REPORT

health technology assessment

MANAGEMENT OF DIABETES & SCREENING FOR MICROALBUMINURIA IN DIABETES

HEALTH TECHNOLOGY ASSESSMENT UNIT
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MINISTRY OF HEALTH
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Management of Diabetes & Screening for Micro-Albuminuria In Diabetics
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EXECECUTIVE SUMMARY

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The resulting build up of glucose in the blood can result in a range of diabetic complications, including macrovascular and macrovascular complications. The symptoms of marked hyperglycemia include polyuria, polydypsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. The acute, life-threatening consequences of diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome. There are two types of diabetes namely Type 1 and Type 2 diabetes. There are also other specific types of diabetes, which is caused by genetic defects of the ß-cell. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. People with Diabetes mellitus (DM) have a continuing need for preventive care and hospital treatment and the health service costs for DM is substantial.

OBJECTIVES

This assessment determines the effectiveness, safety and cost implications of management of diabetes mellitus; and cost implications of screening for microalbuminuria in diabetics.

RESULTS

Oral drug

The results from the assessment showed that among the oral drugs, there is good evidence of safety and effectiveness of Gliclazide, Glimepiride, Metformin, Acarbose, Repaglinide, Rosiglitazone in NIDDM patients. In adequately controlled NIDDM patients, there is sufficient evidence that combination therapy is safe and effective.

Insulin

There is sufficient evidence of safety and effectiveness of insulin aspart, insulin detemir, insulin glargine, and insulin lispro. There is inconclusive evidence with regards too safety and effectiveness of inhaled and oral insulin.

Diet and exercise

There is sufficient evidence that diet control and exercise are important in both the prevention and treatment of type 2 diabetes.

Monitoring

There is inconclusive evidence that self-monitoring of diabetes mellitus improves glucose control in type 1 and type 2 diabetes. There is sufficient evidence that Glycated serum haemoglobin (HbA1c) is effective for monitoring blood glucose control in diabetes, while there is some evidence that near patient HbA1c is effective in inpatient care. There is inconclusive evidence on the benefits of fructosamine testing, and insufficient evidence on the benefits of fasting plasma glucose testing.

Cost

With respect to cost, there is evidence that intensive glucose control is cost effective.

Microalbuminuria

There is good evidence that all diabetics need to be screened for microalbuminuria. While a timed urinary albumin excretion rate overnight or over a 24 hour period is most sensitive, random sample testing using a dipstick (spot urinary albumin concentration) or albumin: creatinine ratio are found to be more convenient. There is some evidence that the newer screening test kits are effective.

RECOMMENDATIONS

The recommendation of this assessment is for NIDDM patients, oral drugs like Glicazide, Glimepiride, Metformin, Acarbose, Repaglinide, Rosoglitazone are recommended either singly or in combination. For IDDM, insulin aspart, insulin detemir, insulin glargine, and insulin lispro are recommended. Diet control and exercise of recommended for all diabetics. Self monitoring of diabetes using HbA1c is recommended for all patients despite the lack of evidence on improvement in glucose control due to other benefits of monitoring. Screening for microalbuminuria is recommended for all diabetics either by spot albumin concentration or by albumin: creatinine ratio testing.

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1 INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The resulting build up of glucose in the blood can cause a range of diabetic complications, including microvascular and macrovascular complications. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the ß-cells of the pancreas with consequent insulin deficiency, to abnormalities that result in resistance to the action of insulin. The abnormalities in carbohydrate, fat, and protein metabolism in diabetes are caused by deficient action of insulin on target tissues. This deficient action of insulin results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia.

The symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. The acute, life-threatening consequences of diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.

Types of Diabetes Mellitus

Type I diabetes (ß-cell destruction, usually leading to absolute insulin deficiency)
Immune-mediated diabetes.

Type II diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance)

Other Specific Types of Diabetes

Genetic defects of the ß-cell.

Complications of Diabetes Mellitus

The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. The long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputation, and Charcoat joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Glycation of tissue proteins and other macromolecules, and excess production of polyol compounds from glucose are among the mechanisms thought to produce tissue damage from chronic hyperglycemia. Patients with diabetes also have an increased incidence of atherosclerotic cardiovascular, peripheral vascular, and cerebrovascular disease. Hypertension, abnormalities of lipoprotein metabolism, and periodontal disease are often found in people with diabetes. The emotional and social impact of diabetes and the demands of therapy may cause significant psychosocial dysfunction in patients and their families.

People with DM have a continuing need for preventive care and hospital treatment and the health service costs for DM is substantial. The health service cost of DM was estimated by one study to exceed £259 million in 1984 and was said to be accounted for

5% of health service cost in another study. The costs of DM to patients, their families and to society can also be considerable because of loss of earnings and production, and the need for support of individuals affected by DM.

2 OBJECTIVES

1. To determine effectiveness, safety and cost implications of management of diabetes mellitus
2. To determine effectiveness, and cost implications of screening for microalbuminuria in diabetics.

3 METHODOLOGY

A literature search was carried out on various aspects as indicated in Appendix 1. In management of diabetes, the focus will only be on treatment and follow-up. Diagnosis is not included.

4 RESULTS AND DISCUSSION

4.1 Treatment

4.1.1 Oral Drugs

ORAL HYPOGLYCAEMICS

Sulphonylureas

a) GLICLAZIDE

Safety

Harrower (1991) reported that Gliclazide has a low incidence of side effects; there are few problems with hypoglycaemia. This was supported by a randomized controlled trial (RCT) of 800 patients, where the incidence of hypoglycemia was particularly low (0.2 hypoglycemia/100 patient months) in the elderly population, which represented almost 40% of the samples (Drouin, 2000).

Effectiveness

With regards to efficacy, Gliclazide retains its efficacy longer than other sulphonylureas, and glycaemic control was achieved in 65% of patients treated with Gliclazide. Conversion from other oral hypoglycaemics to Gliclazide led to an improvement in control except in patients previously treated with Glibenclamide (Harrower, 1991). Gliclazide was also found to be effective in controlling blood glucose in another study, with a mean end point difference in HbA1c of –0.08 (0.08%), significantly lower than the equivalence limit ($p<0.001$) (Drouin, 2000).

b) GLIMEPIRIDE

Safety

Glimepiride is a well-tolerated oral glucose-lowering agent. According to Rosenstock et al (1996), adverse events and laboratory data demonstrated that Glimepiride has a favourable safety profile. A review by Hoechst et al (1995) showed that Glimepiride maintained a more physiological regulation of insulin secretion than Glibenclamide during physical exercise, suggesting that there may be less risk of hypoglycaemia with Glimepiride

Draeger et al (1996) reported that while fewer hypoglycaemic reactions occurred with Glimepiride than with Glibenclamide (105 vs. 150 episodes), both were well tolerated.

Effectiveness
Glimepiride provides metabolic control equivalent to a higher dosage of Glibenclamide (Draeger et al, 1996). It also had a more rapid onset of action and a longer duration of action as well. Glimepiride achieved metabolic control with the lowest dose (1-8 mg daily) of all the sulphonylureas (Hoechst et al, 1995).

Goldberg et al (1996) found that while Glimepiride in 1, 4, 8 mg doses was effective the 8 mg dose was found to be beneficial for patients who are difficult to treat. A study by Rosenstock et al (1996) also demonstrated that maximum effectiveness can be achieved with 8 mg four times a day of glimepiride in Type I diabetes patients.

Biguanides
a) METFORMIN
Safety
Metformin was well tolerated by all diabetics (Giugliano et al, 1993, Swislocki et al, 1999). It does not adversely affect hormonal and symptomatic responses to hypoglycemia, which is relevant with regards to the safety of the combination of Metformin with insulin therapy (Fruehwald-Schultes et al, 2001).

A study by Lalau et al (1990) also concluded that the metabolic tolerance of metformin therapy is satisfactory in the elderly Type II diabetic patient provided the dosage is adjusted to renal function.

Effectiveness
Metformin has been found to provide beneficial effect on glycaemic control (Giugliano et al, 1993, Swislocki et al, 1999). Metformin lowered blood glucose and glycosylated hemoglobin significantly. Metformin and sulphonylureas have an equal effect on fasting blood glucose and glycosylated hemoglobin but the body weight is significantly lowered after metformin compared with sulfonylurea treatment (Johansen, 1998).

Garber et al (1997) also reported that Metformin lowered fasting plasma glucose and HbA_{1c} generally in a dose-related manner. Benefits were observed with as little as 500 mg of Metformin, while maximal benefits were observed at the upper limits of the recommended daily dosage.

b) ACARBOSE

Safety
Several studies showed that Acarbose was well tolerated in the management of Type II diabetes (Wainstein & Jedwab, 1997; Rosentock, 1998). It has low incidence of side effects and high acceptance of treatment by both patients and physicians (Sieradzki & Soszynski, 1999). The adverse events were non-systemic and primarily gastrointestinal in nature (Coniff & Krol, 1997; Scorpiglione et al, 1999; Kendrup et al, 1999; Campbell, 1996; Deerochanawong et al, 1996; Yee & Fong, 1996; Sels et al, 1998). A surveillance study by Mertes (1998), found that when used in long term management of diabetes, Acarbose was well tolerated (Mertes, 1998).

