-130.

15. Meigs JB, Singer DE, Sullivan LM, et al. Metabolic control and prevalent cardiovascular disease in non- insulin dependent diabetes mellitus (NIDDM): the NIDDM patient out-comes research group. Am J Med 1997; 102: 38- 47.

16. Stern MP. The effect of glycaemic control on the incidence of macrovascular complications of type2 diabetes. Arch Fam Med 1998; 7/2:155-162.

17. Sowers JR, Lester MA. Diabetes and cardiovascular disease. Diabetes Care 1999; 22:C14-C20.

18. Reiber G, Pecoraro RE, Koepsell 1. Risk factors for amputation in patients with diabetes mellitus. Ann Int Med 1992; 117: 97- 105.

19. Murros K, Fogelhdm R, Kettuuen S, Vuorela AL, Valve J. Blood glucose, glycosylated haemoglobin, and outcome of ischeamic brain infarction. J Neurol Sci 1992; 11: 59- 64.

20. Jorgensen HS, Nakayama H, Raa Schou HO, Oslen TS. Stroke in patients with diabetes: the Copenhagen Stroke Study. Stroke 1994; 25:1977-84.

21. Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long term follow up study. BMJ 1997; 14: 1303 –1307.

22. Moss SE, Klein BEK, Meuer MS. The association of glycaemia and cause specific mortality in a diabetic population. Arch Int Med 1994; 2473-2479.

23. Anderson DKG, Svardsudd. Long- term glycaemic control relates to mortality in type 2 diabetes. Diabetes Care 1995; 18: 1534- 1543.

24. Lyons TJ. Glycation and oxidation: a role in the pathogenesis of atherosclerosis. Am J Cardiol 1993, 71: 26B- 3IB.

25. Stringer HAR, Van Swieten P, Heijnen HFG, Sixma JJ, Pannekoke H. Plasminogen activator inhibitor-1 released from activated platelet play a key role in thrombolysis resistance. Arterloscler Thromb 1994;41: 1452- 1458.

26. Jokl R, Colwell JA. Clotting disorders in diabetes. In International Textbook of Diabetes Mellitus. 2nd ed. Alberti KGMM, Defranzo RA, Zimmet P, keen H, Eds. Chichester, U.K., Wiley 1996 P: 229- 235.

27. Myane EE, Bridges JM, Weaver JA. Platelet adhesiveness, plasma fibrinogen, and factor VIII levels in diabetes mellitus. Diabetologia 1970, 6: 436-440.

28. Kannel WB, D'Agostino RB, Wilson PWF, Belager AJ, Gagnon DR. Diabetes, fibrinogen, and risk of cardiovascular disease: the Framingham experience. Prog Cardiol 1978; 120: 672-676.

29. Santen RJ, Willis PW, Fajans SS. Atherosclerosis in diabetes mellitus. Arch Intern Med 1972; 130: 833- 842.

30. Juhan-Vague 1, Roul C, Alessi MC, et al. Increased plasminogen activator inhibitor activity in non-insulin dependant diabetic patients. Relationship with plasma insulin. Throm Haemost 1989; 61: 370-373.

31. Garacia Frade LJ, De La Calle H, Torrado MC et al. Hypofibrinolysis associated with vasculopathy in non-insulin dependent diabetes mellitus. Thromb Res 1990; 59: 51-59.

32. Auwerx J, Bouillou R, Collen D, et al. Tissue type plasminogen activator antigen and plasminogen activator inhibitor in diabetes mellitus. Arteriosclerosis 1988; 8: 68-72.

33. Lormeau B, Debussche X, Dieval J, et al. Fibrinolyse et diabete sucre: un role dans les complications degeneratives? Ann Interne Med 1993; 144: 108-116.

34. Valensi P, Moura 1, Le Mangoarou M, et al. Short-term effects of continuous subcutaneous insulin infusion treatment on insulin secretion in non-insulin dependent overweight patients with poor glycaemic control despite maximal oral antidiabetic treatment. Diabetes Metab 1997; 23: 51-57.

35. West KM, Ahuja MM, Bennett PH, et al. The role of circulating glucose and triglyceride concentrations and their interaction with other risk factors as determinants of arterial disease in nine diabetic population samples from the VMO multinational Study. Diabetes Care 1993; 6:361-369.

36. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The medical management of hyperglycaemia over a 10-year period in people with diabetes. Diabetes Care 1996; 19:744-750.

37. Ohkubo Y, Kishikawa H, Araki E, Miyata T, et al. Intensive insulin therapy prevents the progression of diabetic micro-vascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diab Res Clin Pract 1995; 28:103-117.

38. Abraira C, Colwell JA, Nuttall FQ, Sawin CT, et al. Veterans Affairs Cooperative Study on Glycaemic Control and Complications in Type 11 Diabetes (VA CSDM): results of the feasibility trial. Diabetes Care 1995; 8; 1113-1123.

39. The United Kingdom Prospective Diabetes Study Group (UKPDS 33). Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 11 diabetes. Lancet 1998; 352:837-853.

40. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 1985; 34: 222-234.

41. Henry RR, Walace P, Gumbiner B, Lyon R, Dietler T, Glauber HS. Intensive conventional insulin therapy for type 11 diabetes: Metabolic effect during a 6-mo outpatient trial. Diabetes Care 1993; 16:21-31.

42. Yki-Jarvinen H, Lauppila M, Kujansus E, Lahti J, Marijanen Niskanen L. et al. Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1992; 327:1426-1433.

43. Ilkova H, Glaser B, Tunckale H, Isagriacik N, Cerasi E. Induction of long-term glycaemic control in newly diagnosed type 11 diabetic patients by transient intensive insulin treatment. Diabetes Care 1997; 20(9): 1353-1356.

44. Kobayashi T, Nakanishi K, Murase T, Kosaka K. Small doses of subcutaneous insulin as a strategy for preventing slowly progressive B-cell failure in islet cell antibody-positive patients with clinical features of NIDDM. Diabetes 1996;45: 622-26.

45. Meyer L, Grulet H, Guerci B, Gross A. Durlach V., Leutenegger M. Short term intensive insulin therapy in insulin-requiring diabetes, effectiveness and factors predicting success. Diab Metab 1997; 23:75-79.

46. Scarlett JA, Gray RS, Griffin J, Olefski JM, Kolterman OE. Insulin treatment reverses the insulin resistance of Type 11 diabetes mellitus. Diabetes Care 1982;5: 353-363.

47. Gormley MJJ, Hadden DR, Wood R, Sheridan B, Andrews WJ. One month Insulin treatment of Type 11 diabetes. The early and medium-term effects following insulin withdrawal. Metabolism 1986; 35: 1029-36.

48. Andrews WJ, Vasquez B, Nagulespan M, et al. Insulin therapy in obese non-insulin dependent diabetes induces improvement in insulin action and secretion that are maintained for two weeks after insulin withdrawal. Diabetes 1984; 33: 634-642.

49. Garvez WT, Olefski JM, Griffin J, Hammam RF, Kalterman OG. The effect of insulin treatment on insulin action and insulin secretion in type II diabetes mellitus. Diabetes 1985; 34:222-234.

50. Foley JE, Kashiwagi A, Verso MA, Reaven G, Andrews J. Improvement in vitro insulin action after one month of insulin therapy in obese non -insulin dependent diabetics. J Clin Invest 1983; 72:1901-09.

51. Grulet IT,Gross A, Pasqual C, Durlach V, Leutenegger M. Remission of insulin requirement in late secondary failure to oral hypoglycaemic agents (IRD): results at 24 months and analysis of predictive factors. Diabetes Res Clin Pract 1991; 3:189 - 198.

52. The Diabetes Control and Complications Trial Group. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in DCCT. A randomized, controlled trial. Ann Intern Med 1998; 128/7:517-23.

53. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:984-986.

54. University Group diabetes program. Effects of hypoglycaemic agents on vascular complications in patients with adult-onset diabetes. V111. Evaluation of insulin therapy: final report. Diabetes 1982; 31 (supp5): 1-78.

55. Kilo C, Miller JP Williamson JR. The Achilles heel of the University Group Diabetes Program. JAMA 1980; 243:450-7.

56. Genuth S. Exogenous insulin administration and cardiovascular risk in noninsulin and insulin -dependent diabetes mellitus. Annals Intern Med 1996; 124: 104-109.

