CHAPTER 2

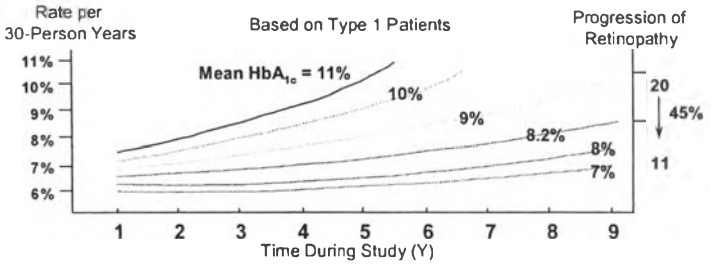
REVIEW OF THE RELATED LITERATURES

Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is complex and requires that many issues, beyond glycemic control, be addressed. A large body of evidence exists that supports a range of interventions to improve diabetes outcomes.

Intensive blood glucose control reduces long-term diabetic complications

Several landmark studies concerning the benefits of intensive glycemic control and long-term diabetic complications are now established; firstly, the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes in United states; secondly, the Japanese study for insulin treated type 2 diabetes; and thirdly the United Kingdom Prospective Diabetes Study (UKPDS) for type 2 diabetes.

The Diabetes Control and Complications Trial[6,7] (DCCT) is a multicenter trial designed to test the proposition that the complications of diabetes mellitus are related to elevation of the plasma glucose concentration. The study design was simple. Two groups of patients were followed long term, one treated conventionally (goal: clinical well-being; called the standard treatment group) and another treated intensively (goal: normalization of blood glucose; called the intensive treatment group). The intensive treatment group was clearly distinguished from the standard treatment group in terms of glycated hemoglobin levels and capillary blood glucose values throughout the duration of the study. Normalization of glucose values was not achieved in the intensively treated cohort as a group because mean glucose values were ~40% above normal limits. Nonetheless, over the study period, which averaged 7 years, there was an approximately 60% reduction in risk between the intensive treatment group and the standard treatment group in diabetic retinopathy, nephropathy, and neuropathy. The benefit of intensive therapy resulted in a delay in the onset and a major slowing of the progression of these three complications. Finally, the benefits of intensive therapy were



BENEFITS OF TIGHT GLUCOSE CONTROL

Keeping blood glucose levels close to normal reduces the risk of :

• Eye disease	by	76%
• Kidney disease	by	50%
• Nerve disease	by	60%
• Cardiovascular disease	by	35%

DCCT, Diabetes, 1995; 44:968

Figure 2 Diabetes Complication Control Trial (DCCT)

seen in all categories of subjects regardless of age, sex, or duration of diabetes.

A second report from the Japanese group, lead by Ohkubo Y and coworkers, comparing multiple insulin injection therapy (MIT) with conventional therapy (CT) for prevention of microvascular complications in Japanese patients with type 2 diabetes mellitus (NIDDM) in a 6-year randomized controlled trial. 110 patients who had type 2 diabetes and received 1 to 2 daily injections of intermediate-acting insulin were enrolled in the study. Patients were divided into a primary prevention cohort (n = 55) (no retinopathy or microalbuminuria) and a secondary intervention cohort (n = 55) (simple retinopathy or microalbuminuria). 102 patients (93%) (mean age 49 y, 52% women) completed the study. Patients were allocated to CT or to MIT . CT consisted of 1 to 2 daily insulin injections to maintain a fasting blood glucose level < 7.8 mmol/L without symptoms of hyperglycemia or hypoglycemia. MIT consisted of ≥3 daily insulin injections to maintain a fasting blood glucose level < 7.8 mmol/L, post-prandial level < 11.1 mmol/L, hemoglobin A1c level < 7.0%, and mean amplitude of glycemic excursions < 5.6 mmol/L. Near normoglycemia was achieved within 3 months and was maintained

throughout the study by patients receiving MIT. MIT led to fewer patients developing worsening diabetic retinopathy than did CT (13% vs. 38%). MIT also led to fewer patients developing diabetic nephropathy (10% vs. 30%). The differences in retinopathy and nephropathy were similar in both cohorts. Nerve conduction velocity improved over 6 years in patients receiving. The groups did not differ for episodes of hypoglycemia. It is concluded in this study that Intensive glycemic control with multiple insulin injections delayed the onset and progression of retinopathy, nephropathy, and neuropathy in Japanese patients with type 2 DM. However, several aspects of this study require closer scrutiny. Although the patients were described as having type 2 DM, they do not share the phenotypic characteristics commonly seen in European and North American patients with type 2 DM. Specifically, the body mass index was in the low normal range, and the insulin dose was similarly low, approximately 50% of that observed in the DCCT and much lower than the usual insulin requirements of patients with type 2 DM. In addition, the patients in this study do not appear to share the common characteristics of central obesity, insulin resistance, hypertension, elevated triglyceride levels, and low high-density lipoprotein levels frequently seen in Caucasian, African American, Hispanic, and aboriginal persons with type 2 DM.

Despite these limitations, the study by Ohkubo and colleagues is consistent with other observations that showed that hyperglycemia, irrespective of its cause, has similar effects on the microvascular complications of diabetes. The clinical implications are clear, namely, that the management of diabetes, both type 1 DM and type 2 DM, requires a serious and concerted effort to obtain the best possible glycemic control to improve long-term outcome.

The Third report, United Kingdom Prospective Diabetes Study (UKPDS) is another landmark diabetes study. This is the largest and longest study on type 2 diabetic patients that has ever been performed. The study recruited 5,102 patients with newly diagnosed type 2 diabetes in 23 centers within the U.K. between 1977 and 1991. Patients were followed for an average of 10 years to determine *1*) whether intensive use