In Type II diabetes subjects on weight-maintaining diets, long-term Acarbose therapy results in a small weight loss, but has no effect on energy or nutrient intakes. This weight loss may be due partly to reduced doses of concomitant oral agents, and partly to energy loss due to increased colonic fermentation (Wolever et al, 1997).

Another study also reported showed good tolerability to Acarbose 78.6% of the patients had no adverse events; 19% reported meteorism/flatulence, 3.2% diarrhea. Hypoglycemia was found in only 0.8% type I and 0.6% Type II patients who received concurrent insulin or glibenclamide treatment (Spengler and Catagay, 1995). A study by Sieradzki and Soszynski (1999) confirm that Acarbose can prevent reactive hypoglycemia by reducing the early hyperglycemic stimulus to insulin secretion, and in the treatment of reactive hypoglycemia.

Acarbose caused mild or moderate intestinal symptoms in 50% of patients within the first 4 weeks, but in only in 13.8% of the patients within the last 4 weeks in one study (Hoffman & Spengler, 1997). Hotta et al (1993) reported that the incidence of side effects tapered during trial, suggesting that some of the effects were not related to the drug (Hotta et al, 1993). Fischer et al (1998) found in their study that the frequency of flatulence decreased with the duration of drug therapy, but did not find a linear relationship between doses of Acarbose and the gastrointestinal side effects (Fischer et al, 1998).

Acarbose was also found to increase serum butyrate level in subjects with impaired glucose tolerance, supporting the hypothesis that increased colonic butyrate production in human subjects can be detected by raised serum butyrate (Wolever & Chiasson, 2000). Another study by Weaver et al (1997) showed that Acarbose effectively augmented colonic butyrate production by several mechanisms - it reduced starch absorption, expanded concentrations of starch-fermenting and butyrate-producing bacteria and inhibited starch use by acetate- and propionate-producing bacteria.

Coniff et al (1995) in a RCT of 290 patients reported that Acarbose alone or in combination with Tolbutamide caused significantly more gastrointestinal adverse events (mainly flatulence & soft stools or diarrhoea) than Tolbutamide or placebo, but these are generally well tolerated. Clinically significant elevations in hepatic transaminase levels in some patients returned to normal when therapy was discontinued.

Effectiveness

Acarbose acts as a potent, competitive inhibitor of intestinal alpha-glucosidases. Apart from attenuation of postprandial increases in blood glucose levels, other effects include a decreased beta-pancreatic response to meals, and influences on gut hormone secretion and plasma lipid levels. Acarbose can be used as first line therapy in patients with Type II diabetes poorly controlled by diet alone, and help control Type I diabetes in patients with ‘brittle diabetes’ (Salvatore & Giugliano, 1996).

A study by Coniff et al (1995), found that the control of glycemia was significantly better with Acarbose compared with diet alone. In Type II diabetes patients inadequately controlled on conventional oral agents, Acarbose in moderate doses resulted in beneficial effects on glycemic control especially postprandial glycemia and mean body weight (Yee & Fong, 1994; Campbell et al, 1996; Deerochanawong, 1996; Soonthornpun et al, 1998; Sieradzki & Soszynski., 1999; Holman et al, 1999). Even a low dosage of 25 mg thrice a day Acarbose was found to reduce fasting and postprandial blood glucose levels while in

a dosage of 200 mg thrice a day had the greatest effect on these parameters (Fischer et al, 1998).

Results from another study showed that Acarbose may prevent reactive hypoglycemia by reducing the early hyperglycemic stimulus to insulin secretion, and in the treatment of reactive hypoglycemia (Ozgen et al, 1998). Acarbose increases insulin sensitivity but not insulin release in elderly patients with diabetes (Meneilly et al, 2000).

In patients treated with Acarbose, the drug significantly reduced HbA1c levels especially post prandial plasma glucose levels (Hotta et al, 1995; Costa & Pinol, 1997; Coniff & Krol, 1997). The addition of Acarbose to patients on Metformin and diet therapy showed statistically significant reductions in HbA_{1c}, and fasting and postprandial plasma glucose and serum insulin levels (Rosentock et al, 1998).

In another study Acarbose produced significant reductions in postprandial blood glucose levels, and HbA_{1C} level was also significantly lower after 12 months of therapy in all patients except those on diet and insulin (Rodger NW et al, 1995).

In a study by Hoffman & Spengler (1997), both Acarbose and Metformin showed the same improvement of efficacy criteria. With respect to lipid profile, Acarbose was superior to Metformin.

Long term intake of Acarbose also improves carbohydrate metabolism and produces a hypolipidemic effect. Tested lipid parameters improved during 8-week observation: serum cholesterol level decreased, and significant improvement was noted in triglyceride levels (Rosliakova et al, 2000).

Acarbose also has a positive therapeutic effect on glucose tolerance in cystic fibrosis patients with glucose intolerance, as shown by attenuation of postprandial plasma glucose increase and a significant decrease in insulin secretion response (Kendrup et al, 1999).

Sels et al (1998) studied the effects of Acarbose in persons with Type I diabetes and found that Acarbose in dosages up to 3 x 100 mg/day can be a valuable adjunct to insulin in improving metabolic control. In Type II diabetes inadequately controlled with conventional oral agents, additional use of Acarbose can be considered as a useful alternative in improving glycaemic control if they are reluctant to accept insulin therapy (Lam et al, 1998).

c) REPAGLINIDE

Safety

There were 6 RCTs that reported Repaglinide as a safe oral blood glucose lowering agent in patients with Type II diabetes and well tolerated (Goldberg et al, 1998; Wolffenbuttel & Landgraf, 1999; Landgraf et al, 1999; Marbury et al, 1999; Strange et al, 1999; Jovanovic, 2000).

A study by Schatz (1999) showed that the frequency of hypoglycaemia was identical for Repaglinide and Sulphonylureas. However, fewer nocturnal hypoglycaemic events were observed with Repaglinide. No increase was seen in the occurrence frequency of hypoglycaemic events in elderly patients (> 65 years) compared with younger patients.

Effectiveness

All doses of Repaglinide tested were effective in patients with Type II diabetes (Strange et al, 1999). A study by Jovanovic et al (2000), reported that Repaglinide 1 mg or 4 mg treatment decreased mean fasting plasma glucose (FPG) values. However, Strange et al (1999) found that the therapeutic reduction of serum glucose levels produced by Repaglinide is dose-dependent for the 0.25 to 4.0mg dose range.

Landgraf et al (1999) in an RCT comparing Repaglinide and Glibenclamide in Type II diabetic patients previously treated with sulphonylureas, found both equally effective. Repaglinide may however offer an improvement in PPG (postprandial blood glucose) compared with Glibenclamide thereby helping to reduce the relative long-term risk of diabetic complications. Repaglinide is associated with a decrease in HbA_{1c}, fructosamine, and blood glucose concentrations (Van Gaal et al, 2001). Another study also reported that Repaglinide, given as a prandial glucose regulator, is shown to be an effective treatment of patients with Type II diabetes, and is better than Glipizide (Madsbad et al, 2001) or Glyburide (Wolffenbuttel & Landgraf 1999, Marbury T et al, 1999) in controlling HbA_{1c} and fasting blood glucose levels.

Goldberg et al (1998) reported that Repaglinide was efficacious in lowering blood glucose concentrations and found high concentration of fasting and postprandial insulin and C-peptide.

d) ROSIGLITAZONE

Safety

There was no increase in adverse events with Rosiglitazone, and it is safe as monotherapy in patients with Type II diabetes inadequately controlled with lifestyle intervention (Raskin Rappaport et al, 2000; Nolan et al, 2000; Lebovitz et al, 2001; CCOHTA report 2003/14). In Type II diabetes, it was found that Rosiglitazone at total daily doses of 4 and 8 mg was well tolerated (Phillips et al, 2001) and is well tolerated at doses up to and including 12 mg dose (Nolan et al, 2000). For LDL and HDL cholesterol, the observed increase appeared to be dose-related (Phillips et al, 2001).

Effectiveness

Rosiglitazone improves glycaemic control by significantly decreasing the FPG levels when given in a once daily dose to treat Type II DM (Nolan et al., 2000) and produced dosage dependent reductions in HbA_{1C} (Phillips et al., 2001). However, Rosiglitazone given twice daily significantly reduced fasting and postprandial glucose concentration and the 4 mg dose twice daily (total of 8 mg daily) should be the maximum clinical dose (Raskin Rappaport et al, 2000).

COMBINATION THERAPY

Safety

The combination of Rosiglitazone and a sulphonylurea was safe and well tolerated in patients with Type II diabetes. The overall incidence of adverse experiences was similar with no significant cardiac events, hypoglycaemia or hepatotoxicity (Wolffenbuttel et al, 2000).

With regards to Miglitol, Standl et al (2001) reported that it can be safely added to long-term combination therapy in people with Type II diabetes inadequately controlled with Glibenclamide plus Metformin. Cases of flatulence and diarrhea were reported by patients receiving Miglitol, but no cases of hypoglycaemia were reported.

In another study, Coniff et al, (1995) reported that Acarbose alone or in combination with Tolbutamide caused significantly more gastrointestinal adverse events (mainly flatulence and soft stools or diarrhoea) than tolbutamide, but these are generally well tolerated. Clinically significant elevations in hepatic transaminase levels occurred in some but returned to normal when the therapy was discontinued.