57. Abraira C, Colwell J, Nuttal F, Sawin CT, Hendersen W, et al. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Arch Intern Med 1997; 157: 181-188.

58. Stout RW. Insulin and atherosclerosis. In:Stout RW, ed. Diabetes and atherosclerosis. Dordrecht : Kluwer Academic Publishers, 1992;165-201.

59. Pyorala K. Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. Diabetes Care 1979; 2: 131-41.

60. Despres JP, Lamarche B, Mauriage P, et al. Hyperinsulinemia as independent risk factor for ischemic heart disease. N Engl J Med 1996; 334: 952- 47.

61. Hellman R, Regan J, Rosen H. Intensive therapy program for diabetes management:

effect on cardiac-specific mortality. Diabetes Care 1997; 20: 258-64.

62. Hadden DR, Patterson CC, Atkinson AB, et al. Macrovascular disease and hyperglycaemia 10-year survival analysis in type 2 diabetes mellitus: the Belfast Diet Study Diab Med 1997;14:663-72.

63. Yudkin JS, Managing the diabetic patient with acute myocardial infarction. Diabetic Medicine 1998; 15:276-281.

64. Clark RS, English M, McNeil GP, Newton RW. Effect of infusion of insulin in diabetics with acute myocardial infarction. Br Med J 1985; 291: 303-305.

65. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, et al, On behalf of the DIGAMI Study Group. A randomized trial of insulin glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction: effect on mortality at 1 year. J Am Coll Cardiol 1995. 26: 57-65.

66. Malmberg K for the DIGAMIC (diabetes, Insulin Glucose infusion in Acute Myocardial Infarction Study Group. Prospective randomized study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. Br Med J 1997; 314: 1512-1515.

67. Jain SK, Nagi DK, Slavin BM, Lumb PL, Yundkin JS. Insulin therapy in type 11 diabetic patients suppresses plasminogen activator inhibitor (PAL-1) activity and pro - insulin like molecules independently of glycaemic control. Diabetic Med 1993; 10:27-32.

68. University Group Diabetes Program. A study of the effects of hypoglycaemic agents on vascular complication in patients with adult-onset diabetes multiple 11. Mortality results. Diabetes 1970; 10 (Suppl. 2): 785-830.

69. Smits P, Thien T. Cardiovascular effects of sulphonylurea derivatives. Diabetologia 1995; 38: 116-21.

70. Pogatsa G. Potassium channels in the cardiovascular system. Diabetes Res Clin Pract 1995; 28 (supp 1): S91-S98.

71. Engler RI, Yellon DM. Sulfonylurea KATP blockade in type 2 diabetes and preconditioning in cardiovascular disease. Time for reconsideration. Circulation 1996; 94:2297-2301.

72. Engler RL, Yellon DM. Sulphonylurea KATP blockade in type 2 diabetes and preconditioning in cardiovascular disease: time for reconsideration. Circulation 1996; 94: 2297-2301.

73. Emanuele N, Azad N, Abraira C, Henderson W, Cowel J, et al. VA CSDM. Effect of intensive glycaemic control on fibrinogen, lipids, and lipoproteins. Arch Intern Med 1998; 158: 2485-90.

74. Cusi K, Cunningham GR, Comstok JP. Safety and efficacy of normalizing fasting glucose with bedtime NPH insulin alone in NIDDM. Diabetes Care 1995. 18: 843-845.

75. The Diabetes Control and Complications Trial (DCCT). Research Group. Effect of intensive diabetes management on macro-vascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol 1995; 75: 894-903.

76. Chait A, Bierman EL, Alberts JJ. Low density lipoprotein receptor activity in cultured human skin fibroblasts: mechanism of insulin-induced stimulation. J Clin Invest 1979; 64: 1309-1319.

77. Feingold KR, Grunfeld C, Pang M, et al. LDL subclass phenotypes and triglyceride metabolism in NIDDM. Arteioscler Thromb 1992; 12: 1496-1502.

78. Schonfeld G, Birge C, Miller JP , Jessler G, Santiago J**.** Apolipoprotein B levels and altered lipoprotein composition in diabetes. Diabetes 1974; 23: 827-834.

79. Howard BV, Knowler WC, Vasquez B, Kennedy AL, Pettitt DJ, Bennett PH. Plasma and lipoprotein cholesterol and triglyceride in the Pima Indian Population: comparison of diabetic and non-diabetics. Arteriosclerosis 1984; 4:462-471.