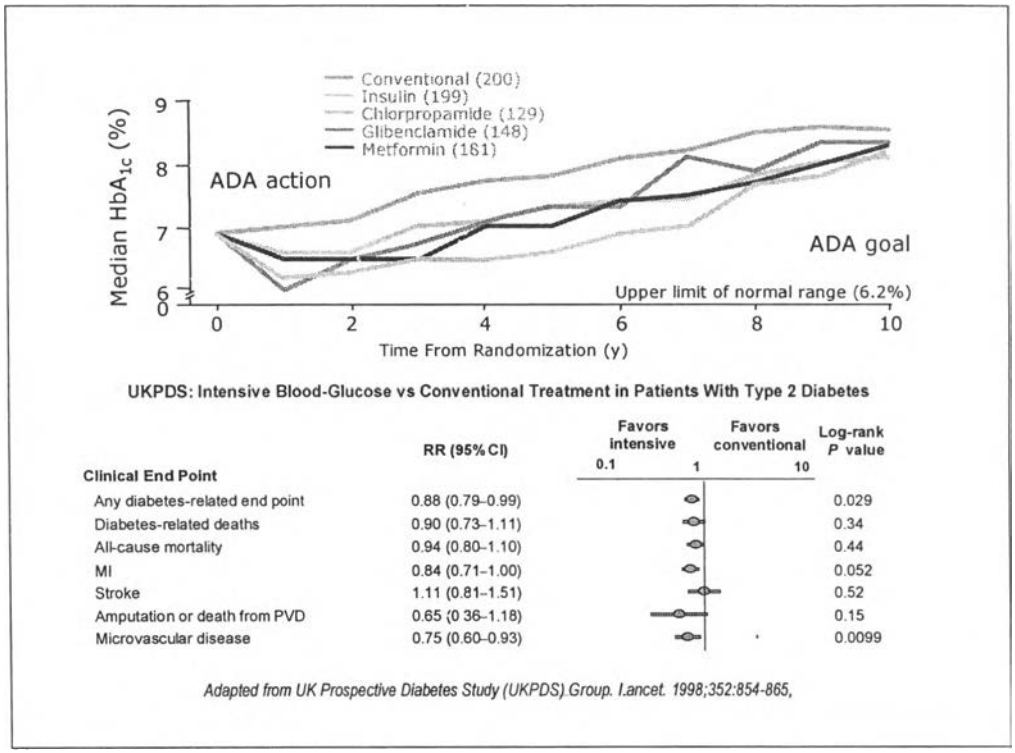


Figure 3 United Kingdom Prospective Diabetes Study (UKPDS)

of pharmacological therapy to lower blood glucose levels would result in clinical benefits (i.e., reduced cardiovascular and microvascular complications) and 2) whether the use of various sulfonylurea drugs, the biguanide drug metformin, or insulin have specific therapeutic advantages or disadvantages. In addition, patients with type 2 diabetes who were also hypertensive were randomized to "tight" or "less tight" blood pressure control to ascertain the benefits of lowering blood pressure and to ascertain whether the use of an ACE inhibitor (captopril) or ß-blocker (atenolol) offered particular therapeutic advantages or disadvantages.

The UKPDS results establish that retinopathy, nephropathy, and possibly neuropathy are benefited by lowering blood glucose levels in type 2 diabetes with intensive therapy, which achieved a median HbA_{1c} of 7.0% compared with conventional therapy with a median HbA_{1c} of 7.9%. The overall microvascular complication rate was decreased by 25%. These results materially increase the evidence that hyperglycemia causes, or is the major contributor, to these complications. Epidemiological analysis of the UKPDS data showed a continuous relationship between the risks of microvascular

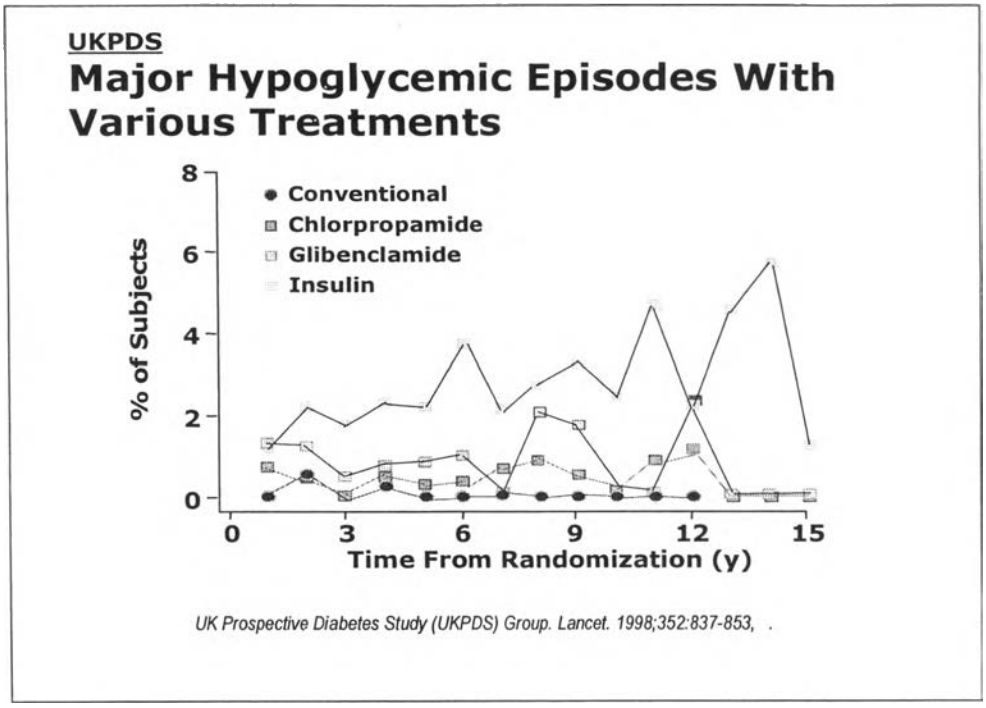


Figure 4 Hypoglycemia in UKPDS

complications and glycemia, such that for every percentage point decrease in HbA_{1c} (e.g., 9 to 8%), there was a 35% reduction in the risk of complications. The results demonstrate that the risks of complications can be significantly lowered even in the range of hyperglycemia where HbA_{1c} levels are <8.0%. There was no evidence of any glycemic threshold for any of the microvascular complications above normal glucose levels (i.e., HbA_{1c} >6.2%).

Intensive blood glucose control and hypoglycemia

Intensive control was found to increase the risk of severe hypoglycemia and weight gain, especially in people with type 1 diabetes. In UKPDS, the highest average annual incidence of major hypoglycemic events was 2.3% of patients per year in those receiving insulin therapy. Serious hypoglycemia may result in altered consciousness, coma, or convulsions resulting in injury to the patient or others. Hypoglycemia may also have harmful effects on neuropsychological and intellectual function in children, although in DCCT participants, these adverse effects were not observed. In older people, low blood glucose may lead to strokes or heart attacks. The intensive treatment group in the

DCCT had a threefold greater risk of severe hypoglycemia than the standard treatment group. The risk of hypoglycemia must be taken into consideration, although the danger may be reduced by frequent blood glucose monitoring; adjustment of insulin dosage; alteration of the timing, frequency, and content of meals; and change in exercise/activity patterns. Thus, comprehensive self-management training is essential. The intensive treatment group also experienced significant weight gain, which can have adverse medical and emotional consequences

The role of post-prandial blood glucose in diabetes mellitus

In the fasting state, the suppression of insulin production and stimulation of glucagon production control the concentration of blood glucose. These processes allow the liver to mobilize glucose from its glycogen stores and synthesize glucose from amino acids and pyruvate (gluconeogenesis). In addition, when insulin levels are low, the uptake of glucose by muscle is minimized, and adipocytes release free fatty acids. This homeostatic mechanism affects a stable plasma glucose level in the fasting state so that the brain, which has no energy stores, has a sufficient supply of nutrients for normal activity.

In the fed state, insulin is released in two phases. The first phase, a short, small burst released on food intake or an increase in plasma glucose concentration, preempts and decreases the post-prandial glucose elevation. Later, a more sustained, second-phase insulin release directly proportional to the plasma glucose elevation occurs. In response to this biphasic release of insulin, the liver takes up glucose, converting it to glycogen (animal starch). The muscle and adipose tissues also take up glucose, storing it as glycogen and triglycerides, respectively. Furthermore, the production of free fatty acids in adipocytes is suppressed. The loss of first-phase insulin release has adverse metabolic and physiologic consequences, even if the second-phase release is adequate or even excessive.

