Prof. M Vishwanathan Oration

FACTORS AFFECTING COMPLIANCE IN TYPE 2 DIABETIC PATIENTS: EXPERIENCE FROM THE DIABETES OUTCOMES IN VETERANS STUDY (DOVES)

Jayendra H Shah*, Glen H Murata, William C Duckworth***, Richard M Hoffman****, Christopher S Wendel#**

It is my distinct pleasure and privilege to accept your invitation to deliver the Professor M. Viswanathan Memorial Oration for the Research Society for Study Diabetes in India (RSSDI). Professor Viswanathan was a relentless crusader against diabetes and has been acknowledged as the "Father of Diabetology" in India. I am truly honored and humbled to be recognized to give this oration, bearing the name of a great clinician, educator and researcher in the field of diabetes.

I am sure that certain aspects of compliance with diabetes treatment are unique to the United States of America (USA). However, many of these compliance issues are similar between the USA and India. I will begin by describing the public health problem of diabetes in the USA and how the patient-physician relationship, metabolic syndrome of type 2 diabetes and controversies affect compliance in diabetic regimen. I will then share with you the results of our ongoing Diabetes Outcomes in Veterans Study (DOVES).

In the USA, diabetes is approaching an epidemic proportion. It is estimated that in the year 2002 over 16 million Americans will have diabetes mellitus. Of these, approximately 6 million Americans are undiagnosed (1). The majority of these patients (90%) suffer from non-insulin dependent, type 2 diabetes. The majority of type 2 diabetic patients will fail to respond to diet and oral agents and will eventually require insulin therapy to control hyperglycemia. Diabetes is the 7th most prevalent cause of death in the USA. The cardiovascular complications are a major cause of mortality and hospitalization in these diabetic patients. In the USA, diabetes is the leading cause of blindness and accounts for 50% of non-traumatic amputations. Every year, 25% of new cases of end-stage renal disease originate from diabetes. In diabetic patients, age matched mortality is three times higher, the incidence of macrovascular disease is four times higher, the incidence of peripheral vascular disease and gangrene 20 times more likely, and overall medical costs four times higher than patients without diabetes. Thus, the health care cost for this common, chronic and complex disease in the USA approaches 102 billion dollars per year (2).

Diabetes leads to microvascular complications of nephropathy, retinopathy and neuropathy, which are related to duration of diabetes and overall glycemic control. Compared with type 1 diabetes, microvascular complications are less frequent in type 2 diabetes. The macrovascular complications of atherosclerotic heart disease, stroke and peripheral vascular disease are responsible for most of the mortality in type-2 diabetes.

According to United Kingdom Prospective Diabetes Study (UKPDS), macrovascular mortality is 70 times higher than microvascular mortality in type 2-diabetes (3). Atherosclerosis is responsible for over 80% of the mortality in patients with type 2 diabetes, of which 75% is due to coronary atherosclerosis and 25% is attributed to cerebrovascular or peripheral vascular disease (4). Over 50% of the newly diagnosed type 2 diabetic patients suffer from coronary artery disease. Of all the patients hospitalized for complications of diabetes, over 70% are due to atherosclerosis complications. Obviously, our long-term goal should be to treat diabetes to prevent microvascular and macrovascular complications.

TYPE 2 DIABETES – A METABOLIC SYNDROME

Type 2 diabetes presents itself as a metabolic

**This oration was delivered by Prof. Jayendra H Shah at the RSSDI Annual Conference, 2002. Chief Medical Officer (JHS), Southern Arizona VA Health Care System (JHS & CSW). **Research Officer (JHS), Veterans Integrated Service Netwark-18. ***Departments of Medicine and Radiology, University of Arizona College of Medicine, Tucson, Arizona (JHS); ****Department of Medicine, New Mexico VA Health Care System, Albuquerque, New Mexico (GHM and RMH); #Department of Medicine, Carl T. Hayden VA Medical Center Phoenix, Arizona (WCD)*

syndrome with a spectrum of hyperglycemia, obesity, insulin resistance, hypertension, complex dyslipidemia, atherosclerosis, and endothelial dysfunction. It is well known that obesity plays an important role in the development of insulin resistance and thus, type 2 diabetic metabolic syndrome. In 1991, only seven states in the USA had obesity rates over 15%. By 1998, 45 of 50 states have obesity rates over 15%. No wonder the incidence of type 2 diabetes is also proportionally increased in the USA. It has been observed that the android type of obesity is frequently associated with hypertension, type 2 diabetes, and coronary artery disease (5-7). A link between type 2 diabetes, coronary artery disease, and hypertension appears to be hyperinsulinemia and insulin resistance. Furthermore, evidence supports the hypothesis that insulin resistance may play a major role in the pathogenesis of hypertension, obesity, type 2 diabetes and links them to increased risks of coronary artery disease (8-13). From these observations, it is obvious that in type 2 diabetic patients, glycemic control, weight reduction and control of hypertension and hyperlipidemia are essential in reducing long-term complications.