80. Duvillard L. Pont F. Florentin P, Gambest P, Verges B. Significant improvement of apolipoprotein B-Containing lipoprotein metabolism by insulin treatment in patients with non-insulin-dependent diabetes mellitus. Diabetologia 2000; 43: 27-35.

81. Kim HJ, Kurup IV. Nonenzymatic glycosylation of human plasma low density lipoprotein evidence for in vitro and in vivo glycosylation. Metabolism 1982; 31: 348-353.

82. Steinbrecher UP, Witztum JL. Glycosylation of low density lipoprotein to an extent comparable to that seen in diabetes slows their catabolism. Diabetes 1984; 33:130-134.

83. Hunt JV, Smith CCT, Wolff SP. Autoxidative glycosylation and possible involvement of peroxides and free radicals in LDL modification by glucose. Diabetes 1990; 39:1420-1424.

84. Steinberg D, Witztum JL. Lipoprotein and atherogenesis Current concepts. JAMA 1990; 264: 3047-3052.

85. Ganda OP, Akin CF. Hyperfibrinogenemia: an important risk factor for vascular complications in diabetes. Diabetes Care 1992; 15: 1245-1250.

86. Mayne EE, Bridges JM, Weaver JA. Platelet adhesiveness, plasma fibrinogen and factor VIII levels in diabetes mellitus. Diabetologia 1970; 6:436-440.

87. Missov RM, Stolk RP, Van der Bom JE, et al. Plasma fibrinogen in NIDDM: the Rotterdam Study. Diabetes Care 1996; 19: 157-159.

88. Stone MC, Throp JM. Plasma Fibrinogen: a major coronary risk factor: JR Coll Gen Pract 1985; 35: 565-569.

89. Meade JW, Mellows S, Brozvic M, et al. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. Lancet 1982; 2: 533-537.

90. Juhan-Vague I, Vague P, Aleesi MC, et al. Relationship between plasma insulin, triglyceride, body mass index and plasminogen activator inhibitor I Diabetes Metab 1987; 13: 331-336.

91. Vague P, Juhan-Vague I, Aillaud MF, et al. Correlation between blood fibrinolytic activity, plasminogen activator inhibitor level, plasma insulin level and relative weight in normal and obese subjects. Metabolism 1986; 2: 250-253.

92. Lormeau B, Debussche X, Gross S, et al. Acute hyperinsulinism has no effect on fibrinolysis in lean and obese subjects. Diabetes 1991 (Suppl. 1, abstr); 40: 494.

93. Landin K, Tengborn L, Ghmielewska J, et al. The acute effect of insulin on tissue plasminogen activator and plasminogen activator inhibitor in man. Thromb Haemost 1991; 65: 130-133.

94. Potter Van Loon BJ, De Bart ACW, Radder JK, et al. Acute exogenous hyperinsulinaemia does not result in elevation of plasma plasminogen activator inhibitor-1, concentration in man. Fibrinolysis 1990; 4: 93-94.

95. Grant PJ, Kruithof EKO, Felley CP, et al. Short infusions of insulin, triacylsycerol and glucose do not cause acute increase in plasminogen activator inhibitor-1, concentration in man. Clin Sci 1990; 79: 513-516.

96. Markkolo HV, Puliakainen I, Yki-Jarvinen H. No evidence for short-term regulation of plasminogen activator inhibitor activity by insulin in man. Thromb Haemost 1992; 67: 117-120.

97. Calles-Escandon J, Mirza SA, Sobel BE, Schneider DJ. Induction of hyperinsulinemia combined with hyperglycaemia and hypertriglyceridemia increases plasminogen activator inhibitory in blood in normal human subjects. Diabetes 1998; 47: 290-293.

98. Anderson PW, Zhang XY, Tian J, Correale JD, Xixp, Yang D, Graf K, Law RE, Hsueh WA. Insulin and angiotensin II are additive in stimulated TGF-β1 and matrix mRNAs in mesangial cells. Kidney Int 1996; 50. 745-753.