Effectiveness

Gregorio et al (1999) in a study on the effects of increasing sulphonylurea dosages or adding metformin in the poorly controlled elderly Type II diabetic patients found improvements in glycemic levels, decrease in $HbA_{1c,}$ and concluded that either high sulphonylurea dosage or combining lower sulphonylurea dosages with Metformin are effective in an aged but healthy population. Metformin provides additional benefits counteracting several cardiovascular risk factors but must be administered with caution.

Miglitol when added to long-term combination therapy in people with Type II diabetes inadequately controlled with Glibenclamide plus Metformin, produced a statistically, significantly greater reduction in HbA1c and postprandial glucose (Standl et al, 2001).

The combination of sulphonylurea and Rosiglitazone was found to be effective in patients with Type II diabetes producing significant decrease in HbA_{1c} and fasting plasma glucose levels (Wolffenbuttel et al, 2000). A study by Fonseca et al (2000) also reported that combination treatment with once-daily Metformin and Rosiglitazone improves glycaemic control, insulin sensitivity and beta-cell function more effectively than treatment with Metformin alone.

With regards to intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment in patients with Type II diabetes, Turner (1998) in UKPDS 33, reported risk reduction in microvascular endpoints, including the need for retinal photocoagulation. There was no difference for any of the three intensive agents (Chlorpropamide, Glibenclamide, or insulin). In another study by the same author in UKPDS 34 study, it was found that intensive blood-glucose control with Metformin in overweight patients with Type II diabetes will decrease progression of microvascular disease and may reduce the risk of heart attacks.

Coniff et al (1995) reported in a multicenter placebo controlled trial comparing Acarbose with placebo, Tolbutamide and Tolbutamide-plus-acarbose in Type II diabetes patients that Acarbose plus Tolbutamide was superior to Tolbutamide alone.

A combination of insulin-Metformin also resulted in significant improvement in glycemic control in diabetic patients, with a significant decrease in blood lipids (triglyceride and cholesterol), increase in HDL-cholesterol and a reduction in blood pressure. The fasting insulin level was significantly lower after six months of combined insulin-metformin treatment as shown by a 25% reduction in the daily dose of insulin (Giugliano et al, 1993). The new glyburide/metformin combination medication may facilitate earlier, more appropriate and more effective treatment for patients with Type II diabetes (Blonde, 2000).

4.1.2 INJECTABLE DRUGS

Insulin

a) INSULIN ASPART

Safety
Raskin et al (2000) reported patients receiving insulin aspart were reported to suffer fewer hypoglycemic events than those patients receiving buffered regular human insulin (Bode & Strange, 2001; Amiel et al, 2001), with a slower rate of increase in HbA_{1c} (Amiel et al, 2001).

A study by Colagiuri et al (2001), found that mild hypoglycemia and severe nocturnal hypoglycemia was less with insulin aspart. In subjects with impaired hepatic or renal function, Lyness et al (2001) reported that the pharmacokinetics of insulin aspart was similar in these patients suggesting that there should be comparable safety profiles in spite of these conditions.

Effectiveness
Insulin aspart was effective in controlling average daily blood glucose levels and maintaining serum fructosamine (Bode & Strange, 2001). Furthermore, due to favorable pharmacokinetics, insulin aspart is superior to human insulin for control of postprandial blood glucose concentrations (Setter, 2000; Brunner et al, 2000, Rosenfalck, 2000; Raskin et al, 2000). Thus, post-prandial dosing with insulin aspart offers an attractive and feasible therapeutic option for well-controlled patients with Type I diabetes mellitus (Brunner et al, 2000).

Studies also showed that HbA_{1c} was significantly lower for insulin aspart compared to human insulin (Raskin et al, 2000; DeVries et al, 2001).

b) INSULIN DETEMIR

Safety
Results from an RCT indicate that insulin detemir may provide more predictable fasting blood glucose with lower intra-subject variation and reduced risk of hypoglycemia compared with NPH (Hermansen et al, 2001).

Effectiveness
Insulin detemir may reproduce physiological basal insulin action derived from a flatter time-action profile (Kaku, 2001). Selam et al (2001), showed that patients treated with insulin detemir group had lower fasting glucose levels, lower intra-individual variation in fasting glucose and less hypoglycemic episodes.

Roberts et al (2001), found similar effects on patients with Type I diabetes on a basal-bolus regimen of either NPH or insulin detemir twice daily and regular insulin.

In a randomized controlled trial of type 1 diabetic subjects, Hermansen et al (2001) found that insulin detemir was as effective as NPH in maintaining glycemic control when administered at a higher molar dose.

c) INSULIN GLARGINE

Safety
Raskin et al (2000) and Rosenstock et al (2000) reported that basal insulin therapy with insulin glargine once a day appears to be as safe as NPH insulin in lowering fasting plasma glucose levels in patients with Type I diabetes. In Type II diabetes insulin

glargine, produced less hypoglycemic episodes hypoglycemia with glucose levels <50 mg/dL, and nocturnal hypoglycemia, compared to NPH (Fonseca et al, 2001).

Forjanic-Klapproth et al (2001) reviewed the findings of 4 phase 3 studies involving 1104 patients treated with insulin glargine and 1103 treated with NPH. Approximately half of all patients in the 4 trials were type 1diabetes. Of the 2 studies on patients with Type II diabetes, the United States study showed more and the European study showed less retinopathy progression with NPH than with glargine by at least 3 steps on fundus photography. In addition, the European study showed greater development of macular edema on photography but less progression to non proliferative retinopathy on clinical examination.

In a study on the effects of insulin glargine on cultured human skeletal muscle cells, compared with human insulin and insulin like growth factor, found equivalent metabolic responses with no augmented mitogenic effect (Ciaraldi et al, 2001).

Effectiveness

Insulin glargine is found to be as effective as once- or twice-daily NPH in improving and maintaining glycemic control (Raskin et al, 2000; Rosenstock et al, 2000; Pieber et al, 2000; Gillies et al, 2000; Rosenstock et al, 2001). Fasting plasma glucose levels were also more stable in patients using insulin glargine than in patients using NPH insulin (Rosenstock et al, 2000). Insulin gargine induces a smoother metabolic effect than NPH insulin, from which a better substitution of basal insulin requirements may follow (Heinemann et al, 2000).

In a review of four large clinical trials of 28 weeks duration, a single bedtime dose of insulin glargine, in combination with preprandial short-acting insulin, was found to be as effective or more effective than once or twice daily NPH plus short-acting insulin in improving glycaemic control in patients with Type I diabetes mellitus. In 3 large comparative trials, insulin glargine decreased glycosylated haemoglobin and/or fasting blood glucose levels to similar levels as NPH insulin in insulin-dependent or non-insulin-dependent Type II diabetes mellitus patients, either used as monotherapy or in combination with oral hypoglycaemic agents (Gillies et al, 2000).

d) INSULIN LISPRO

Safety

Schmauss et al (1998) concluded that insulin lispro in CSII therapy is safe and may improve postprandial glucose excursions. Insulin lispro, as part of a basal bolus regimen, reduces nocturnal hypoglycemia in patients with Type I diabetes who maintain tight glycemic control during intensive insulin therapy (Heller et al, 1999), while Bastyr et al (2000) reported that insulin lispro demonstrated lower risk of nocturnal hypoglycaemia in Type II diabetic patients.

The study by Raskin et al (2001) showed that no differences between treatments in basal or bolus insulin doses, weight gain, or the incidence and rate of hypoglycemia, hyperglycemia, or pump occlusions. However when used in external pumps, insulin lispro provides similar adverse event profile as regular human insulin. Another study also reported no significant differences for the rate of hypoglycemia, and no severe case of ketoacidosis with insulin lispro treatment, (Renner et al, 1999).

Cheta et al (1998) reported only one serious adverse event occurred during the study that is a ketoacidosis due to a technical dosing error. Ten patients reported mild hypoglycemic episodes. The outcome of clinical study and of Quality of Life, Lispro is effective, and it is broadening beneficially the spectrum of insulin.

Glazer et al (1999) also reported no clinically or statistically significant differences in the frequency of treatment-emergent adverse events or progression of retinopathy, neuropathy, or cardiovascular disease reported with each therapy. There was no difference between insulin lispro and Humulin R in the occurrence and progression of kidney disease as measured by changes in serum creatinine levels.

Effectiveness
The postprandial glucose concentrations were significantly lower during treatment with insulin lispro (Garg et al, 1999; Valle et al, 2001; Raskin et al, 2001). In addition, the 1 and 2-hour postprandial blood glucose levels were significantly lower with insulin lispro, resulting in smoother daily glucose profiles as compared with regular human insulin (Renner et al, 1999).

Insulin lispro was also associated with a significantly lower HbA_{1c} than was buffered regular human insulin (Garg et al, 1999; Renner et al, 1999; Valle et al, 2001) and is an effective option for the outpatient management of ketonuria (Travaglini et al, 1998).