Since our goal is to prevent microvascular and macrovascular complications of diabetes, are we treating type 2 diabetic patients optimally? Our personal experience and data from literature suggest that optimal glycemic control is not achieved in many type 2 diabetic patients. A significant proportion of adults in the USA with the diagnosis of type 2 diabetes have a hemoglobin A_{1c} (HbA_{1c}) above 8.0% (14). Why do we fail to achieve near-normal glycemic control in type 2 diabetic patients? Frequently, non-compliance of the diabetic patient has been blamed for the treatment failure. However, attributing treatment failure to the patient's improper behavior and non-compliance may be unjust (15).

COMPLIANCE AND ADHERENCE

Frequently, in medicine, compliance and adherence are used as interchangeable terminology. It has been reported that, in general, diabetic patients are non-adherent to their treatment and only a small number of diabetic patients were found adherent or compliant with all aspects of diabetic care (16-17). The adherence to different aspects of diabetes care has been variable. For example, adherence to an exercise program varied from 19% to 30% (18-19), accuracy and frequency of taking insulin varied from 20% to 80% (17, 20), and home blood glucose monitoring varied from 57% to 70% (17, 21).

One can define compliance as "the extent to which a person's behavior coincides with medical or health advice" (22). For diabetic patients, "behavior" is taking oral medications and/or insulin injections, following diets, performing home blood glucose monitoring and making several lifestyle changes. The word compliance indicates that patients obey physicians' instructions. The patient's conformity to medical goals are defined by their physicians, whereas adherence "characterizes the patients as independent, intelligent and autonomous people, who take more active and voluntary roles in defining and pursuing goals for their medical treatment" (23). Alternatively, adherence might be defined as "the degree to which a patient follows a predetermined set of behaviors or actions (established cooperatively by the patient and provider) to care for diabetes on a daily basis" (24). Thus, the health care provider, inclusive of physician, plays an equally important role in achieving patient adherence to diabetic treatment regimens. Although many factors are responsible for metabolic control in type 2 diabetes, for the purpose of this presentation, we will review four specific areas as they relate to adherence of diabetic regimens. These include: a) the patient-physician relationship; b) controversies in achieving glycemic control; c) diabetes knowledge, exercise and diet; and d) utility of home blood glucose monitoring to predict glycemic control, hypoglycemia and hyperglycemia.

PATIENT-PHYSICIAN RELATIONSHIP

The interaction between the physician and patient is important in the management of type 2 diabetes. It is not uncommon that poor communication between the patient and physician may lead to poor compliance. In a survey of diabetic patients and their primary care physicians, a significant dissociation was observed between what physicians thought they recommended and what patients understood. For example, 78% of physicians reported that they recommended HbA_{1c} test, but only 33% of patients stated that their physician recommended the test. Similarly, 95% of physicians reported that they referred their patients to an eye specialist, yet only 43% of the patients thought their primary care physicians did so. (25). Physicians should also understand cultural, economic and geographic features of the community in which the patient lives before recommending a diabetic regimen. In a rural community, access barriers like distance, transportation and society's beliefs play an important role in compliance (26).

It has been proposed that the quality of the patient-physician relationship is associated with adherence to diabetes treatment (27). These investigators used the attachment theory of Bowlby (28) who proposed that individuals internalize earlier experiences with their primary care providers and determine whether they are worthy of care (view of self) or whether others, i.e. physicians, can be trusted to provide care (view of others). Four attachment categories have been identified in adults: secure, dismissing, preoccupied and fearful (29). Diabetic patients with a dismissing attachment had significantly worse glucose control than diabetic patients in the other categories (27). These patients with a dismissing attachment develop a positive view of self and become compulsively self-reliant. They develop a negative view of others and, therefore, they are uncomfortable being close to or trusting others. Among diabetic patients with a dismissing attachment style, those who rated their patient-physician communication as poor had, even significantly higher HbA_{1c} than those who rated their communication as good (27). Thus, the patient-physician relationship plays an important role in the compliance of diabetic patients in their overall diabetic regimen.

CONTROVERSIES

Many primary care providers believe that intensive glycemic control of type 2 diabetic patients is risky, expensive, burdensome, time-consuming and inconvenient to patients and providers. Therefore, if the primary care providers are not convinced about benefits of intensive glycemic control, they many not help their patients achieve proper glycemic control. Many primary care providers cite a deleterious effect of insulin during intensive treatment of diabetic patients. It is well known that, invariably, diabetic patients gain weight following insulin therapy (30-31). In most patients, this weight gain is limited to a few pounds. However, even a small degree of weight gain in an obese type 2 diabetic patient, who is motivated to lose weight, can create conflict in achieving his or her desired goal. The hyperinsulinemia caused by insulin treatment in obese type 2 diabetic patients may perpetuate the deleterious effect of insulin and insulin resistance by triggering and increasing cardiovascular risk factors (32-33). Furthermore, the degree of hyperinsulinemia caused by insulin treatment predicted major vascular complication in type 2 diabetic patients (34). The price one must pay for tighter glycemic control is frequent hypoglycemia (35-37). In the Diabetic Control and Complication Trial (DCCT), more than 50% of hypoglycemic events following insulin treatment occurred during sleep (38). Recurrent hypoglycemia can result into cognitive dysfunction and non-cognitive psychological abnormalities (39-41). Also, it has been shown that insulin therapy in type 2 diabetic patients has been associated with significant elevation of both systolic and diastolic blood pressures (42). These potential adverse effects of insulin, especially recurrent hypoglycemia, may cause reluctance to intensive glycemic control by diabetic patients and their physicians.