First-Phase Insulin Release

One of the earliest changes in the development of type 2 diabetes is the loss of first-phase insulin release, which occurs with fasting glucose levels of about 110 mg/dl. The loss can be documented by measuring plasma insulin concentrations over the 10 minutes immediately after an intravenous glucose load, calculated on the basis of the patient's weight. Lack of first-phase insulin release, an excellent predictor of both types of diabetes, is thought to be the earliest sign of the adverse effects of hyperglycemia on insulin-producing b-cells and insulin-sensitive tissues (glucotoxicity).[29] When the first-phase insulin response fails, plasma glucose levels rise sharply after a meal. Initially, this precipitates an increased stimulation of second-phase insulin release that, in the early stages of glucose intolerance, may lead to post-prandial hypoglycemia resulting from elevated plasma insulin remaining after the nutrients have disappeared.[30] High insulin levels also cause down regulation of the insulin postreceptor pathways on the muscle and fat cells, thus increasing insulin resistance.[31]

The higher glucose level in islet cells prompts a decrease in glucose-transporter activity, resulting in a reduction of insulin release,[32] which is reversed by a decrease in plasma glucose level. If there is no decrease, the prolonged hyperglycemia will eventually cause an accelerated loss of insulin-producing b-cells in both type 1 and type 2 diabetes.[29] Thus, metabolic loss of first-phase insulin release results in post-prandial hyperglycemia, an increase in insulin resistance, and a further decrease in insulin production.

Effect of Post-prandial Glucose Levels on Microvascular Complications

The effects of post-prandial hyperglycemia on the development of microvascular complications of diabetes have been well documented. There is evidence that uncontrolled glycemic peaks activate protein kinase C, the enzyme that may link hyperglycemia to microvascular complications.[33] Elevated glucose levels lead to increased intracellular synthesis of diacylglycerol, which, in conjunction with elevated intracellular calcium, activates protein kinase C.[33] The activity of protein kinase C impairs contraction of smooth muscle cells or pericytes, increases production of basement membrane materials, and enhances cell proliferation and capillary permeability. Thus,

activation of protein kinase C by post-prandial hyperglycemia could be responsible for microvascular complications that may be developing even in the early stages of diabetes.[33]

Data from the National Health and Nutrition Examination Survey showed that patients who had 2-hour post-prandial glucose levels of 194 mg/dl had a threefold increase in the incidence of retinopathy, despite normal fasting glucose levels.[28] Studies of Pima Indian and Egyptian populations revealed a similar increase in the incidence of retinopathy in subjects with normal fasting glucose levels but 2-hour post-prandial glucose values of >200 mg/dl.[28]

The development of microvascular complications in patients with type 2 diabetes has been documented in a number of clinical trials. In a long-term study of complications in patients who had type 2 diabetes for more than 25 years, Mohan et al[34] reported that post-prandial glucose levels were associated with diabetic nephropathy. In a recent study of Pima Indian subjects, hyperfiltration, a precursor of diabetic nephropathy, in subjects with impaired glucose tolerance was found to increase with the onset of type 2 diabetes.[35] In a population study, Beghi et al[36] showed that elevated fasting and post-prandial glucose levels, as well as prolonged disease duration, were associated with an increased incidence of diabetic neuropathy.

Post-prandial Glucose Levels and Macrovascular Complications

The glycemic threshold for the development of macrovascular complications is lower than that for microvascular complications, so there is more evidence for an association with post-prandial glycemia. Post-prandial glucose elevations are associated with post-prandial hyperinsulinemia and higher plasma levels of triglycerides, chylomicrons, chylomicron remnants, and free fatty acids. High concentrations of free fatty acids have been associated with endothelial dysfunction,[37] and high triglyceride levels have been linked to low levels of high-density lipoprotein (HDL) cholesterol and a preponderance of small, dense, low-density lipoprotein (LDL) particles. Although only the relationship between fasting-state hypertriglyceridemia and

coronary artery disease (CAD) has been established, post-prandial high triglyceride levels most likely have the same effect.[38] In addition, high post-prandial glucose levels result in protein and cellular glycosylation. Glycosylated LDL particles are more easily oxidized and taken up by macrophages through the scavenger receptor. This, in turn, leads to higher foam cell production, and, ultimately, atherosclerotic plaque. In addition, glycosylated LDL also stimulates platelet aggregation. Glycosylated HDL is less efficient than nonglycosylated in transporting cholesterol back to the liver for metabolism. Additionally, the formation of advanced glycosylated end products in the collagen of the vessel wall itself may directly stimulate or accelerate the atherosclerotic process.[39]

Acute increases in plasma glucose also stimulate the production of free radicals, another factor involved in the atherosclerotic process.[40] Excessive post-prandial plasma glucose levels have also been associated with transient hypercoagulability resulting from increased thrombin production and decreased fibrinogen breakdown. These, in turn, result from the overproduction of plasminogen activator inhibitor, which directly inhibits tissue plasminogen activator activity. Control of post-prandial hyperglycemia reverses this hypercoagulable state.[41]

Endothelial dysfunction is another consequence of post-prandial hyperglycemia. Activation of protein kinase C in the endothelium increases adhesion molecules[42] that facilitate leukocyte uptake into the blood vessel wall; increases production of the vasodilators nitric oxide and prostaglandin; increases expression of the vasoconstrictor endothelin; and induces platelet aggregation.[33]

The Honolulu Heart Study found that the risk of CAD correlated with plasma glucose levels measured 1 hour after a 50-g oral glucose load. The incidence of CAD was twice as high in patients with post-prandial plasma glucose levels between 157 and 189 mg/dl as in those with levels <144 mg/dl,[43] and the incidence of sudden death was doubled with post-prandial plasma glucose levels >151 mg/dl.[44] The Whitehall Study of British male civil servants showed that plasma glucose levels >96 mg/dl 2 hours after a meal were associated with a twofold increase in mortality from CAD.[45] Another British

study, the Islington Diabetes Survey, reported that the incidence of major CAD (defined as major electrocardiographic changes or myocardial infarction) was 17% in subjects with a 2-hour post-prandial glucose level between 120 and 180 mg/dl, compared with 9% in subjects with levels <120 mg/dl.[46] The Bedford Survey showed that protection from CAD was lost in patients with elevated post-prandial glucose.[47] By studying the progression of CAD in young men with previous myocardial infarction, Bavenholm et al[48] found that fasting and post-prandial plasma glucose levels were independently related to disease progression. The Oslo Study indicated that the nonfasting plasma glucose level was a predictor of fatal stroke in diabetic patients, with the risk increasing by 13% for each 18-mg/dl elevation in post-prandial glucose.[49] The Diabetes Intervention Study also showed that post-prandial, not fasting, hyperglycemia was an independent risk factor for myocardial infarction and cardiac death.[50] The Hoorn Study documented an increased risk of peripheral vascular disease in elderly patients with diabetes and in subjects with impaired glucose tolerance.[51] Ankle to brachial pressure indices <0.9 were found in 7% of nondiabetic subjects, 9.5% of subjects with impaired glucose tolerance, 15.1% of patients with newly diagnosed diabetes, and 20.9% of patients with established type 2 diabetes. After logistical regression analysis and correction for other cardiovascular risk factors, the 2-hour post-prandial plasma glucose value remained an independent risk factor for peripheral vascular disease, whereas plasma insulin did not.[53]