E) INHALED AND ORAL INSULIN

Safety
Many of the studies reported that inhaled insulin was well tolerated and had no effect on pulmonary function (Laube et al, 1993, Klonoff, 1999, Laube, 2001, Skyler et al, 2001, Cefalu et al, 2001). There is no evidence of irritation, hypoglycemia, or changes in pulmonary function when administered over short periods (Laube, 2001). No adverse effects were observed on airway reactivity (Henry et al, 2001). It has been suggested that further long-term studies are required to investigate safety aspects and incidence of hypoglycaemic events (Brunner et al, 2001).

Effectiveness
The treatment of diabetes with aerosolized insulin will provide an effective alternative means for controlling plasma glucose levels in diabetic individual (Laube et al 1993, Klonoff 1999, Cefalu et al 2001, Laube et al., 2001, Gerber et al., 2001). The formulations administered via the lung are comparable to, or even faster than, those of subcutaneous injected regular insulin or rapid-acting insulin analogues (Heinemann, 1997, Farr et al, 2000, Heinemann et al, 2001). It has been reported that the therapeutic efficacy of inhaled insulin is comparable to that of the usual subcutaneous insulin treatment regimens, the most important advantage being the enhanced therapeutic comfort of the patient who does not need to inject insulin for meal time glucose control (Harsch et al, 2001) and a less invasive alternative to conventional preprandial insulin injections (Skyler et al, 2001).

In terms of glycemic control, it has been reported that inhalable insulin offers no advantages in Type I diabetics in comparison to an intensified conventional insulin therapy. In addition, there is still no clinical data concerning the efficiency of the inhaled insulin in patients with pulmonary diseases which may cause problems in absorption of inhaled insulin due to the smaller cumulative alveolar surface. In smokers without pulmonary disease, it seems that the inhaled insulin to act stronger and faster (Harsch et

al, 2001). A study to assess the effect of respiratory function of inhaled insulin among healthy and asthmatic individuals without diabetes and non cigarette smokers reported that there was 27% more insulin absorption and 44% more glucose-lowering effect in the healthy group compared with the patients with asthma (Henry et al, 2001).

The inhalation of soluble human insulin is found to feasible, providing a clear dose response, but further long-term studies are required to investigate HbA_{1c} values, and the quality of life (Brunner et al, 2001).

Apart from this, since therapy with inhalable insulin requires larger doses of insulin in comparison to subcutaneous insulin to achieve the same systemic effect, the costs of this therapy need to be clarified, too (Harsch et al, 2001).

4.1.3 NON DRUGS

a) DIET CONTROL

Increased body weight, particularly abdominal weight, is associated with increasing risk for Type II diabetes, and 80% of people with Type II diabetes are overweight or obese. Weight loss and maintenance may be more difficult in obese people with diabetes. A review on various weight-loss strategies found that the net improvement on glycemic control was small after 1 year weight loss, and strategies are needed to improve long-term weight loss, weight maintenance, and glycemic control in patients with Type II diabetes (Hensrud, 2001).

In a randomized controlled trial of 75 Type II diabetes patients, liquid meal replacement are found to be a safe and effective weight loss tool for obese subjects with Type II diabetes, resulting in improvement in body weight, glucose, insulin, hemoglobin A1c and lipid levels (Yip et al, 2001).

Another study found that meals rich in thermally stressed olive oil may increase postprandial serum paraoxonase activity in middle-aged and older diabetic women. This change is potentially anti-atherogenic and may favour the use of olive oil over polyunsaturated fats in the diet of patients with Type II diabetes (Wallace et al, 2001).

Lean (2001) stated that there are three convincing studies using different designs concluding that a modest weight loss in overweight patients with diabetes does increase life expectancy very substantially. This involves reduction in fat intake and an increase in physical activity. Eating carbohydrates does suppress appetite and increase metabolic rate as well as improving insulin sensitivities.

In 1997, a position statement from American Diabetic Association for diabetics patients suggests an assessment of what and when the patients is currently eating, to devise individualized treatment goals for glucose and lipid values and reasonable body weight with modification of usual eating habits, and monitoring blood glucose, glycated hemoglobin, lipids, blood pressure, and body weight, as well as quality of life, to assess if desired nutrition therapy outcomes are met (Rebecca SG et al., 1997).

b) EXERCISE

The type and duration of exercise the magnitude of the effects on glycemic control, insulin sensitivity, and on risk factors for cardiovascular disease must be considered in determining the feasibility and acceptability of an intervention program. Exercise programs should be designed to start slowly, build up gradually, and emphasize

moderately intense exercise performed at least three times a week and preferably five to seven times a week for best results (Hamdy et al, 2001).

A study on benefits of regular physical training in patients with long-standing insulin dependent diabetes mellitus concluded that physical exercise training in patients with Type I diabetes mellitus improves metabolic control and various aspects of HRQOL. Danish Centre for Health Technology Assessment report on Type II Diabetes (2003) concluded that physical activity improves the regulation of blood glucose, triglycerides, while the total cholosterol remains the same. Exercise also enhanced the cardiorespiratory capacity, providing subjective benefit in patients (Wiesinger et al, 2001).

Comprehensive lifestyle therapies, involving diet, exercise, and behavioral modification, can result in weight loss and increased glucose tolerance (Mensink et al, 2003; Danish Centre for Health Technology Assessment 2003).

4.2 MONITORING OF DIABETES MELLITUS

4.2.1 SELF MONITORING IN TYPE 1 DM

A meta-analysis on self monitoring in Type I diabetes reviewed 24 papers, 8 controlled trials and 16 non-controlled trials, and did not provide evidence to support the clinical effectiveness of self monitoring. It has been estimated that the NHS costs of self-monitoring by DM patients can reach £42 million annually (Coster et al, 2000).

4.2.2 SELF MONITORING IN TYPE II DM

A meta-analysis of 6 studies comparing self-monitoring of blood glucose or urine and those who do not, and blood monitoring compared with urine monitoring, found that self-monitoring of blood or urine was not effective in improving blood glucose control in Type II diabetes (Coster et al, 2000). The Danish Centre for Health Technology Assessment (2003) also found that the efficacy of self monitoring of blood glucose in Type II diabetes patients was still poorly documented. On the other hand, it has been reported that more frequent self-monitoring of blood glucose levels is associated with clinically and statistically better glycaemic control regardless of diabetes type or therapy (Karter et al, 2001). This was supported by a study by Harris (2001), which concluded that self-monitoring of blood glucose is more common as HbA_{1c} level increases, suggesting that patients with poorer glycaemic control have a greater tendency to self-monitor.

A randomized controlled trial comparing the efficacy and cost of self monitoring of blood glucose and urine testing in patients with Type II diabetes mellitus not treated with insulin, found that the former is 8-12 times more expensive and does not support widespread use of self monitoring of blood glucose (Allen et al, 1990).

4.2.3 LABORATORY AND NEAR-PATIENT TESTING

a) Glycated serum haemoglobin - HbA_{1c}

There is evidence from randomized controlled trials that glycated serum haemoglobin (GHb) assays should be used to monitor blood glucose control in both Type I and Type II diabetes patients, with indirect evidence from the Diabetes Control and Complications Trial (DCCT) and the UKPDS suggesting that this assay will be clinically effective as well as cost effective. Taking into account the relatively slow change in GHb accompanying changes in plasma glucose, a study recommended that no more than 4 to 6 tests per year in subjects with Type I and Type II tests per year in subjects with stable Type II diabetes may be reasonable. Near patient testing (NPT) for GHb is at an early stage of development, but preliminary data suggests that NPT for GHb in hospital

diabetes clinics has practical clinical use and may contribute efficiency savings if used appropriately, while the use of NPT for GHb in primary care has not been adequately evaluated (Coster et al, 2000).

b) Glycated serum protein - Fructosamine

Cefalu et al (1999) in a study to assess clinical validity of fingerstick fructosamine test compared to laboratory determination in outpatient diabetic management, found that it correlated well to laboratory assessment of fructosamine and glycated Hb. A prospective study concluded that in Type II diabetes, serum fructosamine assay can better reflect average blood glucose concentration over the previous 3-6 weeks and HbA_{1c} assay for the previous 8-10 weeks. HbA1c measurement correlates more significantly with home capillary blood glucose level than the fructosamine assay, even in the preceding 2–3 weeks (Chen et al, 2002).

Carter et al (2000), reported that the addition of fructosamine test improves screening accuracy for large groups of people, while maintaining ease of use and affordability. Once again Carter et al (2001) assessed the impact of this test in assisting individuals having poor glycaemic control, and found that the addition of weekly fructosamine values to daily blood glucose values provides both the patient and clinician valuable information to evaluate the impact of dietary, exercise, and medication changes on glycaemic control by bridging the gap between daily blood glucose values and quarterly HbA_{1c} confirmation of intervention results.

However a randomized control trial, where weekly home fructosamine monitoring was added to daily glucose monitoring, reported no significant difference between those using daily glucose monitoring only and those using daily glucose monitoring and weekly fructosamine meaning that it did not improve glycaemic control (Petiti et al., 2001). The same conclusion was also made by Coster et al (2000), where fructosamine testing have not been shown to be better than GHb for monitoring blood glucose (Coster et al, 2000).

