DRUG MANAGEMENT OF TYPE 2 DIABETES MELLITUS - CLINICAL EXPERIENCE AT A DIABETES CENTER IN SOUTH INDIA

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ABSTRACT

Though India leads the world with the largest number of diabetic subjects, there has been very few studies on the treatment patterns for Indian type 2 diabetes. This study is aimed at determining minimum and maximum drug regimens for tight glycemic control. This study was conducted on 3207 type 2 diabetic subjects attending a diabetes centre over a period of ten years (1992- 2002). The glycemic targets for the study subjects were fixed as fasting blood sugar ≤ 120 mg/dl and post prandial blood sugar ≤ 180 mg/dl. The follow up period of the study patients varied from one year to 9 years. The median follow up period was five years.

The mean age of the study cohort was 53 years; there were 1675 males and 1532 females. Of the total 3207 patients recruited for the study, 70 (2.18%) subjects experienced remission to normoglycemia, 1467 (46%) required single drug regimen, 1266 (39.5%) subjects were on double drug regimen, 282 (8.8%) patients on three drug regimen, 113 (3.5%) subjects on four drug regimen and 9 (0.28%) subjects on a maximum (five) drug regimen. 25% of type 2 diabetic patients required insulin for diabetes control. However inclusion of acarbose and glitazone molecules reduced the insulin requirement by 75% in 15% of type 2 diabetic patients while the remaining 10% of patients were completely withdrawn from insulin. The study result suggested that optimal anti diabetic measures can arrest the further progression of the disease and intensive therapy could help in achieving tight glycemic control.

KEY WORDS: Type 2 diabetes; Drug regimen: Acarbose, Glitazone, Insulin.

INTRODUCTION

Type 2 diabetes is caused by a combination of genetic and environmental factors. There are two main pathological defects in the disease, insulin resistance (a decreased ability of the peripheral tissues to respond to insulin) and β -cell dysfunction (an inability of the pancreas to provide sufficient insulin to compensate for insulin resistance) (1). The treatment for this disease is targeted at both these defects. The treatment regime usually starts with diet when the ß-cells are capable of producing sufficient insulin and then shifts to oral hypoglycemic agents when the ß-cells need a stimulant to release insulin and finally requires insulin itself when the ß-cells stop functioning. However, the recent report from the ADA has suggested that some of the type 2 diabetic subjects may have a remission period where they maintain normoglycemia without any anti-diabetic therapy (2).

Recent estimates from the WHO suggest that by 2025 the number of diabetic subjects worldwide is expected to be as great as 300 million (3). This report also warns about an alarming escalation in the prevalence of type 2 diabetes in developing countries, which parallels the rate of industrialization. It is predicted that India will represent the core of the type 2 diabetes epidemic i.e. more than 20% of the diabetic population all the over the world will be from India (3). Though Indians are at high risk for diabetes, not much is reported about the management of this disease in native Indians. We made an attempt to study the minimum and maximum drug therapy regimens required to have tight glycemic control in a cohort of south Indian type 2 diabetic subjects seen at a private diabetes center in Chennai.

MATERIALS AND METHODS

The study was conducted at the Aruna Diabetes Centre in Chennai. In this retrospective study, three thousand two hundred and seven type 2 diabetic subjects attending the diabetes centre over a period of ten years (1992- 2002) were evaluated. The glycemic targets for the clinic was fixed at fasting blood sugar ≤ 120 mg/dl and post prandial blood sugar ≤ 180 mg/dl. The follow up period of the study patients varied from 1 year to 9 years. The median follow up period was five years.

The interventions were categorized as follows: *Life*

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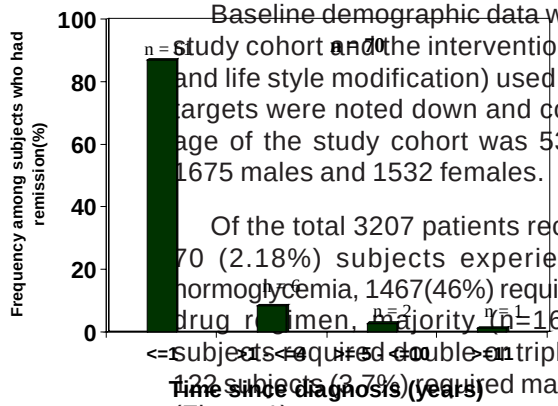
Style Modification: diet and exercise. *Minimum Drug Regimen:* use of single oral anti-diabetic drugs like sulphonylurea, metformin or acarbose. *Double Or Triple Drug Regimen:* use of combination of oral anti-diabetic drugs like sulphonylurea, metformin, acarbose or glitazones. *Maximum Drug Regimen:* The subjects who did not achieve the glycemic targets with double, triple drug regimen were considered as secondary failure to OHA's and were started with the maximum drug regimen. Four drug regimen is either one of the following combination- sulphonylurea, metformin, glitazones and insulin, or sulphonylurea, metformin, acarbose and insulin or sulphonylurea, metformin, glitazones and acarbose. Five-drug regimen was a combination of sulphonylurea, metformin, glitazones, acarbose and insulin.

The aim of the treatment was to control glucotoxicity initially and then to achieve the target for glycemic control. Combination therapy was initiated depending upon the glycemic response and other co-morbid conditions like obesity, coronary artery disease, renal impairment, etc. Fasting and postprandial plasma glucose was estimated using GOD-POD method.

RESULTS

Baseline demographic data were collected for the study cohort and the interventions (both therapeutic and life style modification) used to achieve glycemic targets were noted down and computed. The mean age of the study cohort was 53 years; there were 1675 males and 1532 females.

Of the total 3207 patients recruited for the study, 70 (2.18%) subjects experienced remission to normoglycemia, 1467(46%) required minimum (single) drug regimen, majority (n=1618, 50.5%) of the subjects required double or triple drug regimen and 122 subjects (3.7%) required maximum drug regimen (Figure 1).



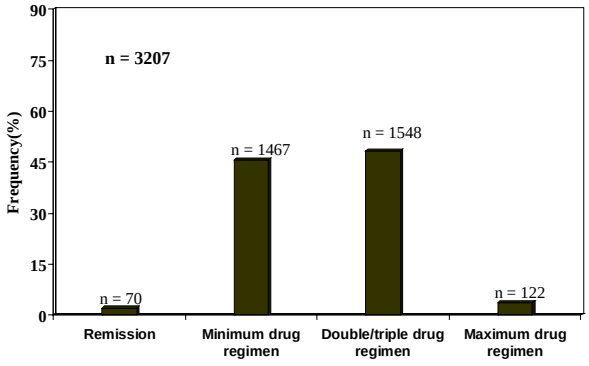


Figure1: Treatment Pattern Followed in the Study Population

Of the 70 subjects who experienced remission to normoglycemia, the period of remission ranged between <1 year to over 15 years. These patients had reported with an initial fasting blood sugar >250 mg/dl and post prandial value of > 350 mg/dl. These subjects were advised life style modification and insulin therapies to correct their high blood glucose, following which they had the remission period. Of these 70 subjects 87.1% (n=61) had remission for ≤ 1 year, 8.5% (n=7) had ≤ 4 years, 2.9% (n=1) ≤ 10 years and 1.4% (n=1) ≤ 20 years (Figure 2).

Single drug regimen: 46% (1467) of the patients were on a single drug. Nearly 88.9% of the subjects who responded to single drug had diabetes duration of less than one year, 10.9% had duration 1- 5 years and 0.14% had duration 6-10 years. None of these subjects had used a single drug for 10 years (Table 1).

Table 1: Duration-wise Distribution of Subjects on Single and Double Drug Regimen

Duration of DM	Male n (%)	Female n (%)	Total n (%)
Single Drug Regimen			
< 1 yr	733 (88.5%)	572 (89.7%)	1305 (88.9%)
1 – 5 yrs	96 (11.6%)	64 (10.0%)	160 (10.9%)
6 – 10 yrs	Nil	2 (0.3%)	2 (0.14%)
> 10 yrs	Nil	Nil	Nil
Double Drug Regimen			
< 1 yr	394 (94.0%)	392 (89.3%)	786 (91.6%)
1 – 5 yrs	25 (6.0%)	46 (10.5%)	71 (8.3%)
6 – 10 yrs	Nil	1 (0.2%)	1 (0.1%)
> 10 yrs	Nil	Nil	Nil

Figure 2: Frequency of Subjects who had Remission to Normoglycemia

Double drug regimen: 39.5% (1266) of the patients were on double drugs (ie) sulphonylurea and metformin or metformin and acarbose for minimum of one year to maximum of ten years (Table 1). This includes patients on single drug 12.7% (408) changing over to double drug 26.8% (858).

Triple drug regimen: 8.8% (282) of the patients were on three drugs for a period of one year to maximum of fifteen years. The third drug is either acarbose or glitazone or insulin (Table 2).

Table 2: Duration-wise Distribution of Subjects on Triple Drug Regimen

Duration of DM	Male n (%)	Female n (%)	Total n (%)
< 1 yr	104 (83.2%)	136 (86.6%)	240 (85.1%)
1 – 5 yrs	20 (16.0%)	21 (13.4%)	41 (14.5%)
6 – 10 yrs	1 (0.8%)	Nil	1 (0.4%)
> 10 yrs	Nil	Nil	Nil

Four drug regimen: 3.5% (113) of patients were on four drug regimen. 13.3% of them (15) were on four molecules even though the duration was at less then 5 years. Four type-2 diabetics were on four drugs at less than forty years of age. Nearly 50% of the subjects had duration of diabetes >10 years (Table 3). 77% of the diabetic subjects under this regimen were more than 50 years of age.

Table 3: Duration-wise Distribution of Subjects on Four and Five Drug Regimen

Duration of DM	Male n (%)	Female n (%)	Total n (%)
Four Drug Regimen			
< 5 yr	9 (19.1%)	6 (9.1%)	15 (13.3%)
6 – 10 yrs	10 (21.3%)	32 (48.5%)	42 (37.2%)
11 – 15 yrs	13 (27.7%)	14 (21.2%)	27 (23.9%)
> 15 yrs	15 (31.9%)	14 (21.2%)	29 (25.7%)
Five Drug Regimen			
< 5 yr	0	0	0
6 – 10 yrs	2 (50%)	1 (20%)	3 (33%)
11 – 15 yrs	1 (25%)	1 (20%)	2 (22%)
> 15 yrs	1 (25%)	3 (60%)	4 (44%)

Five Drug Regimen: Only 9 (0.28%) subjects were on five drug regimen. Of these more than 60% of the subjects had a diabetes duration >10 years. There were none below five years of duration (Table 3).

DISCUSSION

The natural history of type 2 diabetes has a combination of a defect in insulin action and of insulin secretion. There is vast individual variation as in some of the type 2 diabetic subjects might experience more insulin resistance and others may have marked beta cell defect coupled with insulin resistance. This heterogeneity imposes great challenges in management of diabetes. However, from the UKPDS, it is clear that in type 2 diabetic subjects there is a progressive deterioration of beta cells resulting in decreased secretion of insulin. In fact, type 2 diabetic subjects have only 50% of the beta cell secretion at diagnosis of diabetes (4). Very strict glycemic control has been advised to reduce the risk of micro and macro vascular complications (5, 6). Various medical Institutions have formulated treatment algorithms for management of type 2 diabetes which can be comfortably followed by their patients (7, 8). For example, the treatment algorithms from the Texas Diabetes Council (8) suggest initial monotherapy, early dual therapy or combination oral therapy and finally insulin therapy.

Ethnic diversity in the prevalence of diabetes and insulin resistance posses a challenge for the choice of treatment (9 - 12). Furthermore the availability and cost of drugs restricts the choices of drugs for management in different countries. Hence, more data on management of type 2 diabetes in native Indians is required to understand the complexity of disease and to formulate management strategies. This study is an attempt in this direction.

About 2% of the study subjects achieved remission to normoglycemia. Of these more than 60% had the remission period for only one year. The median duration of near normoglycemia remission has been reported to be 40 months in a study by Banerji et al (13). Retrospective study on the effect of diabetic education revealed 30% remission in subjects who attended the diabetes education classes against 3% in those who did not participate in the classes (14). Weight loss which could be an effect of the diabetes education has been consistently shown to be associated with remission (15, 16). Banerji (13) hypothesized that acute hyperglycemia due to various reasons would impact the β cell secretion resulting in diabetes. Once glucotoxicity is corrected, the β

cell secretion recovers and then normoglycemia could be maintained. However, this relapse may not be permanent and may result in progressive decrease of insulin secretion capacity and later lead to frank diabetes. This is corroborated in the present study where more than 90% of the subjects in remission developed diabetes after 5 years. Only 2.8% of the subjects had remission to normoglycemia for 10 years until the end of the study period.

Monotherapy was advised in nearly 46% of the study population. In a study on compliance for antidiabetic drugs in 23,400 patients, 855 had monotherapy which was either metformin, sulphonylurea or other antidiabetic agent (17). The study concluded that compliance for monotherapy was 45% greater compared to polytherapy. Ample evidence from the clinical trials has documented the efficacy of combination therapy in glycemic control (18 – 20). Combination of drugs with complementary action like, one reducing insulin resistance and the other increasing insulin secretion, exert synergistic effects to achieve glycemic control. Earlier, only metformin was the drug of choice for reducing insulin resistance. The discovery of thiazolidiones has been a boon to the type 2 diabetic subjects.

In the present study, nearly 50% of the study subjects achieved the target glycemic control with combination of oral drug therapy. However, due to the progressive nature of the disease, type 2 diabetic subjects sooner or later require insulin to achieve the glycemic targets. Nearly 4% of the study subjects had secondary failure to OHA and required insulin. Combination of OHA with insulin therapy has been shown to decrease the insulin requirement (21, 22). It is hypothesized that the oral drugs through pancreatic and extrapancreatic effect decrease exogenous insulin requirement. However, the benefits of combination therapy have been debated, as the effect does not last beyond few months (23). An earlier report from India on 188 subjects with secondary failure to OHA showed that addition of sulphonylurea (glibenclamide) to insulin had many benefits (23). In the present study, 25% of type 2 diabetic patients required insulin for diabetes control. However, inclusion of acarbose and glitazone molecules reduced the insulin requirement by 75% in 15% of type 2 diabetic patients while the remaining 10% of patients were completely withdrawn from insulin. Glitazones must be used very cautiously as they cause increase in weight due to increase in subcutaneous fat and water retention. One should carefully use these molecules in those with cardiac or renal impairment, and uncontrolled hypertension patients. In this study, it was observed that the maximum drug regimen was common among subjects with longer duration of diabetes and in elderly subjects. As one would expect with increase in duration of diabetes, production of insulin is decreased and hence exogenous insulin is required to control diabetes. In elderly, the drugs required to achieve glycemic control has to be decided with care as the aging could influence the pharmacokinetics of the drugs. Furthermore, drugs without any interaction should be selected as old people might be on other drugs for various other diseases. Infact a stepwise approach is the best advice for the management of diabetes in elderly (28).

This study concludes that optimal anti-diabetic measures can arrest the further progression of the disease and intensive therapy could help in achieving tight glycemic control. But whatever regimens are followed, unless the subject follows a strict diet and exercise pattern, diabetes control would remain elusive.

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REFERENCES

1. Hales C. The pathogenesis of NIDDM. Diabetologia 1994;37:S162-S168.

2. Report of the Expert Committee on the diagnosis and Classification of diabetes mellitus. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997; 20: 1183 -97.

3. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995 - 2025 - prevalence, numerical estimates, and projections. Diabetes Care. 1998; 21:1414-31.

4. UK Prospective Diabetes Study (UKPDS) Group Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53.

5. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998; 317: 703–13.

6. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care. 1999; 22: 99-111.

7. Wyne KL, Drexler AJ, Miller JL, Bell DS, Braunstein S, Nuckolls JG. Constructing an algorithm for managing type 2 diabetes. Focus on role of the thiazolidinediones. Postgrad Med. 2003; 63-72.

8. Spellman CW. Management of diabetes in the real world: tight control of glucose metabolism. J Am Osteopath Assoc. 2003; 103: S8 - S13.

9. Knowler WC, Pettitt DJ, Saad MF, Bennett PH. Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. Diabetes Metab Rev. 1990; 6:1 - 27.

10. McKeigue PM, Pierpoint T, Ferrie JE, Marmot MG. Relationship of glucose intolerance and hyperinsulinemia to body fat pattern in south Asians and Europeans. Diabetologia. 1992; 35: 785–91.

11. Sharp PS, Mohan V, Levy JC, Mather HM, Kohner EM. Insulin resistance in patients of Asian Indian and European origin with non-insulin dependent diabetes. Horm Metab Res. 1987;19: 84-5.

12. Mohan V, Sharp PS, Cloke HR, Burrin JM, Schumer B, Kohner EM. Serum immunoreactive insulin responses to a glucose load in Asian Indian and European Type 2 (non-insulin-dependent) diabetic patients and control subjects. Diabetologia. 1986; 29: 235-7.

13. Banerji MA, Chaiken RL, Lebovitz HE. Long-term normoglycemic remission in black newly diagnosed NIDDM subjects. Diabetes. 1996; 45: 337-41.

14. Hirsch S, Norton M, Harrington P. Education increases the rate of near normoglycemic remission in newly diagnosed NIDDM (Abstract). Diabetes 1995; 44 (suppl 1): 88.

15. Pirart J, Lauvaux JP: Remission in diabetes. *In* Handbook of diabetes mellitus. Vol II. Pieffer E, Ed. Munich, Verlag, 1971, p. 443–502.

16. UKPDS group: UK Prospective diabetes study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients. Metabolism. 1990; 39: 905–12.

17. Dailey G, Kim MS, Lian JF. Patient compliance and persistence with anti-hyperglycemic therapy: evaluation of a population of type 2 diabetic patients. J Int Med Res. 2002; 30: 71-9.

18. Bailey TS, Mezitis NH. Combination therapy with insulin and sulfonylureas for type II diabetes. Diabetes Care. 1990; 13: 687-95.

19. Rendell MS, Glazer NB, Ye Z. Combination therapy with pioglitazone plus metformin or sulfonylurea in patients with Type 2 diabetes: influence of prior antidiabetic drug regimen. J Diabetes Complications. 2003; 17: 211-7.

20. Raskin P, Klaff L, McGill J, et al. Repaglinide vs. Nateglinide Metformin Combination Study Group. Efficacy and safety of combination therapy: repaglinide plus metformin versus nateglinide plus metformin. Diabetes Care. 2003; 26: 2063-8.

21. Mozersky RP, Patel H, Bahl VK, Bahl S, Mook W. Efficacy of combination therapy with insulin and oral hypoglycemic agents in patients with type II diabetes during a 1-year period. J Am Osteopath Assoc. 1996; 96: 346-51.

22. Feinglos MN, Thacker CR, Lobaugh B, et al. Combination insulin and sulphonylurea therapy in insulin-requiring type 2 diabetes mellitus. Diabetes Res Clin. Pract. 1998; 39: 193–9.

23. Zargar AH, Masoodi SR, Laway BA, Wani AI, Bashir MI. Response of regimens of insulin therapy in type 2 diabetes mellitus subjects with secondary failure. J Assoc Physicians India. 2002; 50:641-6.

24. Rosenstock J. Management of type 2 diabetes mellitus in the elderly: special considerations. Drugs Aging. 2001; 18: 31-44.