Optimum Insulin Therapy in Non-insulin-dependent Diabetes Mellitus *

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INTRODUCTION

In general non-insulin dependent diabetes (NIDDM) has been considered to be easier to treat than insulin-dependent diabetes (IDDM). Recently the need for normoglycemia to prevent complications has been recognized also in NIDDM and consensus criteria for desired metabolic targets have been declared.

However, it has also been recognized that the treatment of NIDDM patients frequently is inadequate even in those patients who should achieve the target range. In a recent population based cohort the median of glycosylated haemoglobin was 10.2% in NIDDM patients treated with diet or oral hypoglycemic agents (OHA) and 11.8% in NIDDM patients who used insulin. In a 5 year follow-up study of NIDDM patients the mean of baseline blood glucose averaged 11.2 mmol/l and it remained virtually unchanged at 5 yrs of diet or OHA treatment which did take place in community health centers. Similarly, overall experience from clinical practice is that the majority of NIDDM patients have persistently higher blood glucose levels and HBA_{1c} levels than are acceptable or requested in the consensus recommendations. Consequently, it is evident that current therapeutic approaches are far from satisfactory to achieve and maintain normoglycemia in the majority of NIDDM patients and new approaches to treatment are needed.

A common sequence of therapy in NIDDM starts with diet treatment and exercise followed by sulfonylurea therapy. In addition metformin can be added in patients with inadequate response to sulfonylurea but in general its additive effect to lower blood glucose is limited. In general insulin therapy has been considered to be the last therapeutical option when diet and OHA therapies have failed. It is well-established that after an initially successful response to OHA 5% to 10% per year develop inadequate response or treatment failure. It has been estimated that at 5 year only 50% have maintained an acceptable response to OHA. Recently, the criteria for sulfonylurea failure (SU failure) have been defined to be fasting plasma glucose > 10 mmol/l (> 180 mg/dl) or glycosylated hemoglobin values > 9.5%. Corresponding values for a more stringent criteria are 8 mmol/l and 8.0% respectively. This subgroup of NIDDM patients is the problem group to initiate and optimize insulin therapy whereas insulin is the obvious choice in NIDDM patients who have developed "true" insulin deficiency or if there is need for temporary insulin therapy because of hyperglycemic exacerbations (Table 1).

TABLE 1

Options of insulin therapy in NIDDM

• As an alternative to oral therapy
• As a temporary intervention during periods of poor control
• As a treatment of inadequate response to sulfonylureas or of sulfonylurea failure
• As a replacement to cover insulin deficiency

Rationale for insulin treatment in NIDDM

An optimal insulin regimen should be based on the pathophysiology of NIDDM and also tailored to the needs of an individual patient. To achieve improvement of glycemic control it is necessary to reduce both fasting and postprandial glucose levels. What are the chief differences of insulin management between IDDM and NIDDM patients if we consider the pathophysiology? In IDDM patients insulin administration aims to replace inslin deficiency due to a failure of endogenous insulin secretion. In NIDDM the rationale for insulin therapy derives from the fact that the dominant abnormality is insulin resistance (Table 2). Recognition of the fact that excessive hepatic glucose production (HGP) is the major cause of fasting hyperglycemia in NIDDM is essential. A number of studies have documented a close correlation between HGP and fasting blood glucose levels.

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TABLE 2

Rationale for insulin therapy in NIDDM

- Hepatic overproduction of glucose is the main cause of fasting hyperglycemia in NIDDM
- After a meal, hyperglycemia compensates for insulin resistance by mass action of glucose
- The stimulatory effect of insulin on glucose utilization is counterbalanced by a diminished mass action effect of glucose.

Hepatic glucose output is due to impaired responsiveness of liver to insulin action and consequently glucose production is inappropriate to the prevailing hyperglycemia. To date substantial evidence indicates that dawn phenomenon is apparent also in NIDDM. Regardless of the mechanisms behind the dysregulation of hepatic glucose output it is obvious that optimal insulin treatment in NIDDM should aim to suppress hepatic glucose production. On the other hand, impaired glucose utilization in skeletal muscle seems to be an early abnormality in NIDDM and it reflects the insulin resistance of muscle tissue. It has been demonstrated that plasma glucose excursion during day time are closely related to fasting blood glucose levels. The fact that less insulin is needed to suppress overnight hepatic glucose output than to stimulate glucose utilization is a key point for the understanding of insulin therapy in NIDDM. Clearly some dysfunction of insulin secretion is commonly present in NIDDM and there is gradual deterioration of insulin secretion capacity. When defects of insulin secretion become more advanced and are the major cause of hyperglycemia the patients require similar regimens of insulin treatment as IDDM patients.

In conclusion, objectives of insulin treatment in NIDDM should be to provide adequate basal insulin supplementation to suppress hepatic glucose production, to restore the lack of early prandial insulin secretion and to ensure adequate insulinization to overcome impaired insulin stimulated glucose utilization in peripheral tissue particularly in skeletal muscle (Table 3). In addition the optimal regimens must be simple and safe and allow achievement of target glycemic control. Obviously these requirements in clinical practice impose a dilemma which cannot be solved by use of conventional insulin regimens.

TABLE 3

Requirements of optimal insulin therapy for patients with NIDDM

- To provide adequate basal insulin supplementation to suppress excessive hepatic glucose release
- To restore the lack of early prandial insulin response
- To ensure adequate insulinization to overcome impaired insulin stimulated glucose uptake in peripheral tissues

Choices of insulin regimens for management of NIDDM

A variety of insulin regimens have been used to ensure glycemic control in NIDDM patients with treatment failure. Overall single or twice daily injections of NPH insulin alone or mixed with regular insulin have been advocated as an initial option in USA, where 30% of NIDDM patients are estimated to be insulin treated. As emphasized previously overall glycemic control is not adequate among conventionally insulin treated NIDDM patients which indicates that these regimens are not optimal. Clearly the option to administer intermediate acting insulin before breakfast does not recognize the need to suppress overnight excessive glucose production. Subsequent addition of a second injection before supper or mixing with regular insulin may ensure modest benefit but only seldom allows to achieve satisfactory glycemic control. Again the regimen is not based on current understanding of the pathophysiology in NIDDM or on the optimization of pharmacokinetics of available insulin preparations.

A number of studies have demonstrated that intensive insulin treatment, consisting of multiple injections of regular insulin combined with different modes of administration of basal insulin, has beneficial effects on deficient insulin response, excessive glucose production and diminished glucose utilization in muscle. The practical cost is that doses of insulin needed are usually very high and the result is clear hyperinsulinism. In practice these regimens are difficult to accomplish among aged patient population which represent the majority of NIDDM group in need of insulin therapy.

The recognition of these clinical dilemmas has led to re-evaluation of insulin regimens for NIDDM patients. The critical question is which is the best way to suppress overnight HGP and to reduce fasting blood glucose level? The administration of intermediate or long acting insulin at bedtime to guarantee sufficient basal insulin delivery is not a new idea, but the concept was revived in the late 1970 by Hollman and Turner and later, as part of combination therapy in the late 1980 by Riddle. The rationale of this regimen acknowledges the role of hepatic glucose production as a cause of hyperglycemia in NIDDM and the different responsiveness of liver VS skeletal muscle to insulin. The efficacy of long acting insulin as a basal insulin supplement and an alternative to diet or OHA therapy will be judged when the data from the ongoing prospective Oxford Study will be available. Evening insulin as part of the combination therapy provides a new approach which is gaining popularity because of its feasibility. Preliminary data from clinical studies support the usefulness of this approach to treat NIDDM patients with inadequate response to OHA. The prerequisite is that the patient has residual beta cell function and adequate postprandial insulin response.

Overall, the combined use of insulin and OHAs has been tested in several trials during the last decade. The rationale for this therapeutic option was the discovery of "extrapancreatic" action of sulfonylureas. However, the current data indicate that the benefits of combination therapy are mainly due to the improvement of B-cell function by sulfonylureas whereas insulin alleviates hyperglycemia by reducing HGP. The prevailing controversy on the efficacy of combination therapy is partly due to the differences in clinical practice on two sides of the ocean. In the majority of American studies sulfonylurea has been prescribed to a patient who is on insulin becuase of previous OHA failure while in European studies insulin has been prescribed to a NIDDM patient with OHA failure. Serious concerns have been raised because the selection criteria of patients have been variable and there are multiple other intrinsic differences as well as differences of treatment regimens (Table 4). Nonetheless, a recent meta-analyses of combined insulin-sulfonylurea studies which were randomized controlled trials, revealed that this regimen led to modest improvement of glycemic control when compared to insulin alone.

TABLE 4
Trial hazards in the studies of insulin treatment in NIDDM

- Design of many trials have been unsatisfactory
- Study populations have displayed intrinsic differences
- Treatment regimens have been variable
- Most trials have had small sample sizes and short durations

Comparison of different insulin regimens in NIDDM

Although there are strong arguments based on data from numerous clinical trials that insulin therapy provides benefits in the management of NIDDM patients with OHA failure, the efficacy and feasibility of different insulin regimens have not been compared in a randomized controlled trial. In particular, controversy exists on the role of combination therapy and whether or not the response is different when the intermediate insulin is given in the morning or at bedtime. Questions 'whether better glycemic control could be achieved with two injections of insulin or with intensive insulin therapy compared to combination therapy are also open.

Therefore we have compared four different insulin-treatment regimens with continued oral hypoglycemic drug therapy in NIDDM patients with treatment failure on OHA (Yki-Jarvinen H et. al. New Engl J Med 1992; 327; 1426-33). Objectives of the study were to define the optimal insulin treatment for NIDDM patients if following variables were considered; glycemic control, hyperinsulinism, weight gain, symptomatic hypoglycemias, subjective well-being, attitudes, and treatment satisfaction and costs. For this purpose 153 patients with NIDDM were randomly allocated to treatment with one of the following five regimens for three months. (1) oral hypoglycemic drug therapy plus NPH insulin given at 7 a.m. (the morning -NPH group), (2) oral hypoglycemic drug therapy plus NPH given at 9 p.m. (the evening-NPH group), (3) NPH and regular insulin (ratio 70 units to 30 units) given before breakfast and dinner (the two-insulin-injection group), (4) NPH insulin at 9 p.m. and regular insulin before meals (the multiple- insulin-injection group) and (5) continued oral hypoglycemic therapy (the control group). The

patients were recruited at six hospitals located in different parts of Finland and none of the hospitals had a special clinical research center. At randomization the five groups were comparable with respect to age, BMI, duration of diabetes, HbA_{1c}, fasting blood glucose level, fasting C-peptide level and concentrations of serum cholesterol and triglycerides. During the run-in period of 6 weeks the parameters of glycemic control improved slightly in each group. Figure 1 shows the mean of diurnal blood glucose measurements performed at home.

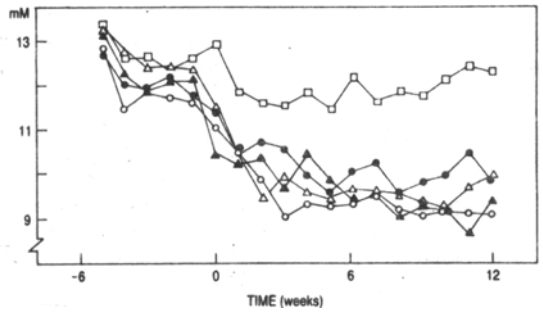

Figure 1. Means of diurnal blood glucose levels during the six week run-in period and during treatment in patients with NIDDM in the control group (□) , the morning NPH group (○), the evening NPH group (●), the two injection group (Δ) and the multiple injection group (▲). Each diurnal profile included blood glucose measurements before and 1½ hours after breakfast, lunch and dinner and at 10 p.m. and 4 a.m. (YkiJarvinen H et al. N Engl J Med 1992; 327; 1426-33).

The glycemic control during the treatment period improved similarly in each treatment group and the response was significantly better than in the control group. The mean value for glycosylated hemoglobin (HbA_1) decreased similarly in all four insulin treatment groups (1.7, 1.9, 1.8 and 1.6 percent respectively) and the fall was significantly higher than in the control group (Figure 2). We conclude that all insulin-regimens were equally effective to improve glycemic control.

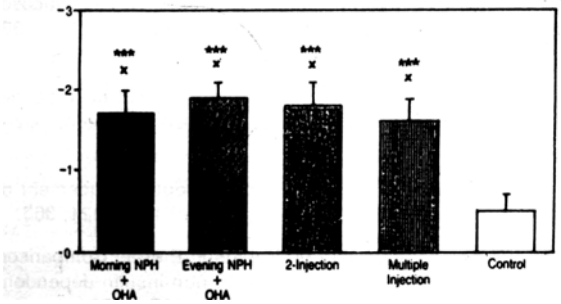

Figure 2. Mean changes of glycosylated hemoglobin (%) during treatment in patients with NIDDM. The differences of HbA_1 were significant from the control group at 12 wks ($p<0.05$) and from the baseline ($p<0.001$) (Yki-Jarvinen H et al. N Engl J Med 1992; 327; 1426-33).

The mean diurnal serum free insulin concentration at 3 months of treatment are shown in Figure 3. At 3 months the mean of diurnal free insulin concentration was increased significantly in the morning-NPH group, in the two-injection group and in the multiple-injection group compared with the values at the baseline but not in the evening NPH group. The respective insulin doses were similar in the two combination treatment groups (morning NPH, 19±1 IU/day, evening-NPH group, 20±2 IU/day) and significantly lower than in the two only insulin-treatment groups (two-injection group total 43± 2 IU/day and multiple-injection group total 45± 3 IU/day). Notably the evening NPH group resulted in less hyperinsulinemia than the other treatment groups.

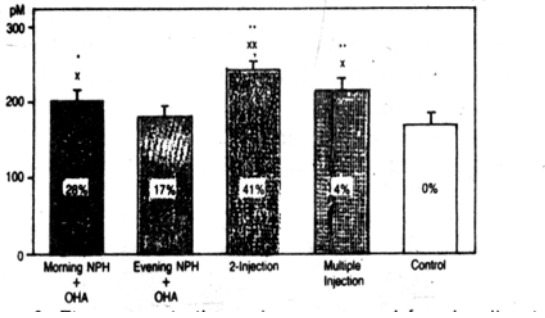

*Figure 3. The concentrations of mean diurnal free insulin at 12 wks of treatment. The figure inside the columns indicate the mean percentage change from the respective value at baseline *$p<0.05$, **$p<0.01$ for differences from values at baseline, $^{x}p<0.05$, $^{xx}p<0.01$ for differences from the respective value of control group at 12 wks (Yki-Jarvinen H et al. N Engl J Med 1992; 327; 1426-33).*

A common excuse to avoid insulin treatment is fear of weight gain. Indeed some weight gain has occurred in the majority of clinical trials during insulin treatment of NIDDM patients. However, it should be recognized that observed initial weight gain might be a sign of insulin's effectiveness rather than a side effect. Accordingly, in this study the patients in all the treatment groups gained weight during the three-month period (Figure 4). However, the increment of weight gain was smallest in the evening-NPH group and significantly less than in the other insulin-treatment groups. Calculated gained weight per decreased percent of HbA1 were 1.29, 0.63, 1.00 and 1.81 kg% decrease in HbA_1 in the morning-NPH group, the evening NPH group, the two injection group and multiple-injection group, respectively. Our data also demonstrated that all treatment regimens improved the subjective well-being of the patients.

In conclusion all four regimens of insulin therapy improved similarly the overall glycemic control at-

least at short term. These favorable results indicate that NIDDM patients with OHA failure will benefit from insulin therapy and combination therapy. Considering together the data on glycemic control, degree of hyperinsulinemia, weight gain and subjective attitudes we conclude that in NIDDM patients (1) multiple insulin injection therapy is the least attractive insulin regimen, (2) combination treatments produced equivalent improvement of glycemic control but with a less insulin dose than the two insulin treatments, (3) combination therapy with evening NPH is the most feasible insulin regimen. Finally, it remains to be established whether improved glycemic control reduces the risk of diabetic complications in NIDDM and improves the patients' long-term well-being. The easy use of combination regimens and the subjective relief of hyperglycemic malaise are reasons to advocate earlier insulin management in NIDDM patients.

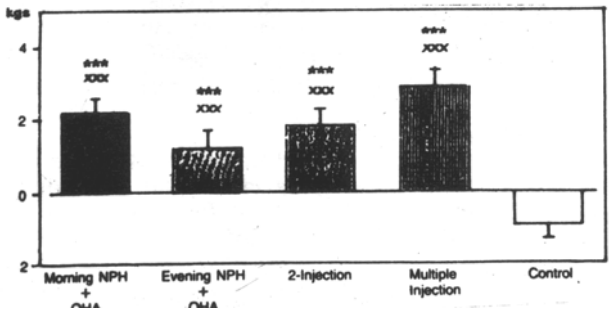

Figure 4. Changes of eight (kgs) during treatment in patients with NIDDM. ***p<0.001, *p<0.05 for differences from the weight at the baseline. ^{xxx}p<0.001, ^{x}p<0.05 for differences from the change in the control group, $^{+}$p<0.05 for differences from the change in each insulin treatment group (Yki-Jarvinen H et al. N Engl J Med 1992; 327; 1426-33).

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