A study assessing the cost effectiveness of a dual test of blood glucose/fructosamine home monitoring system, found that the cost per subject including equipment, supplies and labor was $18.13 (Carter *et al*, 2000).

c) Fasting plasma glucose (FPG)

A review notes that several observational studies conclude that Type II diabetes patients can achieve near normal glucose control by using FPG tests every three months. It has been suggested that GHb be measured regularly, in combination with FPG, to ensure optimal management of diabetes. However, the use of FPG in Type I and Type II diabetes treated with insulin would seem inappropriate and unreliable. However, the optimal frequency of FPG measurement of has not been established (Coster et al, 2000).

4.3 COST EFFECTIVENESS OF DIFFERENT MANAGEMENT STRATEGIES

The UKPDS trial concluded that intensive glucose control significantly increased treatment costs (£695) but substantially reduced the cost of complications (£957) and increased the complication-free period (0.6 years) (Gray et al, 2000).

A cost effectiveness study of insulin therapy for Type II diabetes, showed that multiple injection therapy (MIT) is recommended for the treatment of Type II diabetic patients who require insulin therapy, the reduction of total cost in MIT over conventional injection therapy (CIT) being mainly due to the reduced costs for management of diabetic

complications (Wake et al, 2000). A study using computer-modeled complications of diabetes and various combinations of diabetes management strategies, suggests that optimal management of Type I diabetes patients, including secondary and tertiary prevention, leads to reduced complications and improved life expectancy, with the increased costs of prevention offset by varying degrees by cost savings due to complications avoided (Palmer et al, 2000).

B. SCREENING FOR MICROALBUMINURIA IN DIABETIC PATIENTS

B. 1. INTRODUCTION

Microalbuminuria is an early marker of prognostic significance in diabetic renal disease. In diabetic patients it is a marker that predicts the development of clinical proteinuria, renal dysfunction, and in Type II diabetes mellitus, it is also a marker for cardiovascular events, premature death, as well as being another component of the insulin resistance syndrome. The early detection of microalbuminuria is important for better management to either retard or regress the pathologic changes.

Microalbuminuria is defined as:
Urinary Albumin Excretion Rate (AER): 20-200µg/min (30-300mg/24 hours).
Urine Albumin:Creatinine Ratio (ACR): 30-300 mg/gm (2.5-3.5 gm/mol) creatinine.
Urine Albumin Concentration (ALB): 20-200 mg/l in normal urine output (WHO, 1994; Gilbert et al, 1992).

It has been suggested that in Type I diabetes patients (12-70 years age group) who have had diabetes for at least 5 years, screening should be done at least once a year. Those below 14 years or those having diabetes for less than 5 years seldom or infrequently develop microalbuminuria. In Type II diabetes patients, due to the difficulty in dating the onset of Type II diabetes, screening should be performed from the time of diagnosis in all patients at least once a year until the age of 70 years (Consensus Development Conference, 1994; Bennet et al, 1995; WHO Technical Report, 1994).

When screening, the clinical condition of the patient should be taken into account, and screening should be postponed if one or more of the following conditions are present i.e.urinary tract infection, acute febrile illness, high protein intake, decompensation of metabolic control including ketoacidosis, heart failure, heavy exertion/exercise, on nonsteroidal anti inflammatory drugs or ACE inhibitors. These factors will transiently increase or alter the urinary albumin excretion rate (Bennet et al, 1995; WHO Technical Report, 1994).

B. 2. RESULTS

2.1. METHOD OF SCREENING

It has been suggested that the urinary microalbumin test is a convenient testing method, being able to detect the onset of nephropathy in Type I diabetes patients many years earlier than by screening for proteinuria (WHO Technical Report, 1994). The most widely used screening test in the clinical setting is the standard dipstick, which will detect protein excretion only in the microalbuminuria range (>150 mg/l), although strips that can detect albuminuria as low as 20 mg/l are available for clinical use (Consensus Development Conference, 1994).

The preferred methods for screening are quantitative determination of urinary albumin in a timed urine collection, or an albumin to creatinine ratio of a random urine specimen (Consensus Development Conference, 1994). A timed urinary albumin excretion rate,

either a 24 hours or overnight (8-12 hours) collection, has been said to be the most sensitive assay. An albumin excretion rate greater than 30mg/24 hours or above 20 μg/min, (confirmed in at least 2 urine samples, evaluated within a 6- 12 weeks interval) would confirm diabetic nephropathy (Bennet et al, 1995). However testing for microalbuminuria in a timed sample of urine using a double antibody radioimmunoassay (RIA) is cumbersome and requires special laboratory facilities (Leong, 1998).

A spot urinary albumin concentration has been found to be a worthwhile and robust clinical test in a cohort study. It can be easily incorporated into routine diabetic clinic practice, and shown to provide useful information in the ongoing assessment of patients with Type II diabetes (Beatty et al, 1995).

1.1 Micral Test

Micral- Test II is a rapid test to detect albumin in urine samples. The test strip consists of immunologic, gold labeled antibodies, with an optically read immunoassay, Micral-test has been said to correctly detect diabetic microalbuminuria compared to RIA albumin concentration. However, in low-range microalbuminuria (30-99 mg/24 hours), its sensitivity decreases by 10%, thereby restricting its use in detecting and monitoring microalbuminuria in the very early stages of diabetic nephropathy, where therapeutic intervention is most effective (Hermans, 1994).

A study to assess the usefulness of Micral test in the detection of microalbuminuria suggests that a positive Micral-Test be confirmed by albumin excretion rate of timed urine collection at least three times over a period of months, while those with negative results be subjected to annual re-testing (Gilbert et al, 1992). A multi-center evaluation showed that the Micral-test II test is a reliable, immediate on- site test and reading within 24 hours does not affect the results, although after 24 hours, the results are invalid. The Micral Test II test strip can be used for screening and monitoring (Mogensen et al, 1997). An evaluation suggests that the Micral test with either the first morning urine or random urine specimens offer a simple, rapid, reliable and convenient method for screening of microalbuminuria (Leong et al, 1998). In another study of Micral-test II, it has been suggested that two out of three positive screening tests are required before patient is labeled as incipient diabetic nephropathy, or confirmatory test be carried out by routine laboratory testing. Where facilities for assay of microalbuminuria (by radioimmunoassay, immunoturbidimetry, immmunonephelometry or enzyme immunoassay) and urine creatinine (by Modified Jaffe reaction) are available, a single, random spot urine (upright) and test for urinary Albumin: Creatine ratio is suggested (Zheng et al, 1999).

1.2 The Measurement of Albumin:Creatinine Ratio

Since timed urine collections are sometimes impractical and inconvenient, the measurement of albumin to creatinine ratio using first morning urine sample has been recommended. If this is not possible, a random urine specimen may be used. If a normal ratio obtained, then the test should be repeated annually. If the urinary albumin: creatinine ratio is elevated, this abnormality needs to be confirmed by at least two albumin: creatinine ratios in the microalbuminuric range to confirm microalbuminuria and incipient diabetic nephropathy (Bennet et al, 1995).

Where facilities are available, a random single void (upright) urine sample can be used to measure the urine albumin: creatinine ratio, giving a sensitivity of 99% compared with 24 hours urine collection (Steve et al, 1992).

The measurement of an albumin:creatinine ratio with a cut-off of >2.0 mg/mmol was found to be suitable with specificity of 93% and sensitivity of 97% (Shield et al, 1995).

The urine albumin concentration (UAC/ALB) is less sensitive and specific than that of albumin: creatinine ratio as a screening procedure for microalbuminuria. The variation in creatinine assays apparently has less consequence for albumin: creatinine ratio than variation in albumin concentration measurement (Adries et al, 1999).

1.3 Screening For Urinary Tract Infection

This has been said to be unnecessary unless patient is symptomatic, since the point prevalence of UTI at first screening for microalbuminuria was only 3%. The presence of urinary tract infection does not apparently affect the measurement of urinary albumin excretion unless pyuria is present (Watts et al, 1996).

1.4 Newer screening tests for microalbuminuria

A study on urine albumin levels normalised by creatinine using DCA2000 concluded that it gave good performance characteristics for diagnosis of microalbuminuria in spot morning urine (Ng et al, 2000). Collin et al (2001), also carried out a study on the performance of DCA2000 and found it to be a safe substitute for laboratory based measurements, suitable for screening and monitoring diabetes treatment. Another study of the commercial kit DCA2000 concluded that an early morning specimen should be used instead of timed overnight urine and the A/C ratio is an accurate, reliable and easily determined parameter for the screening of diabetic nephropathy, and its measurement is feasible using the DCA 2000 kit (Khawali et al, 2002).

The Clinitek 50, is a urine chemistry point of care analyser for the semi quantitative measurement of albumin and creatinine, and calculation of albumin: creatinine ratio (ACR). A study on screening for microalbuminuria using Clinitek microalbumin found that it is a good screening test for microalbuminuria (Le Floch et al, 2001). Another study found that it provides useful, immediate clinical information regarding microalbuminuria status for use in diabetic clinic settings or in intensive care (Croal et al, 2001).

The albumin to creatinine ratio and the 24 hours urine collection to measure microalbuminuria are inconvenient and expensive. In order to overcome errors in screening of microalbuminuria using dipstick methods caused by variation in volume in albumin, Parikh et al (2002) determined the relationship between urine spesific gravity (Usg) and urine creatinine (Ucr). Ucr can be derived from from Usg to correct for albumin concentration in the urine which is influenced by urine volume, and a good correlation was found to exist between Usg and Ucr.