Overexposure to insulin in response to post-prandial hyperglycemia has been shown to be a risk factor for cardiovascular events. The Paris Prospective Study found that post-prandial hyperinsulinemia was a better predictor for fatal CAD than either hyperglycemia or diabetes.[54] Similarly, the Helsinki Policemen Study revealed an independent association between fatal and nonfatal CAD events and 1- and 2-hour post-prandial insulin levels that was stronger than that with fasting plasma insulin levels.[55] Finally, a recent report suggested an association between post-prandial levels and intellectual function in elderly Alzheimer's patients who were not ApoE4 positive.[56]

Another factor associated with post-prandial hyperglycemia is post-prandial

hyperlipidemia. Elevated triglyceride levels after a meal predict the development of CAD and are associated with carotid artery atherosclerosis in nonobese white subjects.[57] Therefore, a reduction of post-prandial glucose levels, which also reduces plasma insulin and lipids after a meal, could reduce the incidence of CAD.

Post-prandial Glucose in Gestational Diabetes and Pregnancy Outcomes

In women who have gestational diabetes and require insulin, controlling post-prandial plasma glucose levels has consistently been shown to result in better outcomes than controlling fasting plasma glucose. In a study that compared preprandial and post-prandial monitoring of glycemic control in women with gestational diabetes, 33 women in the post-prandial glucose control group had lower HbA_{1c} levels. Their babies had lower birth weights, lower risk of neonatal hypoglycemia, and were less likely to be born by cesarean section than those of the 33 women randomly assigned to fasting glucose control.[56] The Diabetes in Early Pregnancy Study showed that high birth weight correlated closely with the mothers' third trimester nonfasting glucose levels.[57]

Similarly, Combs et al[58] reported that there was a strong correlation between macrosomia and high post-prandial glucose levels occurring during the 29th to 32nd week of pregnancy. Demarini et al[59] studied two groups of pregnant women with different target levels of post-prandial glucose, <120 and <140 mg/dl, respectively. Neonatal hypoglycemia occurred at a higher frequency in babies born to women in the <140 mg/dl group. Because of these studies, the American Diabetes Association now recommends monitoring both fasting and 1-hour plasma serum glucose levels during pregnancy.[61]

Self-monitoring of blood glucose in management of diabetes mellitus

Self-monitoring of blood glucose refers to checking one's own blood glucose levels at home, at work, or elsewhere using a small meter (or a colored strip). Self-monitoring is recommended because it may lead to improved blood glucose control and to less frequent episodes of hypoglycemia.

The ADA's consensus statements on SMBG[9] provide a comprehensive review of the subject. Major clinical trials assessing the impact of glycemic control on diabetes complications have included SMBG as part of multifactorial interventions, suggesting that SMBG is a component of effective therapy. SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved.[61] Results of SMBG can be useful in preventing hypoglycemia and adjusting medications, Medical nutrition therapy (MNT), and physical activity.

The frequency and timing of SMBG is dictated by the particular needs and goals of the patients.[62] Daily SMBG is especially important for patients treated with insulin to monitor for and prevent asymptomatic hypoglycemia. For most patients with type 1 diabetes and pregnant women taking insulin, SMBG is generally recommended three or more times daily. The optimal frequency and timing of SMBG for patients with type 2 diabetes in stable diet-treated or on oral hypoglycemic pills is not known.[63]

Because the accuracy of SMBG is instrument- and user-dependent[64], it is important for health care providers to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. Advancement of science and technology leads to a better and improved meter with more precision and reliability. The optimal use of SMBG requires proper interpretation of the data. Patients should be taught how to use the data to adjust food intake, exercise, or pharmacological therapy to achieve specific glycemic goals.

Reliability and validity of self-blood glucose monitoring

Reliability is a measurement of the extent to which a method gives the same results when repeated under the same conditions. Validity is a measure of the extent to which a method gives results that correspond to the true result. Often a comparison will be made with a reference method such as the glucose oxidase method performed on laboratory equipment.

Studies comparing different methods have not always used appropriate statistical methods for analysis. Bland and Altman listed five reasons why the correlation coefficient is not a helpful measure of agreement between two methods of measuring the same thing[65]. They point out that it would be surprising if two methods of measuring the same thing did not give results that were strongly associated. The strength of association will be higher if the range of observations is extended. However, a high correlation coefficient does not mean that differences between two methods are small. They suggested that the size and dispersion of the differences between replicate measurements should be used to assess the agreement between methods of measurement. Thus the mean difference between replicates provides an estimate of the bias of one method in relation to the other. The standard deviation of the differences provides a measure of the extent of random error. If the data are normally distributed, then 95% of differences should lie between $\pm$ 2 SD from the mean difference. These limits are referred to as the "limits of agreement". Two methods of measurement are equivalent if the mean difference between them is zero and the limits of agreement are small enough to be unimportant.[66]

In 1987 the ADA recommended that blood glucose measurement made by patients should be within 15% of the reference measurement and that in future meters should have less than 10% variability.[67] However, in 1993, the ADA Consensus Development Panel reported that this target had still not been reached and that new technology was still not meeting these criteria.[68] In 1996, the ADA recommended an even stricter target of less than 5% variability for future home blood glucose meters. A recent study measured the relative accuracy of 17 blood glucose monitors (two visually read, eight colorimetric and seven amperometric).[69] At a mean glucose concentration of

9 mmol/l, monitor readings differed from the reference results by -5.1% to +19.5%, and three meters failed to meet the ADA's total error guidelines for existing meters of less than 15%.

At present there is not sufficient information available concerning the different contributions to analytical error in blood glucose meters. Published information is sufficient to show that portable meters may show significant differences from reference methods and that the magnitude of these difference may vary between different models of meter, between different devices of the same model and according to the blood glucose level. These differences may often be of clinical relevance, but may sometimes be important, particularly at low blood glucose values.

A report by Henry MJ et al., studying the accuracy of self-monitoring of blood glucose values of patients with diabetes during pregnancy deviates substantially from reference values.[70] The patients' glucose values were measured on 6 different SMBG meters; reference values were from the HemoCue B Glucose Analyzer. Over a 5-year period, 1973 comparisons between SMBG values and reference values were recorded during clinic visits and used for this study. They found that one third of SMBG readings deviated significantly, which could adversely affect treatment for half of these patients if diabetes management was based on SMBG values. At the 10.5% deviation level, 34% of SMBG meter readings were out of range; 54% of these would have implied erroneous treatment. At the 15.5% deviation level, 18% were out of range; 63% of these would have implied erroneous management. They concluded that the accuracy of home meters should be verified at regular intervals, and SMBG values should not be the sole criterion for diabetes management during pregnancy.