99. European Diabetes Policy Group. A desktop guide to diabetes mellitus. Diabetic Medicine 1999; 16: 716-750.

100. American Diabetes. Association: Implications of the United Kingdom Prospective Diabetes Study (position statement). Diabetes Care 1999; 22 (Suppl.l): S27-S31.

101. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 1999; 22(supp l): S32-S41.

102. Chow CC, Tsang LW, Sorensen JP, Cockram CS. Comparison of insulin with or without continuation of oral hypoglycaemic agents in the treatment of secondary failure in NIDDM patients. Diabetes Care 1995; 18:307-314.

103. Van der Wal PS, Scheen AJ, Van Gaal L, Schmitt H, Heine RJ. Swin Study Group. Efficacy of bedtime NPH insulin alone, as compared to combination with metformin and/or glipizide in NIDDM patients with secondary failure to oral hypoglycaemic agents. Diabetes 1996; 45(supp 2): 286A.

104. Berger M, Jorgens V, Muhlhauser 1. Rationale for the use of insulin therapy alone as the pharmacological treatment of type 2 diabetes. Diabetes 1999; 22: C71 - C75.

105. Siegler DE, Olsson GM, Skylern JS. Morning vs bedtime isophane insulin in type 2 diabetes mellitus. Diabetic Med 1992; 9:826-833.

106. Yki-Jarvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M. Comparison of bedtime insulin regimens in patient with type 2 diabetes mellitus. Annals Intern Med 1999; 130: 389-396.

107. Makimattila, Nlkkila K, Yki-Jarvinen H. Causes of weight gain during insulin therapy with and without metformin in patients with type 2 diabetes mellitus. Diabetologia 1999; 42: 406-412.

108. Olefsky JM, Kolterman OG, Scarlett JA. Insulin action and resistance in obesity and non-insulin-dependent type 11 diabetes mellitus. Am J Physiol 1982; 243:E15-E30

109. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-1607.

110. Kortelainen ML, Sarkioja T. Extent and composition of coronary lesions and degree of cardiac hypertrophy in relation to abdominal fatness in men under 40 years of age. Atheroscler Thromb Vasc Biol 1997; 17:574- 579.

111. Shaper AG, Wannameltee SG, Walker M. Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes in a cohort study of middle aged men. BMJ 1997; 314: 1311-1317.

112. Jarrett RJ. Why is insulin not a risk factor for coronary heart disease. Diabetologia 1994. 37: 945-947.

113. Ellis D, Avner ED, Transue D, Yunis EJ, Drash AI, Beeker DJ. Diabetic nephropathy in adolescence: Appearance during improved glycaemic control. Pediatrics 1983; 71:824-829.

114. Yoshimizu H, Nunol K, Nomyama R, et al. Persistent proteinuria developed after strict control of hyperglycaemia in three cases of non- insulin dependent diabetes mellitus. In: T. H. Lee, K. B. Huh and S. Baba (eds), Recent advantages in insulin therapy. Elsevier, Amsterdam, PP 221-224.

115. Chantelau E, Kohner EM. Why some cases of retinopathy worsen when diabetic control improves. Worsening retinopathy is not a reason to withhold intensive insulin treatment. BMJ 1997; 315; 1105-06.

116. Henricsson M, Nilsson A, Janzon L, Groop L. The effect of glycaemic control and the introduction of insulin therapy on retinopathy in non-insulin dependent diabetes mellitus. Diab Med 1997; 14:123 -131.

117. Emanuele N, Klein R, Abraira C, Colwell J, Comstock J, et al. Evaluation of retinopathy in the VA Cooperative Study on Glycaemic Control and Complications in type 2 diabetes. Diabetes Care 1996; 19: 1337- 1381.

118. Gudat U, Chantelau E. Rapid-progressive diabetische retinopathle bel stoffwechsel normaliserung: Wer ist gefahrdet ? Klin Med 1992; 47:108-113.

119. United Kingdom prospective Diabetes Study Group- 24. A 6-year, randomized, controlled trial comparing sulfonylurea, insulin and metformin therapy in patients with newly diagnosed Type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med 1998; 128/ 3:165-75.

120. Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycaemic control in patients with type 2 diabetes mellitus. JAMA 1998; 80: 1490-1496.

121. UK Prospective Diabetes Study Group (UKPDS 37). Quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control. Diabetes Care 1999; 22: 1125-1136.