2.2 COST IMPLICATIONS

Cost benefit analyses of for management of patients with Type I diabetes and microalbuminuria have recently been performed in few studies. These studies showed that considerable projected cost benefits were contributed by early intervention for microalbuminuria in Type I diabetes patients. However similar analysis for Type II diabetes have not been performed, but it is expected that comparable savings would be achieved in this patient population (Bennet et al, 1995).

5 CONCLUSIONS

MANAGEMENT OF DIABETES MELLITUS

5.1 Treatment

5.1.1 Oral Drugs

There is good evidence of safety and effectiveness of Glimepiride, Metformin, Acarbose, Repaglinide, Rosiglitazone in Type II diabetes patients. In adequately controlled Type II diabetes patients, there is sufficient evidence that combination therapy is safe and effective.

5.1.2 Insulin

There is sufficient evidence of safety and effectiveness of insulin aspart, insulin detemir, insulin glargine, and insulin lispro. With respect to inhaled and oral insulin, there is inconclusive evidence of safety and effectiveness.

5.1.3 Diet control and exercise

There is sufficient evidence that diet control and exercise is important in both the prevention and treatment of Type II diabetes.

5.2 Monitoring of diabetes mellitus

There is inconclusive evidence that self-monitoring of diabetes mellitus improves glucose control in Type I and Type II diabetes. There is sufficient evidence that Glycated serum haemoglobin (HbA_{1c}) is effective for monitoring blood glucose control in diabetes, while there is some evidence that near patient HbA_{1c} is effective in inpatient care. There is inconclusive evidence on the benefits of fructosamine testing, and insufficient evidence on the benefits of fasting plasma glucose testing.

5.3 Cost effectiveness of different management strategies

With respect to costs, there is evidence that intensive glucose control is cost effective.

SCREENING FOR MICROALBUMINURIA IN DIABETIC PATIENTS

There is good evidence that all diabetics need to be screened for microalbuminuria. While a timed urinary albumin excretion rate overnight or over a 24 hour period is most sensitive, random sample testing using a dipstick (spot urinary albumin concentration) or albumin: creatinine ratio are found to be more convenient. There is some evidence that the newer screening test kits are effective.

6 RECOMMENDATIONS

For treatment of Type II diabetes patient oral drugs like Glimepiride, Metformin, Acarbose, Repaglinide, Rosiglitazone are recommended either singly or in combination. For Type I diabetes, insulin aspart, insulin detemir, insulin glargine, and insulin lispro are recommended. Diet control and exercise is recommended for all diabetics. Self monitoring of diabetes using HbA1c is recommended for all patients despite the lack of evidence on improvement in glucose control due to other benefits of monitoring.

Screening for microalbuminuria is recommended for all diabetics either by spot albumin concentration or by albumin:creatinine ratio testing.

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LIST OF ABBREVIATION

ADA	American Diabetes Association
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complication Trial
RCT	randomised controlled trial
SMBG	Self monitoring of blood glucose
UKPDS	United Kingdom Prospective Diabetes Study
HbA_{1c}	Haemoglobin A_{1c}
GHb	Glycated haemoglobin

Appendix 1

The details of the literature search on various aspects are as follows:

Oral hypoglycaemia
The database used was MEDLINE. The keywords used were gliclazide, glimepiride, metformin, acarbose, repaglinide, rosiglitazone, pioglitazone and combination therapy and safety, effectiveness, cost effectiveness. They were used singly and in combination.

Years: 1990 -2002
Limits: Full text, abstract, English article, human
Articles used: 68

Insulin
A MEDLINE database search was carried out using the key word Insulin aspart, insulin glargine, insulin detemir, insulin lispro, inhaled and oral insulin, safety, effectiveness, cost effectiveness. They were used singly and in combination.

Years: 1990 -2002
Limits: full text, abstract, English article, human
Articles used: 42

Monitoring Of Diabetes Mellitus
Abstract reviews from the MEDLINE databases. Subject heading used were: monitoring of diabetes mellitus, fructosamine monitoring, home glucose monitoring.

Years: 1996-2002
Limits: Abstract, human
Number of articles used:15

Management of diabetes- diet and exercise
A MEDLINE database search was carried out using the key words together or in combination: diet, exercise, lifestyle modification, in Type I and Type II DM, not pregnant, not hypertensive/hypertension, not hypercholesterolemia.

Years: 1996-2002
Limits: Abstract, human,
Number of articles used: 9 (2 Full articles and 7 Abstracts)

Screening for Microalbuminuria
A MEDLINE database search was carried out using the key words together or in combination: methods of screening, methods of sampling, microalbuminuria, spot morning urine, screening test for microalbuminuria, Micral test, nephropathy.

Years: 1994-2002
Limits: Abstract, human,
Number of articles used: 19

EVIDENCE TABLE – MANAGEMENT OF NIDDM PATIENTS- DRUG THERAPY –ORAL

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	GLICLAZIDE - SAFETY				
1	Harrower AD (1991) Efficacy of Gliclazide in comparison with other sulphonylureas in the treatment of NIDDM. Diabetes Res Clin Pract ; 14 Suppl 2:S65-7	RCT First Study - 224 patients, 3 months Second study - 112 patients , 1 year Third study - 24 pts 5 years	Good glycaemic control was achieved in 65% of patients. Conversion from other oral hypoglycaemics to gliclazide led to an improvement in control except in cases previously treated with glibenclamide. On the basis of HbA1c levels, the best results were obtained with glibenclamide and gliclazide, leading to normal HbA1c levels in 74% and 80% of patients, respectively. Gliclazide has the lowest secondary failure rate (7%) and was significantly better than glipizide (25.6% failures in 5 years), but the difference relative to glibenclamide (17.9%) just failed to reach the threshold of significance. Conclusion, gliclazide is a potent hypoglycaemic agent which compares favourably with others of its type. It retains its efficacy longer than other sulphonylureas. Gliclazide may therefore be considered a first choice for the therapy of diet-failed NIDDM pts.	Good to fair	
2.	Drouin P(2000) Diamicron MR once daily is effective and well tolerated in type 2 diabetes: a double-blind randomized, multinational	RCT 800 pts 10 months	Diamicron® MR was as efficient as Diamicron® in controlling blood glucose, with a mean end point difference in HbA1c of –0.08 (0.08%), significantly lower than the equivalence limit ($p<0.001$).	Good to fair	Diamicron® MR, a new gliclazide formulation taken once daily at lower dose (30-120 mg/day) was