The DCCT study showed that in type 1 diabetic patients, intensive glycemic control significantly delayed the onset and slowed the progression of microvascular complications. However, macrovascular complications were reduced, but not significantly, presumably due to low incidence of macrovascular complications in young patients (36). Similarly, under UKPDS, the intensive treatment in type 2 diabetic patients overall benefited “diabetes-related events” due to improved microvascular complications outcomes. However, diabetes-related mortality and all-cause mortality were not improved. In UKPDS, macrovascular events outnumbered microvascular events, and cardiovascular mortality was not significantly reduced (3). In contrast, a pilot trial of 110 type 2 diabetic patients in the Kumamoto study from Japan showed clear benefits of intensive treatment in reducing overall microvascular and macrovascular complications (43). However, findings from this study may not be applicable to type 2 diabetic patients of Veterans Administration (VA) Medical Centers in USA because patients in the Kumamoto study were younger. In addition, patients in the Kumamoto study were more insulin sensitive, their mean BMI was 21, (versus 31 in VA patients) and they had no hyperlipidemia, hypertension or ECG abnormalities, whereas 90% of type 2 diabetic patients seen in the VA clinics have these abnormalities. Projecting the estimates of the DCCT in type 1 diabetic patients to a younger type 2 diabetic patients, a significant risk reduction in the risk of blindness and renal failure would occur by reducing HbA_{1c} from 9% to 7%. In contrast, newly diagnosed, older type 2 diabetic patients would have relatively minor lifetime risk reductions of either blindness or renal failure by intensively treating hyperglycemia and reducing HbA1c from 9% to 7% (44-45). It has also been shown that a greater increase in microvascular complications occurs with an increase in HbA_{1c} from 9% to 11% than those occurring with a change of HbA_{1c} from 7% to 9%. A decrease in complications in diabetic patients is not a linear function of decrease in HbA_{1c}, i.e. tighter glycemic control (45). Primary care physicians know it is much easier, less risky, and more economical to control hyperglycemia at the HbA_{1c} level between 8% and 9% rather than 6% and 7%. Therefore, for goal setting of optimal attainment of glycemic control, the diabetic patient's primary care physician plays an important role, which ultimately leads to patient compliance or adherence.

DIABETES KNOWLEDGE, EXERCISE AND DIET

Many factors have an effect on glycemic control in diabetic patients. Depression, cognitive functioning, diabetes knowledge, family support, exercise, dietary habits, lifestyle, treatment regimens, and access barriers are some of the potential predictors of glycemic control in diabetic patients. Higher diabetic knowledge scores in a group of older type 2 patients was associated with better glycemic control when randomly assigned to diabetic education programs compared with those randomly assigned to usual care (46). Similarly, a study of 165 diabetic patients who received outpatient diabetes education for one week showed a significant increase in the knowledge score, which was associated with a significant fall in HbA_{1c} at 6 months (47).

A comprehensive study was undertaken in 1999 to examine the association between clinical, demographic, lifestyle, socioeconomic and psychological variables and clinical outcomes, including glycemic control and disease outcome in insulin-treated type 2 diabetic patients. This Diabetes Outcomes in Veterans Study (DOVES) was conducted in the Southwestern United States at the large VA Medical Centers in Tucson, Phoenix and Albuquerque (48). The evaluation of diabetes knowledge in these type 2 diabetic patients showed overall poor performance on the knowledge test. The knowledge test was positively correlated with years of education and scores on the Mini-Mental status exam. The knowledge score was inversely correlated with age of the patients and depression score. Patients who preferred the English language scored significantly better than those who did not. There were significant ethnic differences in the group. For example, Hispanic patients significantly answered fewer questions correctly on the diabetes knowledge test, were more depressed, and scored lower in the Mini-Mental status exam compared to non-Hispanic white patients (49).

In a subset of DOVES study, we evaluated psychological, clinical and social factors that affect adherence to American Diabetes Association Dietary Recommendations (ADA-DR) by 252 insulin treated type 2 diabetic patients. The manuscript describing findings in details of this study is under preparation. In summary, patients in this study completed an extensive psychological evaluation of 14 attitudes and behaviors relating to diabetes care and a food frequency questionnaire. The compliance with ADR-DR increased with age and duration of diabetes treatment, was higher for those with better self-care skills and adherence to self-care behaviors. Better compliance with ADA-DR was associated with diminishing work hours and living alone. Poor compliance with ADA-DR was not related to psychological factors, diabetes knowledge, literacy, cognitive functioning or disabilities related to preparing meals. Our study suggested that patients at high risk for dietary non-compliance are younger and married, have been on shorter duration of insulin treatment, live in a remote area, and work long hours. Dietary compliance is related to self-care abilities, adherence to self-care and adherence to meal plans (50). We believe that efforts to improve dietary compliance should focus on improving self-care skills and on providing dietary alternatives for married and working patients. Improving motivation or level of knowledge may not be effective in changing dietary habits in type 2 diabetic patients residing in the Southwestern United States.