Table 1 Description of 14 published meter evaluations

Report	Observer Training	inter-device variability	in use assess-ment	patient accept-ablility	report % diff from reference	present error grid analysis	report correlation
Frindik,[75] 1983	No	No	No	No	No	Yes	Yes
Silverstein,[76] 1983	Yes	No	No	No	No	No	Yes
Aziz,[77] 1983	Yes	No	No	No	No	No	Yes
Gifford,[78] 1986	No	No	No	No	No	No	Yes
Clarke,[79] 1987	No	No	No	Yes	No	Yes	Yes
North,[80] 1987	Yes	No	No	No	No	No	Yes
Tate,[81] 1991	Yes	Yes	No	No	No	No	Yes
Devreese,[82] 1993	Partial	No	Partial	No	No	Yes	Yes
Moses,[83] 1997	Partial	No	No	No	No	No	No
Chan,[84] 1997	Yes	Yes	Yes	Yes	No	Yes	Yes
Brunner,[85] 1998	No	No	No	No	No	Yes	No
Poirier,[86] 1998	No	No	No	No	No	Yes	Yes
Nillakupt K,[87] 1998	No	No	No	No	No	Yes	Yes

Impact of self-blood glucose monitoring in type1 Diabetes

Larsen ML, and coworkers[88] reported an observational study of the effect of long-term glucose monitoring in a cohort of 240 type 1 diabetic subjects of a university hospital in Denmark, followed up for more than 2 years. At 1 year, HbA1c decreased from 10.1% to 9.5% in the monitored group compared with no change in the control group. The decrease could be largely attributed to improvement in glycemic control in the poorly controlled group (baseline HbA1c > 10%) whose HbA1c dropped from 11.6% to 10.0%. The proportion in the monitored group with poor glycemic control declined from 46% at baseline to 30% at 1 year, compared with an increase in the proportion of poorly controlled non-monitored patients from 45% at baseline to 50% at 1 year. 36 of 115 monitored patients compared with 17 of 107 control patients had additional clinic visits (31% vs 16%). Hospitalization for hypoglycemic or hyperglycemic episodes was less frequent in monitored patients (12 of 115) compared with controls (23 of 107) {10% vs. 21%).

Schiffrin A and Belmonte M[89] performed a crossover design study to assess the importance of frequent capillary self-blood glucose (CBG) monitoring. Twenty-one insulin-dependent diabetic patients, previously treated with continuous subcutaneous insulin infusion (CSII), multiple subcutaneous insulin injections (MSI), and a combination of CSII and MSI (combined CSII-MSI) monitored their CBG determinations 5-7 times daily for 3 months. Diabetic control was significantly better during periods of frequent self-glucose monitoring. They concluded that frequent self-glucose monitoring is critical for the long-term maintenance of glycemic control of type 1 diabetes.

A recent meta-analysis reviewed by Coster S, et al: [90] evaluating the effectiveness of self monitoring for improving blood glucose control in patients with Type 1 diabetes. The search included the authors' personal reference collections; searches of Medline, Embase, IBSS (Index of Bibliography of Social Science) and the Cochrane Library; as well as hand searches of Diabetes Care, Diabetic Medicine and Diabetologia for the years 1990-1999. The results are shown in table 2-5 and also in figure 1

Table 2 Quality ratings for controlled studies in type 1 DM

Study	Reporting	External validity	Internal validity		Overall
			Bias	Confounding	
Carney,[91] 1983	7	0	4	3	14
Daneman,[92] 1985	6	1	4	2	13
Gordon,[93] 1991	6	2	4	3	15
Mann,[94] 1991	7	1	4	2	14
Miller,[95] 1983	6	1	3	3	13
Starostina,[96] 1994	8	0	4	2	14
Terent,[97] 1985	7	3	5	3	18
Woth,[98] 1982	8	0	3	3	14
Mean (SD)					**14.4 (1.6)**

Table 3 Quality ratings for non-controlled studies in type 1 DM

Study	Reporting	External validity	Internal validity		Overall
			Bias	Confounding	
Belmonte,[99] 1998	8	0	3	0	11
Dorchy,[100] 1997	8	0	4	2	14
Geffner,[101] 1983	4	0	1	2	7
Gill,[102] 1986	5	0	2	1	8
Hemansson,[103] 1986	7	1	2	1	11
Kelly,[104] 1981	4	1	3	2	10
Lam,[105] 1986	7	0	1	0	8
Lombrail,[106] 1986	5	0	2	2	9
Peveler,[107] 1993	6	0	1	0	7
Sonksen,[108] 1978	7	0	3	1	11
Strowig,[109] 1998	7	0	4	0	11
Walfford,[110] 1978	4	1	1	0	6
Wing,[111] 1985	5	3	2	3	13
Wysocki,[112] 1992	5	0	2	0	7
Ziegler,[113] 1989	6	0	3	3	12
Ziegler,[114] 1993	7	0	3	3	13
Mean (SD)					9.9 (2.5)

Table 4 Controlled trial of self monitoring in type 1 DM

Study	Intervention	Groups in study	Duration	Main measures	Dropouts
Carney, 1983	Urine monitor v.s. SMBG	SMBG Urine testing	9 m	HbA1c	0
Daneman, 1985	Urine monitor+ SMBG v.s urine monitor	Urine monitor+SMBG then urine monitor only Urine monitor only, then urine monitor+SMBG	26 wk	GHb	0
Gordon, 1991	3 different frequencies of SMBG	SMBG4-point, twice daily SMBG4-point, once daily SMBG2-point, daily	36 wks	GHb Fructosamine Blood glucose	4
Mann, 1991	Education+ SMBG	Education (n=20) Education+SMBG(n=19)	72 wks	HbA1c Hospital admission	1
Miller, 1983	SMBG v.s urine monitoring	Urine monitor then SMBG SMBG then urine	40 wks	HbA1c Blood glucose 24-hr urine glucose	1
Starostina, 1994	Urine v.s SMBG SMBG v.s no monitoring	SMBG Urine monitor No monitor	104 wks	HbA1 weight cost	15
Terent, 1985	Education or SMBG or SMBG +education v.s control	SMBG Education Education+SMBG Convetional care	78 wks	HbA1	Not stated
Worth, 1982	Urine monitor v.s. SMBG	6 groups with different sequences of testing methods	60 wks	GHb Blood glucose urine glucose	0

Figure 5 Result of meta-analysis of self monitoring on HbA1c in type 1 DM

Study	No. of subjects Intervention/control	Differences in HbA1c (95% CI)
Blood monitoring v.s. urine monitoring		
Mann,1991	19/20	-0.10(-0.88 to 1.08)
Carney,1983	43/43	-0.72(-1.40 to 0.04)
Terent,1985		
Education	10/9	-1.10(-2.87 to 0.67)
No education	8/10	-1.30(-3.19 to 0.59)
Miller,1993	18 (crossover)	-0.40(-3.95 to 3.15)
Pooled effect		**-0.57(-1.07 to 0.06)**