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	study. J Diabetes Compilations Jul-Aug; 14(4): 185-91		Similar results were obtained for FPG.		compared with Diamicron® (80-320 mg/day) taken twice daily in type 2 diabetic outpatients.
	GLICLAZIDE – EFFECTIVENESS				
1	Harrower AD Efficacy of Gliclazide in comparison with other sulphonylureas in the treatment of NIDDM (1991) Diabetes Res Clin Pract 14 Suppl 2:S65-7	RCT First Study - 224 patients, 3 months Second study - 112 patients , 1 year Third study - 24 pts 5 years	The results of the three studies show that gliclazide has a low incidence of side effects, few problems with hypoglycaemia, and retains its efficacy longer than other sulphonylureas. Gliclazide may therefore be considered a first choice for the therapy of diet-failed NIDDM patients.	Good to fair	
2.	Drouin P (2000) Diamicron MR once daily is effective and well tolerated in type 2 diabetes: a double-blind, randomized, multinational study. J Diabetes Compilations Jul-Aug; 14(4): 185-91	RCT 800 pts 10 months	The safety of Diamicron® MR and Diamiron® was equally high. The incidence of hypoglycemia was particularly low (0.2 hypoglycemia/100 pts months) in the elderly population, which represent almost 40% of the included pts.	Good to fair	Diamicron®MR, a new gliclazide formulation taken once daily at lower dose (30-120 mg/day) was compared with Diamicron® (80-320 mg/day) taken twicw daily in type 2 diabetic outpatients
	GLIMEPIRIDE-SAFETY				
1.	Rosenstock J; Samols E; Muchmore DB; Scneider J (1996)	RCT 416pts	Adverse events and laboratory data demonstrate that glimepiride has s favorable safety profile.	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Glimepiride, a new once daily sulphonylurea. A double blind placebo controlled study of NIDDM pts. Glimepiride Study Gp. Diabetes Care Nov; 19(11) : 1194-9	14 weeks	Conclusion : - Glimepiride is a well tolerated oral glucose-lowering agent.		
2	Hoechst AG, Frankfurt, Federal Republic of Germany (1995). Clinical profiles of glimepiride. Diabetes Res Clin Pract Aug; 28 Suppl: S139-46	Review	Glimepiride maintained a more physiological regulation of insulin secreation than glibenclamide during physical exercise, suggesting that there may be less risk of hypoglycaemia with glimepiride.	Good to fair	
3	Draeger KE, Wernicke-Panter K; Lomp HJ; Schuler E; Rosskamp K (1996) Long term treatment of type 2 diabetic pts with the new oral antidiabetic agent. Glimepiride (Amaryl) a double blind comparison with glibenclamide. Horm Metab Res. Sep; 28(9): 419-25	RCT 524 pts 1 year	Both treatment groups showed an equivalent safety profile. Adverse events were consistent with the nature of the diabetic patient population studied. Fewer hypoglycaemic reactions occurred with glimepiride than with glibenclamide (105 vs. 150 episodes). Both treatments were well tolerated.	Good to fair	
	GLIMEPIRIDE –EFFECTIVENESS				
1	Draeger KE, Wernicke-Panter K; Lomp HJ; Schuler E;	RCT	The long term follow up (457) pts confirmed that glimepiride (1-8 mg) once	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Rosskamp K (1996) Long term treatment of type 2 diabetic pts with the new oral antidiabetic agent. Glimepiride (Amaryl) a double blind comparison with glibenclamide. Horm Metab Res. Sep; 28(9): 419-25	524 pts 1 year	daily provides equivalent metabolic control to a higher dosage (2.5-20.0 mg) of glibenclamide.		
2	Hoechst AG, Frankfurt, Federal Republic of Germany (1995) Clinical profiles of glimepiride. Diabetes Res Clin Pract Aug; 28 Suppl: S139-46	Review	Glimepiride had a more rapid onset of action than glibenclamide, with longer duration of action. Glimepiride achieved metabolic control with the lowest dose (1-8 mg daily) of all the sulphonylureas.	Good to fair	
3	Goldberg RB; Holvey SM; Schneider J (1996) A dose response study of glimepiride in patients with NIDDM who have previously received sulphonylureas agents. The glimepiride Protocol # 201 Study Gp. Diabetes Care Aug; 19(8) : 849-56	RCT 304 pts 14 weeks	At each pt visit, reduction from baseline FPG was greater in each glimepiride gp than in the placebo group. Changes from baseline to endpoint after 1 , 4 & 8 mg glimepiride exceeded those after placebo by 2.4, 3.9 & 4.1 mmol respectively for FPG; by 1.2,1.8 & 1.9 % points ; respectively, for HbA1c and by 3.5,5.1 & 5.2 mmol/L respectively for 2-hr PPG. Greater reductions in these parameters were observed with 8 & 4 mg than with 1 mg, indicating a dose-response relationship. Glimepiride in 1-,4-,8-mg doses was effective and the 4-& 8-mg once daily	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			doses were significantly more potent than the 1-mg dose. Because the 8-mg dose controlled HbA1c values in a greater number of pts with high baseline HbA1cb levels than did the 4-mg dose, this higher dose might be beneficial for pts who are difficult to treat.		
4	Rosenstock J; Samols E; Muchmore DB; Scneider J (1996) Glimepiride, a new once daily sulphonylurea. A double blind placebo controlled study of NIDDM pts. Glimepiride Study Gp. Diabetes Care Nov; 19(11) : 1194-9	RCT 416pts 14 weeks	FPG and HbA1c values were similar at baseline in all treatment groups. The placebo group's FPG value increased from 13.0 mmol/L at baseline to 14.5 mmol/L at endpoint. In contrast, FPG values in the four glimepiride groups decreased from a range of 12.4-12.9 mmol/L at baseline to a range of 8.6-9.8 mmol/L at the endpoint. 2 hour postprandial plasma glucose (PPG) findings were consistent with FPG findings. In the placebo group, the HbA1c value increased from 7.7% at baseline to 9.7% at endpoint, whereas HbA1c values for the glimepiride groups were 7.9-8.1% at baseline and 7.4-7.6% at endpoint. There were no meaningful differences in glycaemic variables between daily doses of 8 & 16 mg or between once and twice daily dosing. Glimepiride is an effective oral glucose lowering agent. The results of the study demonstrate max. effectiveness can be achieved with 8 mg qd of glimepiride in NIDDM pts.	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	METFORMIN -SAFETY				
1	Giugliano D, Quatraro A, Consoli G, Minei A, Ceriello A, De Rosa N, D'Onofrio F (1993) Metformin for obese, insulin-treated diabetic patients: improvement in glycaemic control and reduction of metabolic risk factors. Eur J Clin Pharmacol 44(2):107-12	Randomized Controlled Trial 50 patients	Metformin was well tolerated by all diabetics	Abs	
2	Swislocki AL, Khuu Q, Liao E, Wu E, Beza F, Lopez J, Kwan G, Noth RH (1999) Safety and efficacy of metformin in a restricted formulary. Am J Manage Care Jan;5(1):62-8	A retrospective review n = 251	MET provided sustained beneficial effects on glycemic control and was well tolerated. Any effects on weight, blood pressure, and serum lipids were not demonstrable in this analysis	Abs	
3	Fruehwald-Schultes B, Kern W, Oltmanns KM, Sopke S, Toschek B, Born J, Fehm HL, Peters A (2001) Metformin does not adversely affect hormonal and symptomatic responses to recurrent hypoglycemia.	Clinical Trial 15 young healthy men were treated with 850 mg metformin	The data indicate that metformin does not adversely affect hormonal and symptomatic responses to hypoglycemia. This finding appears to be relevant with regard to the safety of the combination of metformin with insulin therapy.	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	J Clin Endocrinol Metab Sep;86(9):4187-92				
4	Lalau JD, Vermersch A, Hary L, Andrejak M, Isnard F, Quichaud J (1990) Type 2 diabetes in the elderly: an assessment of metformin (metformin in the elderly). Int J Clin Pharmacol Ther Toxicol Aug;28(8):329-32	24 patients aged between 70-88 years	It is concluded that provided the dosage is adjusted to renal function, the metabolic tolerance of metformin therapy is satisfactory in the elderly type 2 diabetic patient	Abs	
	METFORMIN –EFFECTIVENESS				
1	Johansen K (1999) Efficacy of metformin in the treatment of NIDDM : meta-analysis Diabetes Care Jan. 22(1) : 33-7	Meta-analysis 9 RCT comparing metformin with placebo & 10 RCT comparing metformin with sulphonylureas. All RCTs published since 1957.	The weighted mean difference (WMD) between metformin and placebo after treatment for FPG was –2.0 mmol/l & for glycosylated hemoglobin – 0.9% . Sulphonylurea & metformin lowered blood glucose & glycosylated hemoglobin equally, while there was a significant WMD of body wt –2.9 kg because of a 1.7 kg mean increase after sulphonylurea & a 1.2kg mean decrease after metformin glycosylated. Metformin lowered blood glucose & glycosylated hemoglobin significantly; compared with placebo. Metformin & sulfonylurea have an equal effect on fasting blood glucose & glycosylated hemoglobin but the body wt is	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			significantly lowered after metformin compared with sulfonylurea treatment because of an increase in body wt after sulphonylurea treatment.		
2	Garber AJ; Duncan TG; Goodman AM; Mills DJ; Rohlf JL (1997) Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. Am J Med Dec; 103(6): 491-7	RCT 451 pts 14 wks	Metformin improved glucose variables as compared with placebo. The adjusted mean changes in fasting plasma glucose from baseline associated with each metformin group at week 7, 11, or at endpoint exceeded those associated with placebo by 19 to 84 mg/dL at dosages of 500 to 2000 mg daily respectively. The corresponding between group differences in glycated hemoglobin (HbA1c) ranged from 0.6% to 2.0% at dosages of 500 to 2000 mg daily, respectively. All between-group differences were significant ($p<0.05$) except for the difference between placebo and metformin 500 mg in fasting plasma glucose at end point ($p=0.054$). Conclusions: Metformin lowered fasting plasma glucose and HbA1c generally in a dose-related manner. Benefits were observed with as little as 500 mg of metformin; maximal benefits were observed at the upper limits of the recommend daily dosage.	Good	
	ACARBOSE – SAFETY				
1	Wainstein J, Jedwab M (1997) Efficacy and safety of acarbose treatment of NIDDM. Harefuah Feb 16; 132(4): 258-63, 311	RCT 169 pts 19+12 wks	A substantial decrease in HbA1c levels from 8.5% to 7.5% ($p<0.001$) and in postprandial serum glucose levels from 283.6 mg/dl to 248.5 mg/dl ($p<0.01$) was seen during treatment. On follow-up,	Good	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			HbA1c levels increased by 0.45% and postprandial serum glucose rebounded from 256.4 mg/dl to 287.9 mg/dl. Acarbose was shown to be effective in treating NIDDM and to be and well-tolerated.		
2	Rosentock J, Brown A, Fisher J, Jain A, Littlejohn T, Nadeau D, Sussman A, Taylor T, Krol A, Magner J (1998) Efficacy and safety of acarbose in metformin-treated patients with type 2 diabetes. Diabetes Care Dec; 21(12): 2050-5	RCT 31 wks	Gastrointestinal side effects were more frequently reported in the acarbose-treated patients. No significant differences in liver transaminase elevations were observed between patients treated with acarbose and those treated with placebo. The results demonstrate that the addition of acarbose to patients with type 2 diabetes who are inadequately controlled with metformin and diet is safe and generally well tolerated.	Good to fair	
3	Sieradzki J; Soszynski P (1999) Evaluation of acarbose efficacy and safety for treatment of diabetes mellitus. Testing of observations under general health care conditions. Przegl Lek 56(5): 335-41	RCT 480 pts (the whole pts population consisted of 600 pts) 8 wks	The study showed low significance of side effects and high acceptance of the treatment by the patients and the physicians	Good	Fasting blood glucose was the criteria of inclusion into the analysis.
4	Coniff R; Krol A (1997) Acarbose: a review of US clinical experience. Clin Ther Jan-Feb; 19(1): 16-26; discussion 2-3	Review article	Adverse events were nonsystemic and primarily gastrointestinal in nature.	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
5	Scorpiglione N; Belfiglio M; Carinci F; Cavaliere D; De Curtis A; Franciosi M; Mari E; Sacco M; Tognoni G; Nicolucci A (1999) The effectiveness, safety and epidemiology of the use of acarbose in the treatment of patients with type II diabetes mellitus. A model of medicine-based evidence. Eur J Clin Pharmacol Jun; 55(4): 239-49	RCT 1027 pts 1 year	One third of the patients could not assume the drug for the whole study period, mainly due to gastrointestinal side effects.	Good	
6	Kendrup H; Bongers H; Spengler M: Kusenbach G: Skopnik H (1999) Efficacy and safety of acarbose min patients with cystic fibrosis and impaired glucose tolerance. Eur J Pediatr Jun; 158(6): 455-9	RCT 12 pts 2 wks	Gastrointestinal disturbances were recorded in 67% of the patients during therapy with acarbose.	Good to fair	
7	Campbell LK; White JR; Campbell RK (1996) Acarbose: its role in the treatment of diabetes mellitus. Ann Pharmacother Nov; 30(11): 1255-62	Review article	Adverse effects are gastrointestinal and can be diminished by starting with an initial dosage of 25 mg tid. Depending on patient response, the dosage can be increased up to a maximum of 100 mg tid over time.	Good to fair	
8	Deerochanawong C; Serirat S; Kornthong P (1996) Efficacy of acarbose as	Open study	The most common side effects were mild to moderate flatulence and abdominal distension. There was no significant changes in body weight, lipid profiles and	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	monotherapy in NIDDM patients. J Med Assoc Thai Feb; 79(2): 69-75		other biochemical parameters.		
9	Yee HS; Fong NT (1996) A review of the safety and efficacy of acarbose in diabetes mellitus. Pharmacotherapy Sep-Oct; 16(5): 792-805	- Review article	Acarbose can potentiate the hypoglycaemic effects of sulphonylureas or insulin. It has not been associated with weight gain and hyperinsulinemia, both of which can occur with sulphonylureas or insulin. Gastrointestinal adverse effects are common with acarbose, and may decrease with continued treatment. Although rare, elevated serum transaminase levels have been reported.	Good to fair	
10	Sels JP; Verdonk HE; Wolffenbuttel BH (1998) Effects of acarbose (Glucobay) in persons with type 1 diabetes: a multicentre study. Diabetes Res Clin Pract Aug; 139-45	RCT 62 pts 16 wks	No significant changes were observed for total cholesterol, HDL-cholesterol, triglycerides, Apo A1 and Apo B, and Lp(a). The most frequent reported adverse events were flatulence (43%), diarrhoea (27%), and abdominal pain (11%).	Good to fair	
11	Mertes G (1998) Efficacy and safety of acarbose in the treatment of type 2 diabetes: data from a 2-year surveillance study.	Surveillance study 2035 pts 2 years	Doses of acarbose were generally low, and hence well-tolerated. The incidence of acarbose-associated adverse effects and withdrawals was 7.5 and 2.5% respectively. No sustained adverse changes in laboratory parameters occurred.	Good	This study was open with no control group

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Diabetes Res Clin Pract Apr; 40(1): 63-70				
12	Wolever TM; Chiasson JL; Josse RG; Hunt JA; Palmason C; Rodger NW; Ross SA; Ryan EA; Tan MH (1997) Small weight loss on long-term acarbose therapy with no change in dietary pattern or nutrient intake of individuals with non-insulin-dependent diabetes. Int J Obes Relat Metab Disord Sep; 21(9): 756-63.	RCT 354 pts 12 months	In subjects with NIDDM on weight-maintaining diets, long-term acarbose therapy results in a small weight loss, but has no effect on energy or nutrient intakes. The weight loss induced by acarbose may be due partly to reduced doses of concomitant oral agents and partly to energy loss due to increased colonic fermentation.	Good	77 pts on diet alone, 83 also treated with metformin, 103 also treated with sulphonylurea and 91 also treated with insulin.
13	Spengler M; Catagay M (1995) The use of acarbose in the primary-care setting: evalution of efficacy and tolerability of acarbose by postmarketing surveillance study. Clin Invest Med 1995 Aug; 18(4): 325-31	Post marketing surveillance study 10,462 pts 12 wks	Tolerability was good: 78.6% of the patients had no adverse events; 19% reported meteorism/flatulence; 3.2% diarrhea. Hypoglycemia was found in 0.8% of type I and 0.6% of type II patients who received concurrent insulin (n=8) or glibenclamide (n=1) treatment. Laboratory investigations gave no indication of other adverse effects, e.g. elevated levels of transaminase or creatinine.	Good	829 IDDM, 9440 NIDDM, 193 not classified. Of the Type II pts, 28.9% were treated with diet only; 58.1% additionally with sulphonylureas; 8.6% with insulin; and 4.3% with both sulphonylureas

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
					and insulin.
14	Sieradzki J; Soszynski P (1999) Evaluation of acarbose efficacy and safety for treatment of diabetes mellitus. Testing of observations under general health care conditions. Przegl Lek 56(5): 335-41	RCT 21 pts 3 months	Before treatment, 18 pts had hypoglycemic symptoms during oral glucose tolerance test (OGTT). Frequency of hypoglycemic attacks was reduced from 4 times a week to 1. C-peptide levels in 24-hour urine collection did not change significantly. These results confirm that acarbose may be of value in preventing reactive hypoglycemia by reducing the early hyperglycemic stimulus to insulin secretion, and in the treatment of reactive hypoglycemia.	Good to fair	
15	Hoffman J; Spengler M (1997) Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II Study. Am J Med Dec; 103(6): 483-90	RCT 96 pts 24 wks	Slight body weight changes were observed with acarbose (-0.8 kg) and metformin (-0.5 kg), but not with placebo. Acarbose led to mild or moderate intestinal symptoms in 50% of the patients within the first 4 weeks, but in only 13.8% of the patients within the last 4 weeks.	Good to fair	
16	Hotta N; Kakuta H; Sano T; Matsumae H; Yamada H; Kitazawa S; Sakamoto N (1993) Long-term effect of acarbose on glycaemic control in non-insulin-dependent diabetes	RCT 24 wks	The incidence of side effects (mainly gastrointestinal symptoms such as flatulence and abdominal distension) was high at 78.9% in the acarbose group and 61.1% in the placebo group. However, there was no significant difference between the groups, and side effects in the acarbose group tapered during trial, suggesting that	Good to fair	

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	mellitus: a placebo-controlled double-blind study. Diabet Med Mar; 10(2): 134-8		some at least wre not related to the drug.		
17	Fischer S, Hanefeld M, Spengler M, Boheme K, Temelkova-Kurktschiev T (1998) European study on dose-response relationship of acarbose as first-line drug in non-insulin-dependent diabetes mellitus: efficacy and safety of low and high doses. Acta Diabetolo Apr; 35(1): 34-40	RCT 495 pts 24 wks	The frequency of flatulence decreased with the duration of drug therapy, but we could not find a linear relationship between doses of acarbose and the gastrointestinal side effects.	Good	Less than 3 patients stopped tablet intake due to adverse events.
18	Wolever TM; Radmard R; Chiasson JL; Hunt JA; Josse RG; Palmason C; Rodger NW; Ross SA; Ryan EA; Tan MH (1995) One-year acarbose treatment raises fasting serum acetate in diabetic patients. Diabet Med Feb; 12(2): 164-72	RCT 85 pts 1 year	Compared to placebo, acarbose significantly increased fasting serum acetate. Acarbose treatment had no significant effect on serum cholesterol or non-esterified fatty acids, but was associated with a significant increase in flatulence. There was no relationship between changes in serum acetate and changes in HbA1c, serum cholesterol or symptoms. In conclusion, acarbose treatment increases serum acetate in subjects with diabetes who tolerated therapy for a 1-year period. The magnitude of change in acetate was unrelated to side effects or changes in blood glucose control or serum lipids.	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
19	Weaver GA; Tangel CT; Krause JA; Parfitt MM; Jenkins PL; Rader JM; Lewis BA; Miller TL; Wolin MJ (1997) Acarbose enhances human colonic butyrate production. J Nutr May; 127(5): 717-23	RCT -	Acarbose effectively augmented colonic butyrate production by several mechanisms; it reduced starch absorption, expanded concentrations of starch-fermenting and butyrate-producing bacteria and inhibited starch use by acetate- and propionate-producing bacteria.	Good to fair	
20	Coniff RF; Shapiro JA; Seaton TB; Bray GA (1995) Multicenter placebo controlled trial comparing acarbose with placebo, tolbutamide & tolbutamide-plus-acarbose in NIDDM Am J Med May; 98(5): 443-51	RCT 290 pts 30 wks	Acarbose alone or in combination with tolbutamide caused significantly more gastrointestinal adverse events (mainly flatulence & soft stools or diarrhoea) than tolbutamide or placebo, but these are generally well tolerated. Clinically significant elevations in hepatic transaminase levels occurred in 3 patients in the acarbose group and 2 in the acarbose-plus-tolbutamide group. