Insulin therapy in Type 2 Diabetes
When to Start?

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Abstract:

Chronic hyperglycemia in type 2 diabetes is responsible for both microvascular and macrovascular complications that can lead to considerable morbidity and mortality. Several studies have shown that maintaining good glycemic control can prevent or halt the progression of these life threatening complications. With time a large number of type 2 diabetics fail to achieve the recommended glycemic targets with diet, exercise and oral anti diabetic agents, and most of them ultimately require insulin therapy. Actually many studies have shown that the early introduction of insulin therapy for type 2 diabetes, will improve insulin sensitivity and secretory capacity of the B-cells of the pancreas.

Introduction:

Type 2 diabetes is a highly prevalent disease; its incidence is even increasing especially in the developing countries mainly because of the consequences of urbanization. It has been postulated that with the growing problem of obesity, diabetes will become an even more prevalent threat [(1)]. Type 2 diabetes produces, or is a contributor to considerable morbidity, mortality rate has been estimated at 5.5% annually, more over the disease reduces life expectancy by 5-10 years [(2)].

Although there is no cure for diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) [(3)] have shown the importance of strict glycemic control in reducing its associated morbidity and mortality, in this study it was found that for each 1% reduction in HbA1c (A1c), there was a 21% decrease in any endpoint related to diabetes and in diabetes related deaths, a 14% decrease in all-cause mortality and myocardial infarction, a 43% decrease in amputation or death from peripheral vascular disease, and a 37% decreased risk for microvascular complications, each of which was statistically significant [(3)]. Although sulphonylureas therapy has been the mainstay of treatment for type 2 diabetes for decades, the (UKPDS) reported that over a 6 years period about 53% of patients who were randomized to receive treatment with sulphonylureas, needed additional insulin therapy to maintain their glycemic control, reinforcing the concept that hyperglycemia in type 2 diabetes is progressive[(4)].

This article addresses the pathophysiology of type 2 diabetes, try to answer the question (why early insulin?), discusses misconceptions about insulin and the problem of compliance.

Pathophysiology of type 2 diabetes mellitus:

This disease is characterized by hyperglycemia caused by defects in insulin secretion (B-cell dysfunction) and insulin action (insulin resistance by the liver and muscle tissue)[(5)]. In a prospective study of Pima Indians[(6)] (a group at high risk for developing diabetes), the insulin secretory capacity were measured in subjects whose glucose tolerance went from normal to impaired glucose tolerance, to diabetic.

During transition form normal to impaired glucose tolerance there was 27% decrease in the acute insulin secretory response (AIR), which is the average incremental plasma insulin concentration

from the third to the fifth minute after the glucose bolus. During transition from impaired glucose tolerance to diabetic there was an additional 57%decrease in AIR. Another controlled study [7] in patients with type 2 diabetes have shown that the patients secreted about 70% less insulin than control subjects. These two studies demonstrate that insulin secretory defect is a major factor and also the B-cell defect is progressive overtime. This progressive failure in B-cell function seems to be due to the toxic effect of hyperglycemia that results in apoptosis without compensatory increase in B-cell proliferation [8].

So although most type2 diabetic patients are treated initially with diet, exercise and oral agents but eventually most of them will require a treatment strategy that include insulin[4].

Why early insulin?

In an insulin versus sulphonylurea study [9], from Sweden, newly diagnosed type2 diabetics were treated with either glibenclamide or premixed insulin, and the C-peptide glucagone test were performed yearly to check for the C-Peptide response which was shown to be increased significantly in the insulin treated group after 1, and 2 years where as it was decreased in the glibenclamide treated group.

Also the fasting pro insulin level had increased in the insulin treated group relative to the glibenclamide treated group after 4 years of treatment. This showed that early insulin treatment had favourable effect on B-cell function. In certain studies intensive insulin given for brief period to newly diagnosed type 2 diabetics[10-12],or after failure to achieve glycemic goals[13], had resulted in improvement of insulin secretion and insulin sensitivity which lead to better glycemic control which can then be maintained with diet, exercise and oral agents for many months thereafter, this again reinforces the concept of starting early insulin therapy for type 2 diabetics.

Misconceptions about insulin

- The use of insulin has been associated with weight gain, which in turn has been considered a major factor in insulin resistance. In the UKPDS, patients on intensive therapy gained more weight than those on conventional therapy, patients taking insulin gained about 4 Kg compared to 1.7 Kg for those on glibenclamide [14], yet patients in the intensive therapy group had fewer microvascular complications, suggesting that tight glycemic control may be more important in therapeutic-decision making. The use of metformin as an adjunct to insulin provides effective glycemic control without significant weight gain [15].

- Because of the connection among hyperinsulinemia, insulin resistance, and cardiovascular risk factors, the UKPDS [14] compared cardiovascular events among patients randomized to conventional life style and dietary management and those on tight glycemic control regimens with sulphonylureas, metformin (in over weight patients), or insulin. No adverse affects on cardiovascular outcomes were seen with any of the treatment including insulin. Further in the DIGAMI study [16], the effect of intensive insulin therapy on patients with acute myocardial infarction were assessed, after 1 year there was a significant reduction in mortality in the group who received intensive insulin treatment, the absolute reduction in mortality was 11% [16]. Even further, Lakka etal reported that endogenous hyperinsulinemia has only a modest association with increased cardiovascular mortality in middle aged men and that this relation-ship results mainly from co morbid obesity, hypertension and dyslipidemia [17], in addition, no published data link exogenous insulin therapy with clinical cardiovascular disease. Also it has been reported that there is improvement or neutral effects on other cardiovascular risk factors (total cholesterol, LDL cholesterol, HDL cholesterol, Triglyceride, or hypertension) with insulin [18].

• Clinicians are often reluctant to introduce insulin because of the risk of hypoglycemia. Actually in type 2 diabetes the rate of severe hypoglycemia are quite low. In Kumamoto study of type 2 diabetes [19], average A1c results were 7.1% and 9.4% for tight and conventional groups respectively, however only mild hypoglycemic reactions occurred and at similar rates in both groups. In the UKPDS [14], it was found that the rate of major hypoglycemia (defined as episode which require help from another person or medical intervention) was higher for patients taking insulin (2.3%) than for patients undergoing any other intensive therapy or conventional treatment (<1%). Despite the higher risk of hypoglycemia, aggressive therapy with regimen that include insulin can help to reduce morbidity and mortality associated with type 2 diabetes.

Compliance:

Many factors affect compliance. On part of the patient, the believe that the benefits of the therapy are worth the consequences, readiness to change, literacy level, knowledge, competence, skills and a good support system work together to influence the patients acceptance of the therapy. The regimen itself is also a factor, if it is difficult, costly, or has many side effects, compliance may diminish [20]. In the treatment of type 2 diabetes with insulin, reluctance to inject oneself and fear of weight gain or hypoglycemia may hinder compliance [21].

Physicians need to explain to their patients that type 2 diabetes is a progressive disease and that they will need insulin at some point, they need to dispel myths associated with insulin use, allay patients fears, and assure them that insulin will likely improve their symptoms, enhance quality of life, and provide a sense of well-being.

On part of the physician, there may also be some difficulties in starting insulin, concern regarding hypoglycemia, patients fear of needles, and the time necessary to teach self-injection can all emerge as barriers to insulin use

Actually the problem of needle injection is made much less important with the wider use of pen injector and the comfort it provides.

Conclusion:

With the prevalence of diabetes on the rise and with the recognized need for strict glycemic control to prevent and halt the progression of complications, strategies for aggressive treatment must be put into effect. Such strategies might include the early use of insulin, alone or in combination with other anti diabetic agents, physician must weight the risk associated with the use of insulin against the expected benefits.

References :

1. Mokad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS: The continuing increase of diabetes in the U.S. (Letter) Diabetes Care 24; 412, 2001.
2. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer H-M, Byrd-Holt DD: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination Survey, 1988-1994, Diabetes Care 21: 518-524,1998.
3. Stratton IM, Adler Al, Neil HAW, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR . Association of glycemia with macrovascular and microvascular complications of type 2 diabetes : Prospective observational study. BMJ 321: 405-412, 2000.

4. Wright A, Barden ACF, Paisey RB, Cull CA, Holman RR. For the UK Prospective Diabetes Study Group: Sulphonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study. Diabetes Care 25: 330-336, 2002.
5. Defronzo RA: Pharmacological therapy for Type 2 D.M. Ann Intern Med 131: 281-303,1999.
6. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 D.M. JClin Investig. 104: 787-794,1999.
7. Polonsky KS, Given BD, Hirsch LJ, Tillil H, Shapiro ET, Beebe C, Frank BH, Galloway JA, Van Canter E: Abnormal patterns of insulin secretion in NIDDM. N. Engl J Med 318: 1231-1239,1988.
8. Kaiser N, Leibowitz G, Nesher R. Glucotoxicity and beta-cell failure in type 2 D.M J Pediatr. Endocrinol. Metab. 16: 5-22, 2003.
9. M. Alvarsson, G.Sundkuist, I.Lager etal. Effects of insulin vs. glibenclamide in recently diagnosed type 2 diabetic patients: A 4year follow up. Abstract book of the 40th annual meeting 2004 of the EASD OP25.
10. Ryan EA, Imes S, Wallace C. Short term intensive insulin therapy in newly diagnosed type 2 diabetes. Diabetes Care 27:1028, 2004.
11. Ilkova H, Glaser B, Tunckale A, etal. Induction of long term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin therapy Diabetes Care 20; 1353, 1997.
12. Li Y, Xu W, Liao Z, etal. Induction of long term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function Diabetes Care 27: 2597, 2004
13. Garvey WT, Olefsky JM, Griffin J, etal. The effect of insulin treatment on insulin secretion and insulin action in type 2 DM diabetes 34: 222, 1985.
14. Intensive blood-glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) . UK Prospective Diabetes Study (UKPDS) Group. Lancet 352: 837-53, 1998.
15. Aviles – Santa L, Sinding J, Raskin P: Effects of metformin in patients with poorly controlled, insulin treated type 2 D.M : A randomized, double –blind, placebo-controlled trial. Ann Intern Med 131: 182-188, 1999.
16. Malmberg K, for the DIGAMI Study Group . Prospective randomized study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with D.M. BMJ 314: 1512-1515, 1997.
17. Lakka HM, Lakka TA, Toumilehto J, Sivenius J, Salonen JT. Hyper insulinemia and the risk of cardiovascular death and acute coronary and cerebrovascular events in men: the koupio Ischaemic Heart Disease Risk Factor Study. Arch Intern Med 160:1160-8. 2000.
18. The DCCT Research Group : Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trail. Am J Cardiol 75: 894-903. 1995.
19. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes: a randomized prospective 6-year study. Diabetes Res Clin Pract 28: 103-117,1995.
20. Meichenbaum D, Turk DC: Facilitating Treatment Adherence. NewYork, Plenum press, 1987.Nathan DM: Initial management of glycemia in type 2 diabetes mellitus. N Engl J Med 347: 1342-1349,2002