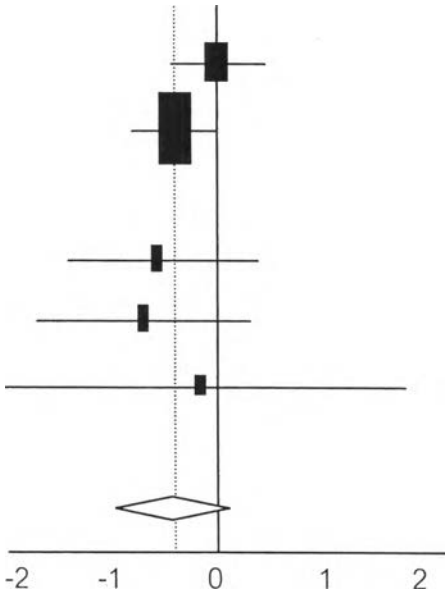


Table 5 Controlled trials of self monitoring on GHb in type 1 DM

Study	Blood testing		Urine testing	
	Before	After	Before	After
Carney, 1983	11.8 ± 0.3	11.0 ± 0.3	12.0 ± 0.3	11.88 ± 0.32
Daneman, 1985				
group 1	10.5 ± 0.6	10.9 ± 0.6	-	10.7 ± 0.6
group 2	9.5 ± 0.3	10.1 ± 0.4	-	10.2 ± 0.4
Gordon, 1991	9.7 ± 1.8	9.7 ± 2.0	-	-
Mann, 1991	14.1 ± 1.3	14.3 ± 1.9	12.7 ± 2.0	12.8 ± 2.4
Miller, 1983				
group 1	11.0	10.5	-	10.5
group 2	11.2	10.4	-	11.0
Starostina, 1994	12.6 ± 0.2	9.2 ± 0.2	12.5 ± 0.2	9.2 ± 0.2
Terent, 1985				
Education	12.3 ± 3.2	10.2 ± 1.9	11.2 ± 2.0	10.2 ± 2.1
No education	11.8 ± 1.4	9.8 ± 3.0	11.1 ± 2.3	10.4 ± 2.1
Worth, 1982				
Visual	10.8 ± 1.8	10.6 ± 2.1	-	10.5 ± 2.0
Meter	-	10.4 ± 1.9	-	-

In summary, these studies reviews did not provide decisive evidence for the clinical effectiveness of SMBG in type 1 diabetes. The results of the meta-analysis showed that the effect of SMBG compared to urine monitoring was small. However because of the low statistical power of the studies, neither an appreciable beneficial effect nor a small adverse effect could be excluded with certainty.

The only study that found a positive result was that by Carney and co-workers. This study found that HbA1c levels in children who were taught SMBG decreased significantly more from baseline than did those in a matched control group who monitored urine over the same time period. This was the case even though patients were not given instruction or advice on how to use their readings in modifying diet, exercise or insulin. This was one of the few studies that did not encourage patients to use self-monitoring results. Subjects in this study only monitored blood twice daily. In the study by Starostina and co-workers tests were performed 3-4 times daily. Schriffin and co-workers suggested that four tests daily or more may be necessary for optimal regulation. However, the study by Gordon and co-workers, which evaluated the frequency of monitoring, found no difference between patients who monitored 4 times weekly to those monitored 14 times weekly. There is, therefore, little consensus on an optimum frequency of SMBG.

Impact of glucose self-monitoring on non-insulin-treated type 2 diabetes mellitus.

A study form French physicians report that that plasma glucose values obtained after the meal are a better marker of metabolic control than values obtained before the meal. On multiple regression analysis, plasma glucose values right after lunch and several hours after lunch correlated significantly and independently with HbA1c, whereas fasting plasma glucose levels did not. In addition, nonfasting plasma glucose had better sensitivity, specificity, and positive predictive value in predicting poor glycemic control than did fasting plasma glucose according to the team. Based on their findings, the group strongly suggest that postlunch or extended postlunch plasma

glucose values be more widely used to supplement, or substitute for, fasting plasma glucose in evaluating the metabolic control of type 2 diabetics.

A systematic review of the efficacy of self-monitoring of blood glucose (SMBG) in type 2 DM subjects by Faas A. and colleagues[13] from 11 studies showed an inconclusive results. Most of the studies were considered as poor quality, included patients using diet and/or with oral anti-diabetic medications. The SMBG regimens and therapeutic decision scheme were different and noncomparable. It is recommended in this review that the application of SMBG should be a semi-fixed regimen with a minimum of four measurements per week, two fasting and two after meals. Additionally, the care provider should give feedback on the patients' self measured glucose levels.

A meta-analysis reviewed by Coster S, et al: to evaluate the effectiveness of self monitoring for improving blood glucose control in patients with type 2 diabetes mellitus. The results are shown in table 6-10 and figure 2

Table 6 Estimate of power calculations for RCTs in type 2 DM

Study	Primary outcome	No. in smallest group	Estimated SD	Detecable difference in GHb(%)	Power score
Allen,[115] 1990	GHb	27	2.75	2.0-3.0	1
Estey[116] 1989	HbA1c	25	1.17	0.5-1.0	3
Fontbonne,[117] 1989	HbA1c	54	2.00	1.0-2.0	2
Gallichan,[118] 1994	Fructosamine	12	NG	NE	0
Miles,[119] 1997	GHb	56	1.80	0.5-1.0	3
Muchmore,[120] 1994	HbA1c	11	1.89	1.0-2.0	2
Rutten,[121] 1990	HbA1c	64	1.33	0.5-1.0	3
Wing,[122] 1986	GHb	21	2.23	1.0-2.0	2

** Crossover trial, not analyzed as such* *** Cluster randomised study*

NG, not given; NE, not estimated

Table 7 Quality ratings for RCTs in type 2 DM

Study	Reporting	External validity	Internal validity		Overall
			Bias	Confounding	
Allen,[115] 1990	9	0	3	3	15
Estey,[116] 1989	8	0	4	4	16
Fontbonne,[117] 1989	10	0	4	2	16
Gallichan,[118] 1994	4	3	3	3	13
Miles,[119] 1997	5	2	3	2	12
Muchmore,[120] 1994	8	0	5	2	15
Rutten,[120] 1990	8	2	4	3	17
Wing,[121] 1986	9	0	4	3	16
Mean (SD)					**15.0 (1.69)**

Figure 6 Result of meta-analysis of self monitoring on HbA1c in type 2 DM

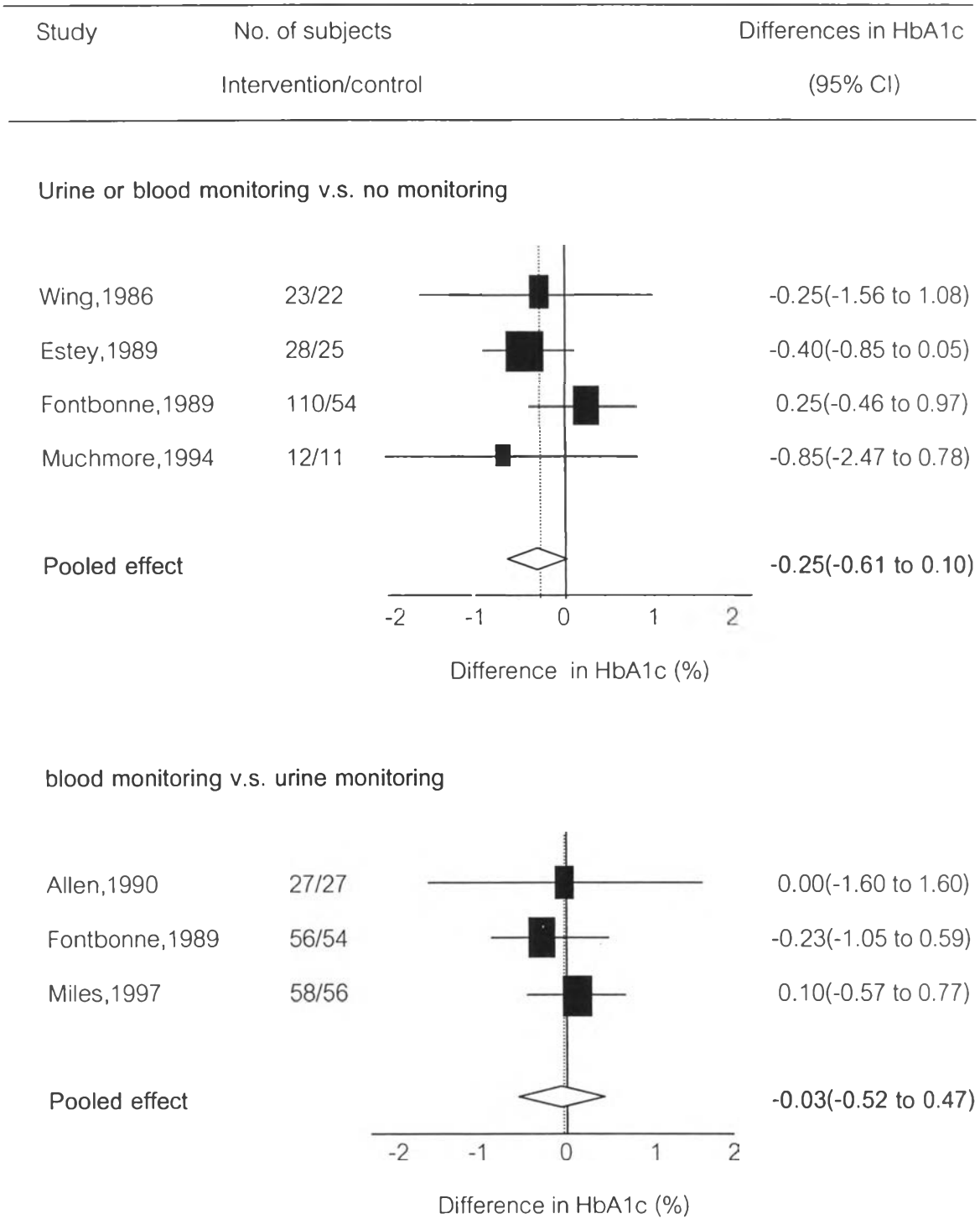


Table 8 Estimate of power calculations for RCTs in type 2 DM

Study	Setting	Design	No. of patients	Inclusion criteria
Allen,[115] 1990	USA, veterans medical center	Randomization in groups of 10	61	FPG > 8.8 and <2.2 mM/l No history of ketoacidosis Not using insulin No prior knowledge of monitoring
Estey,[116] 1989	Canada, medical center	Simple randomization	60	Refer for diabetes education Not on insulin Complete 3 day program Prepared to monitor blood Access to telephone for follow up
Fontbonne,[117] 1989	France diabetic clinics	Individual Randomization	208	Poor control:PG>8.8 mM/l FPG or post-prandial > 11 mM/L 3 times in year Diabetes for > 3 yrs
Gallichan,[118] 1994	UK diabetic center	Simple Randomization	27	On oral hypoglycemic agents
Miles,[119] 1997	UK diabetic clinics crossover trial	Allocation alternated,	150	Newly diagnosed DM
Muchmore,[120] 1994	USA medical center	simple randomization of individuals	29	Obese, elevated HbA1c No recent use of SMBG No calorie-control diet in last 3 months
Rutten,[121] 1990	Netherlands medical center pair matched	Cluster randomization	149	Age 40-75 Not treated with insulin Not receiving treatment for other diseases
Wing,[122] 1986	USA, university medical school	Individual randomization to patient groups	50	Age 35-65 120% or more IBW Use of OHA or insulin DM for >30 yrs

Table 9 Randomized Controlled trials of self monitoring on GHb in type 2 DM

Study	Blood testing		Urine testing		No testing	
	Before	After	Before	After	Before	After
Blood vs. urine						
Allen[115], 1990	12.4±3.3	10.4±2.9	11.7±3.0	9.7±2.6	--	--
Fontbonne[117], 1985	8.2±0.3	--	8.6±0.3	--	8.2±0.3	
Gordon[93], 1991	10.3±2.6	8.8±1.9	10.3±2.3	8.7±1.7	--	--
Blood vs. No testing						
Estey[116], 1989	6.3±1.1	5.6±0.7	--	--	6.1±1.4	5.8±1.5
Muchmore[120], 1994	10.3±0.3	8.7±0.5	--	--	10.4±0.4	9.6±0.6
Wing[122], 1986	10.2±2.5	10.5±2.3	--	--	10.9±2.0	10.4±2.1

In summary, from this meta-analysis, there is no evidence to show that self-monitoring of blood or urine glucose improved blood glucose control measured using GHb or FPG. There is also no evidence that blood glucose monitoring is effective than urine glucose monitoring in improving blood glucose control. The studies reviewed had low statistical power and were poorly conducted and reported. Small but clinically relevant effects might not have been detectable. Patients' perceptions of monitoring were neither completely nor rigorously studied and further work is needed in this area. Urine testing is less costly than blood testing and may be preferred by some patients.

Study in women with gestational diabetes

The pathophysiology of gestational diabetes involves insulin resistance and insufficient post-prandial insulin release, it is logical that post-prandial testing would be most likely to detect hyperglycemia and that targeting insulin therapy to these patients would be the most efficient way to lower the hemoglobin A1c concentration.

Tippetts A and coworkers[123] studied the efficacy of home glucose monitoring in diabetic pregnancy. They performed a randomized, prospective study to evaluate the efficacy of daily home glucose monitoring on the outcome of pregnancies in women with insulin-dependent diabetes mellitus. Home glucose monitoring was compared with a weekly venipuncture protocol. No differences were observed between groups in clinical features (age, parity, White's classification) or representative delivery outcomes (method of delivery, weeks' gestation, or weight at birth). No statistically significant differences were observed between the groups in several aspects of perinatal morbidity. However, home glucose monitoring was associated with fewer readmissions for diabetic control, fewer days in the hospital, and decreased total patient expense.

DeVeciana M. and colleagues,[116] reported a randomized controlled trial comparing the glycemic control and perinatal outcomes achieved by fasting and post-prandial home glucose monitoring with that achieved by fasting and pre-prandial home glucose monitoring in women with gestational diabetes who require insulin treatment. (figure 3) A total of 66 pregnant women (mean age 30 y, mainly Hispanic) who had

gestational diabetes and required insulin at or before 30 weeks of gestation were allocated to either fasting, pre-prandial, and bedtime capillary-blood glucose monitoring (pre-prandial group) (n = 33) or fasting and 1-hour post-prandial monitoring (post-prandial group) (n = 33). Women in both groups were evaluated weekly by a perinatal diabetes team. Women received split-dose insulin regimens, adjusted to achieve fasting blood glucose concentrations of 3.3 to 5.0 mmol/L and pre-prandial concentrations of 3.3 to 5.9 mmol/L in the pre-prandial group and post-prandial concentrations of < 7.8 mmol/L in the post-prandial group. Mean glycosylated hemoglobin values were lower in the post-prandial group than in the pre-prandial group (6.5% vs 8.1%, P = 0.006); mean birth weight was also lower (3469 vs 3848 g, P = 0.01). Post-prandial monitoring led to fewer caesarean sections for cephalopelvic disproportion than did pre-prandial monitoring (12% vs 36%, P = 0.04). Fewer babies born to mothers in the post-prandial group than to mothers in the pre-prandial group were large for gestational age (12% vs. 42%, P = 0.01). They concluded that fasting plus post-prandial blood glucose monitoring improved pregnancy outcomes in women with gestational diabetes who required insulin therapy. This study identified women with gestational diabetes by identifying those with risk factors or by doing routine screening; it did not state whether the adverse outcomes occurred in those with or without risk factors for diabetes. Whether those without risk factors for diabetes have the same risk for adverse outcomes or the same opportunity to benefit from treatment as those with risk factors is not known. Nevertheless, this study strongly suggests that if gestational diabetes is going to be treated, it is the post-prandial glucose that should be monitored and controlled.

Table 10 Quality ratings for studies in pregnancy with diabetes mellitus

Study	Reporting	External validity	Internal validity		Overall
			Bias	Confounding	
Randomized control trials (RCTs)					
Stubbs,[124] 1980	6	0	3	4	13
Goldstein,[125] 1982	3	0	0	4	7
Varner,[126] 1983	7	2	3	3	15
Hanson,[127] 1984	5	3	2	3	13
De Veciana[128] 1995	9	0	3	4	16
Mean (SD)					**12.8 (3.5)**
Case Series					
Peacock,[129] 1979	5	0	3	0	8
Jovanovic,[130] 1980	7	0	2	1	10
Jovanovic,[131] 1981	6	1	2	2	11
Espersen,[132] 1985	5	0	1	0	6
Goldberg,[133] 1986	7	0	4	1	13
Wechter,[134] 1991	6	1	4	2	13
Mean (SD)					**10.2 (2.8)**

Table 11 Randomized Controlled trial of self monitoring in pregnancy with DM

Study	Intervention	Groups in study	Duration	Main measures
Stubbs,[124] 1980	Self-monitor with meter v.s. without meter	SMBG without meter 4/day (n=6) SMBG with meter 7/day (n=7)	at 32-35 week of gestation	Blood glucose Profile of inter-mediary metabolites
Goldstein,[125]1982	SMBG	Reflectance meter (n=9), conventional (n=9)	not documented	Hospital utilization and costs
Varner,[126] 1983	SMBG	SMBG (n=15) conventional(n=15)	started at <20 weeks of gestation	HbA1c Perinatal morbidity Costs
Hanson,[127] 1984	SMBG at home or with hospital care	SMBG (n=54) Hospital care(n=46)	started at 32-36 wks of gestation	Blood glucose HbA1c Maternal and fetal outcomes
De Veciana,[128]	SMBG either before or meals	SMBG before meals (n=33) SMBG after meals(n=33)	started at after screen 24-28 wks of gestation	HbA1c Maternal and after fetal outcomes

Summary

Several home monitoring of blood glucose devices are available in the market, each claimed reliability, accuracy, and "user friendliness," with most of these claims largely unsubstantiated. Accuracy of each monitor was usually studied by comparing the glucose value reported by each HMBG with that determined by a reference method. There is no standard protocol for evaluating blood glucose monitoring devices. Published evaluations have only evaluated a limited number of aspects of meter performance and have not always used appropriate methods to analyze the true reliability of measurements.

For type 2 diabetes mellitus, eighteen papers including eight randomized controlled trials and ten non-randomized studies. The eight RCTs included comparisons of blood testing, urine testing and no testing in subjects with type 2 diabetes. Interventions were not standardized, patient training and adherence were not addressed systematically and no trial required subjects to modify their drug therapy in accordance with self-monitoring results. Three studies had sufficient power to detect differences in glycated hemoglobin (HbA1c) of 0.5-1.0% but none had sufficient power to detect differences $\leq$ 0.5%.

A meta-analysis of six studies showed that mean difference in HbA1c between groups of patients performing blood or urine self-monitoring and those not was -0.25% (95% CI, -0.61 to 0.10). Meta-analysis of data from three studies showed that the difference in HbA1c for those performing self-monitoring of blood glucose compared with those performing urine testing was -0.03% (95% CI, -0.52 to 0.47). Published information on patient outcomes and the avoidance of hypoglycemia was extremely limited.

For type 1 diabetes mellitus, twenty-four papers were retrieved, including eight controlled trials and 16 non-controlled studies. The RCTs included either children or adults and compared different testing frequencies, blood and urine testing, or blood testing and no testing. Only one study had sufficient power to detect differences in HbA1c of $\leq$ 1.0%.

Among the controlled trials, only one suggested a benefit of blood testing for HbA1c. The remaining studies showed no difference between blood or urine testing or different frequencies of blood testing. Three studies found that the frequency of hypoglycemia was low and not different between blood monitoring and control groups. One study reported that blood glucose monitoring revealed asymptomatic hypoglycemia in 11 of 16 children. A meta-analysis of data from studies that compared blood monitoring with urine monitoring in children or adults with type 1 diabetes suggested a mean difference in HbA1c of approximately -0.567% (95%CI, -1.073 to -0.061). Blood testing was noted to be more costly than urine testing but was preferred by patients, possibly because it provided better information.

Blood glucose self-monitoring is well established in clinical practice but the optimal use of the technique has not been established. Present evidence suggests that it may not be essential for all diabetic patients. Randomized studies and cost-effectiveness of blood glucose self-monitoring in type 2 diabetes are needed. Besides GHb, occurrence of hypoglycemia, patients' satisfaction with care, as well as quality of life are also needed to explore.