In another subset of the DOVES study, we examined psychological barriers to exercise in insulin-treated type 2 diabetic patients. The amount of exercise was significantly lower for those diabetic patients with extremity ulcers, peripheral vascular disease, amputation, angina or disability for any activity more strenuous than routine self-care. The poorer perception of long-term benefits, lower cognitive functioning, the presence of amputation or angina and disability for activities more strenuous than shopping, increased the likelihood of low level of exercise. Thus, the most influential determinants for low levels of exercise were diabetic complications, disabilities or cognitive dysfunction. It is unlikely that improving attitudes or motivation will result in increased exercise levels in sedentary type 2 diabetic patients unless it is accompanied by successful physical rehabilitation (51). The systematic analysis of psychological and behavioral factors affecting body mass index (BMI) showed that better perceived adherence to an exercise plan and greater self-care abilities were associated with lower BMI. Linear regression showed that patients with larger BMI met fewer of the dietary objectives of ADA-DR. Patients with larger BMI scored lower in their perceived adherence to self-care and self-care abilities, and were more likely to perceive physical disabilities and barriers to exercise. However, obesity in these type 2 diabetic patients was more likely due to poor dietary habits than lack of exercise (52). Details of the findings of psychological barriers to exercise and psychological and behavioral factors affecting BMI are described in a separate manuscript under preparation.

PREDICTING GLYCEMIC CONTROL, HYPERGLYCEMIA AND HYPOGLYCEMIA

Self-monitoring of blood glucose (SMBG) should be done by insulin-treated type 2 diabetic patients. According to the American Diabetes Association's recommendations, SMBG should be done frequently to meet the goals of appropriate glycemic control and to detect asymptomatic hypoglycemia (53). SMBG in insulin-treated type 2 diabetic patients is variable. In one recent survey, only 39% of those doing SMBG performed the test daily, whereas less than 10% reported that they performed the test two or more times a day (54). A meta-analysis of eight randomized trials showed that there was little evidence that SMBG was effective (55). Only one of six randomized trials of SMBG in type 2 diabetic patients reported favorable results (56). Although SMBG was associated with better glycemic control in two population based surveys (57-58), several other surveys did not support this observation (59-62). It is reasonable to ask whether SMBG is beneficial and feasible in type 2 diabetic patients and whether it leads to accurate assessment of glycemic control and ultimately meaningful improvements in health outcomes (63).

In a subset study of DOVES, we evaluated the utility of SMBG in predicting glycemic control, hypoglycemia and hyperglycemia in insulin-treated type 2 diabetic patients. In this observational study, patients were randomly selected from pharmacy records of active prescriptions of insulin. Patients were asked to perform SMBG four times a day, before breakfast, lunch and dinner and at bedtime for a period of eight weeks. Patients returned to clinic at the end of four and eight weeks of the monitoring period for downloading data from electronic glucose meter provided by the study. HbA_{1c} was measured at baseline, at the end 4, 8, 26 and 39 weeks.

Of the group who completed four times a day monitoring, a simple linear regression showed a highly significant relationship between mean blood glucose from all 8 weeks SMBG and HbA_{1c} determined at the end of 8 weeks, Figure 1, (r=0.79, P<0.0001). The mean SMBG values from week one or any of the eight weeks provided nearly identical prediction equations for week eight HbA_{1c}, using only 12.5% of the all eight week glucose values, figure 2, (64-65). Hypoglycemia, blood glucose ≤ 60 mg/dl (3.3 mmol/l) occurred at least once in 53% of subjects and was detected in 1.7% of all SMBG values. Although hypoglycemia was observed at different times of the day, it was significantly more likely to occur before lunch. Hyperglycemia at blood glucose ≥ 400 mg/dl (≥ 22.2 mmol/l) occurred at least once in 43% of subjects and was found in over 1% of SMBG determinations. Hyperglycemia at lower level, blood glucose ≥ 200mg/dl (≥ 11.1 mmol/l) occurred at least once in 99% of subjects and was found in 30% of SMBG determinations (figure 3). Hyperglycemia at both levels was significantly more common at bedtime (61).

Compliance for SMBG was defined as the number

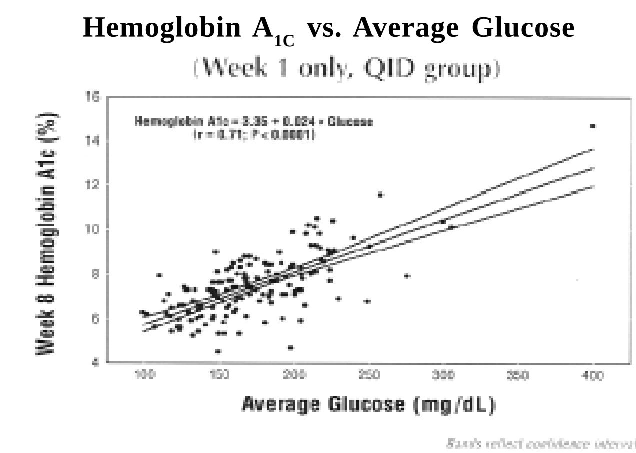

Figure 1: Correlation between Average Blood Glucose Values in each Patient during Entire Eight Week SMBG Period and Hemoglobin A_{1c} at the End of Eight Week Period. R = 0.79; P < 0.0001.

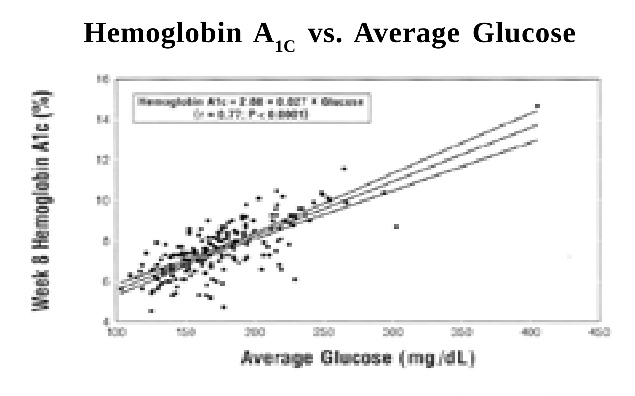

Figure 2: Correlation between Average Blood Glucose Values in each Patient during First Week of Eight Week SMBG Period and Hemoglobin A_{1c} at the end of Eight Week Period. R = 0.71; P < 0.0001.

of blood glucose readings taken, divided by number prescribed, i.e. four times a day for eight weeks. Compliance varied widely from subject to subject. As a group, compliance remained steady for the first six weeks and significantly declined in week seven and eight (66-67). Intensive SMBG may have had a beneficial effect on glycemic control. Linear regression showed that 8 week HbA_{1c} was inversely correlated with SMBG compliance (figure 4).

Even though subjects in this study had been treated

Hemoglobin A_{1C} vs. Compliance

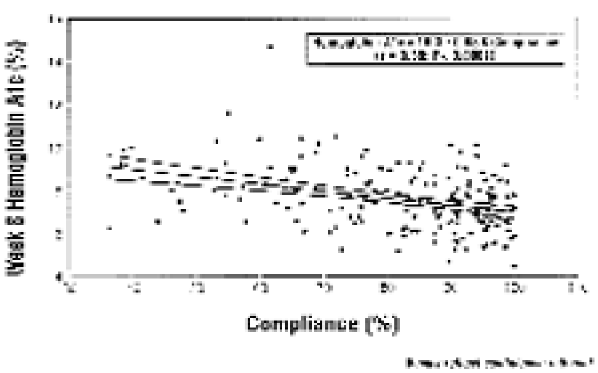

Figure 3: Distribution of Hyperglycemic Events, Blood Glucose ≥ 200 Mg/dl (≥ 11.1 mmol/L), by the Time of the Day. Hyperglycemia of ≥ 200 mg/dl (≥ 11.1 mmol/L) was Significantly more Common at Bedtime (P < 0.001)

Risk of Hyperglycemic Event (Glucose ≥ mg/dL) by Time of Day

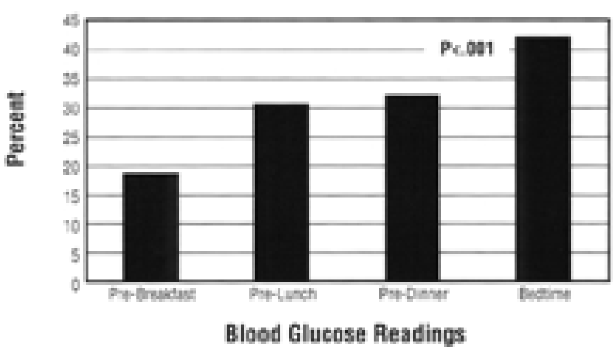

Figure 4: Linear Regression Shows that 8 Week Hemoglobin A_{1c} is Inversely Correlated with SMBG Compliance. R = 0.38; P < 0.0001

with insulin for an average of eight years and were on a stable diabetic regimen for at least two months, repeated measures analysis of variance showed a significant fall in HbA_{1c} during prescribed intensive SMBG from baseline to eight weeks. Once the intensive SMBG was stopped, HbA_{1c} gradually started increasing and rose to significantly higher level at 39 weeks compared to that observed at 8 weeks (figure 5). Since patients glycemic control improved during intensive SMBG (as indicated by a significant decline in HbA_{1c}) while no change in patient's weight was observed nor a change in insulin dose was instituted, we speculate patients achieved better control by improving their diet.

Hemoglobin A_{1C} by week
In 252 subjects with stable DM type 2

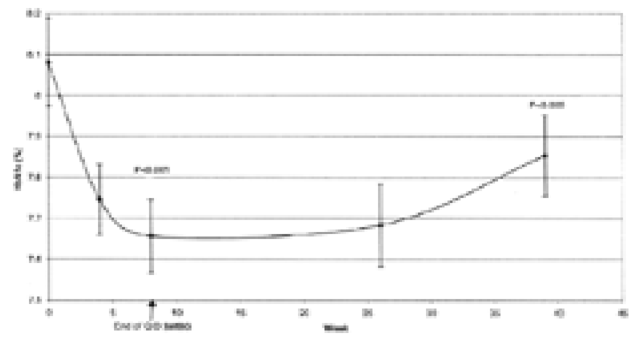

Figure 5: Hemoglobin A_{1c} Significantly Declined at End of Eight Week of Intensive SMBG Four Times a Day (P < 0.0001), While no Interventions in Insulin or Other Treatment was Initiated and Body Weight Remained Unchanged. Hemoglobin A_{1c} Significantly Increased (P < 0.0005) at 39 Weeks (31 Weeks after Discontinuing Intensive SMBG)

In summary, compliance with SMBG is poor and variable from patient to patient in type 2 diabetes. Compliance inversely correlated with HbA_{1c} (higher the compliance, lower the HbA_{1c}). Intensive SMBG had a positive effect in improving HbA_{1c}, which gradually deteriorated once the intensive monitoring was terminated. Pre-lunch SMBG is predictive of patients who are prone to hypoglycemia, as hypoglycemia was significantly more likely to occur before lunch. On the other hand, hyperglycemia was significantly more common at bedtime and bedtime SMBG is more predictive of patients prone to hyperglycemia. The mean blood glucose value from any of the 8 week significantly correlated with week 8 HbA_{1c}. We believe that a tailored, individualized and parsimonious SMBG schedule may provide appropriate information for patient needs while being cost effective and may elicit higher degree of compliance from patients. If, in insulin-treated type 2 diabetic patients, the concern is overall glycemic control, then information can be obtained by SMBG four times a day for one week. If the concern is hypoglycemia, monitoring should focus on pre-lunch blood glucose. Alternatively, if the concern is hyperglycemia, then SMBG should focus on bedtime blood glucose. The structured SMBG, per se, may have a positive effect on glycemic control. Finally, compliance and/or adherence to diabetes regimen is affected by both physicians and type 2 diabetic patients. It is important to realize that we (patients and physicians) can control and alter our desire, attitude, and action for optimal metabolic control, but we certainly have no control on consequences that result from our actions and, therefore, outcomes in the form of diabetic complications.

ACKNOWLEDGEMENT: The Diabetes Outcomes in Veterans Study (DOVES) was supported by a grant (VCR 99-007) from the HSR&D Service and Veterans Integrated Service Network-18, Department of Veterans Affairs. Excellent help and dedication of Dr. Syed Bokhari, Ms. Karen Adams, Ms. Cheri Dalton, and Ms. Patricia Solvas are sincerely appreciated. Thanks are due to Ms. Debbie Andrews for her excellent assistance in preparing this manuscript.

REFERENCES

1. Hirsh I. Diabetes Education (for doctors). Clin Diabetes 1999; 17: 50-1.
2. Direct and Indirect Cost of Diabetes in United States in 1992. Alexandria, VA, American Diabetes Association 1992.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risks of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53.
4. National Diabetes Data Group. Diabetes in America, 2nd ed. NIH; 1995.
5. Vague J. The degree of masculine differentiation of obesities: A factor determining predisposition to diabetes, atherosclerosis, gout and uric calculous disease. Am J Clin Nutr 1956; 4: 20-34.
6. Kaplan NM. The deadly quartet: Upper body obesity, glucose intolerance, hypertriglyceridemia and hypertension. Arch Intern Med 1989; 149: 1514-20.
7. Haffer SM, Fong D, Haxude HP, Pugh JA, Patterson JK. Hyperinsulinemia, upper body obesity, and cardiovascular risk factors in non-diabetics. Metabolism 1988; 37: 338-45.
8. Kannel WB, Brand N, Skinner JJ JR, Dawber TR, McNamara PM. The relation of adiposity to blood pressure and development of hypertension. The Framingham Study. Ann Intern Med 1967; 67: 48-59.
9. Tyroler HA, Heydon S, Harnes CG. Weight and hypertension. Evans County study of blacks and whites. *In*: Paul O *(ed),* Epidemiology and Control of Hypertension. New York: Stratton International, 1975; 177.
10. Sowers JR, Tuck ML. Hypertension associated with diabetes mellitus, hypercalcemic disorders, acromegaly and thyroid disease. Clin Endocrinol Metab 1981; 10: 631-56.
11. Shen DC, Shieh SM, Fuh M, et. al. Resistance to insulin-stimulated glucose uptake in patients with hypertension. J Clin Endocrinol Metab 1988; 66: 580-3.
12. Swislocki ALM, Hoffman BB, Reaven GM. Insulin resistance, glucose intolerance and hyperinsulinemia in patients with hypertension. Am J Hypertension 1989; 419-23.
13. Shah JH. Hypertension and insulin resistance: A risk factor for coronary artery disease. *In:* Advances in Endocrinology, Metabolism and Diabetes, Volume 1. *Ed.* N. Kochupillai. Macmillan India Limited. New Delhi, India 1992; 68-76.
14. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS. Racial and ethnic differences in glycemic control of adults with type 2 diabetes. Diabetes Care 1999; 22: 403-8.
15. Wishner WJ, Lutfey KE. Response to Glasgow and Anderson. Diabetes Care 2000; 23: 1034-5.
16. Kurtz MS. Adherence to diabetic regimens: empirical status and clinical applications. Diabetes Educ 1990; 16: 50-6..
17. Churkoney KA, Hart LK. The relationship between health belief model and compliance of persons with diabetes mellitus. Diabetes Care 1980; 3: 594-8.
18. Kravitz RL, Hays RD, Sherbourne CD, DiMatteo MR, Rogers WH, Ordway L, Greenfield S. Recall of recommendations and adherence to advice among patients with chronic medical conditions. Arch Intern Med 1993; 153: 1869-78.
19. Karmiya A, Ohsawa I, Fujii T, Nagai M, Yamanouchi K, Oshida Y, Sato Y. A clinical survey of exercise therapy for diabetic outpatients. Diabetes Res Clin Pract 1995; 27: 141-5.
20. Watkins JD, Roberts DE, Williams TF, Martin DA, Coyle V. Observation of medication errors made by diabetic patients in the home. Diabetes 1967; 16: 882-5.
21. Gonder-Frederick LA, Julian DM, Cox DJ, Clarke WL, Carter WR. Self-measurement of blood glucose: accuracy of self-reported data and adherence to recommended regimen. Diabetes Care 1988; 11: 579-85.
22. Haynes BR, Taylor WR, Sackett DL. Compliance in health care. Baltimore, MD. Johns Hopkins Univ Press, 1979.
23. Lutfey KE, Wishner WJ. Beyond “compliance” is adherence. Improving the prospect of diabetes care. Diabetes Care 1999; 22: 635-9.
24. McNabb WL. Adherence in diabetes: can we define it and can we measure it? Diabetes Care 1997; 20: 215-8.
25. Lawler FH, Viviani N. Patient and physician perspective regarding treatment of diabetes: compliance with practice guidelines. J Fam Pract 1997; 44: 369-73.
26. Srinivas G, Suresh E, Jagadeesan M, Amalraj E, Datta M. Treatment-seeking behavior and compliance of diabetic patients in a rural area of south India. Ann NY Acad Sci 2002; 958: 420-4.
27. Ciechanowski PS, Katon WJ, Russo JE, Walker EA. The patient–provider relationship: Attachment theory and adherence to treatment in diabetes. Am J Psychiatry 2001; 158: 29-35.
28. Bowlby J. Attachment and loss, Vol II: Separation: Anxiety and Anger. New York, Basic Books, 1973.
29. Bartholomew K, Horowitz LM. Attachment styles among young adults: a test of a four-category model. J Pers Soc Psychol 1991; 61: 226244.
30. The DCCT Research Group. Weight gain associated with intensive therapy in the diabetes control and complication trial. Diabetes Care 1988; 11: 567-73.
31. Henry RR, Gumbiner B, Ditzler T, Wallace P, Lyon R, Glauber HS. Intensive conventional insulin therapy for type 2 diabetes. Diabetes Care 1993; 16: 21-31.
32. Reaven GM. Relationship between insulin resistance and hypertension. Diabetes Care 1991; 14 (54): 33-8.
33. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med 1991; 151: 1141-7.
34. Janka HU, Ziegler AG, Standl E, Mehnert H. Daily insulin dose as a predictor of macrovascular disease in insulin-treated non-insulin dependent diabetes. Diabetes Metabolisme (Paris) 1987; 13: 359-64.

35. Wang PH. Tight glucose control and diabetic complications. Lancet 1993; 342 (8864): 129.

36. The DCCT Research Group. The effect of intensive treatment of diabetes on development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-86.

37. Saudek CD, Duckworth WC, Giobbie-Hurder MS, Henderson WG, Henry RR, Kelly DE, Edelman SV, Zieve FZ, Adler RA, Anderson JW, Anderson RJ, Hamilton BP, Donner TW, Kirkman MS, Morgan NA. Implantable insulin pump vs multiple-dose insulin for non-insulin dependent diabetes mellitus. JAMA 1996; 276: 1322-7.

38. The DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complication trial. Am J Med 1991; 90: 450-9.

39. Gold A, MacLeod K, Deary I, Frier B. Hypoglycemia-induced cognitive dysfunction in diabetes mellitus: effect of hypoglycemia unawareness. Physiol Behavior 1995; 58: 501-11.

40. Davis GA, Jones TW. Hypoglycemia in children with diabetes: incidence, counter-regulation and cognitive dysfunction. J Pediatr Endocrinol Metab 1998; 11: 177-82.

41. Gold AE, Deary IJ, Frier BM. Hypoglycemia and non-cognitive aspect of psychological function in insulin-dependent (type 1) diabetes mellitus (IDDM). Diabetic Medicine 1997; 14: 111-8.

42. Randeree HA, Omar MAK, Motala AA, Seedat MA. Effect of insulin therapy on blood pressure in NIDDM patients with secondary failure. Diabetes Care 1992; 15: 1258-63.

43. Shichiri M, Ohkubo Y, Kishikawa H, Wake N. Long-term results of Kumamoto study on optimal diabetes control in type 2 diabetic patients. Diabetes Care 2000; 23 (suppl. 2): 1321-9.

44. Duckworth WC, McCarren M, Abraira C. Glucose control and cardiovascular complications: The VA Diabetic Trial. Diabetes Care 2001; 24: 942-5.

45. Vijan S, Hofer T, Hayward R. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. Ann Intern Med 1997; 127: 788-95.

46. Gilden JL, Hendryx MS, Clar S, Casia C, Singh S. Diabetes support groups improve health care of older diabetic patients. Am Geriatr Soc 1992; 40: 147-50.

47. Rubin RR, Peyrot M, Saudek CD. Effect of diabetes education on self-care, metabolic control, and emotional well-being. Diabetes Care 1989; 12: 673-9.

48. Murata GH, Shah JH, Wendel CS, Hoffman RM, Adam KD, Bokhari SU, Solvas PA, Duckworth WC. Assessing risk factors for poor glycemic control in stable, insulin-treated patients with type 2 diabetes: The Diabetes Outcome in Veterans Study (DOVES) (submitted for consideration for publication).

49. Adam KD, Dalton C, Murata GH, Duckworth WC, Wendel CS, Bokhari SU, Montagnini MT, Shah JH. Factors affecting diabetes knowledge in insulin-treated veterans with type 2 diabetes mellitus. In the program of 19th HSR&D Annual Meeting, Department of Veterans Affairs, VA Health Services Research: Improving Access and Outcomes. Washington DC, February 2001; 82-3.

50. Shah JH, Murata GH, White RE, Hoffman RM, Wendel CS, Solvas PA, Adam KD, Bokhari SU, Duckworth WC: Factors affecting adherence to American Diabetes Association dietary recommendations (ADA-DR) by insulin-treated type 2 diabetic patients (DP). Diabetes 51, 2002; (Suppl.2): A62.

51. Murata GH, Duckworth WC, Adam KD, Hoffman RM, Solvas PA, Bokhari SU, Wendel CS, Shah JH. Barriers to exercise in insulin-treated veterans with type 2 diabetes mellitus. Diabetes 51, 2002; (Suppl.2): A245.

52. Wendel CS, Murata GH, Shah JH, Bokhari SU, Solvas PA, Adam KD, Duckworth WC. Factors affecting body mass index (BMI) in type 2 diabetes mellitus. Diabetes 51, 2002; (Suppl.2): A405-A406.

53. American Diabetes Association Clinical Practice Recommendations 2001. Diabetes Care 2001; 24 (Suppl): S80-S82.

54. Harris MI. Health care and health status and outcomes for patients with type 2 diabetes. Diabetes Care 2000; 23: 754-8.

55. Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R. Self-monitoring in type 2 diabetes mellitus: a meta-analysis. Diabet Medicine 2000; 17: 755-61.

56. Faas A, Schellevis EG, van Eijk JTM. The efficacy of self-monitoring of blood glucose in NIDDM subjects. Diabetes Care 1997; 20: 1482-6.

57. Karter AJ, Ackerson LM, Darbinian JA, et. al. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes Registry. Am J Med 2001; 111: 1-9.

58. Schiel R, Muller UA, Rauchfub J, Sprott H, Muller R. Blood-glucose monitoring in insulin treated type 2 diabetes mellitus: a cross-sectional study with an intervention group. Diabetes Metabol 1999; 25: 334-40.

59. Oki JC, Flora DL, Isley WL. Frequency and impact of SMBG on glycemic control in patients with NIDDM in an urban teaching hospital. Diabetes Educat 1997; 23: 419-24.

60. Harris MI. Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. Diabetes Care 2001; 24: 979-82.

61. Evans JMM, Newton RW, Ruta DA, MacDonald TM, Stevenson RJ, Morris AD. Frequency of blood glucose monitoring in relation to glycemic control: observational study with diabetes database. BMJ 1999; 319: 838-6.

62. Rindone JP, Austin M, Luchesi J. Effect of home blood glucose monitoring on the management of patients with non-insulin dependent diabetes mellitus in the primary care setting. Am J Managed Care 1997; 3: 1335-8.

63. Kennedy L. Self-monitoring of blood glucose in type 2 diabetes. A time for evidence of efficacy. Diabetes Care 2001; 24: 977-8.

64. Hoffman RM, Shah JH, Wendel CS, Duckworth WC, Adam KD, Bokhari SU, Dalton C, Murata GH. Evaluating once-and twice daily self-monitored blood glucose testing strategies for stable insulin-treated patients with type 2 diabetes mellitus: The Diabetes Outcomes in Veterans Study (DOVES). Diabetes Care 2002; *in press*

65. Shah J, Duckworth WC, Dalton C, Adam K, Bokhari S, Wendel C, Hoffman R, Murata G. A parsimonious cost-effective blood glucose (BG) monitoring (BGM) strategy for insulin-treated type 2 diabetic (DM-2) patients (Pts). Diabetes 50, 2001; (Suppl.2): A252-A253.

66. Murata GH, Duckworth WC, Hoffman RM, Wendel CS, Adam KD, Bokhari SU, Solvas PA, Shah JH. Self-monitoring of blood glucose in type 2 diabetes: Compliance and Validity. The Diabetes Outcomes in Veterans Study (DOVES). Submitted for consideration for publication.

67. Murata GH, Hoffman RM, Wendel CS, Adam KD, Dalton C, Matagnini MT, Bokhari SU, Duckworth WC, Shah JH. Can insulin-treated veterans with type 2 diabetes mellitus monitor their blood sugars four times daily? Program of 19th HSR&D Annual Meeting, Department of Veterans Affairs, VA Health Services Research: Improving Access and Outcomes. Washington DC, 2001; 123-4.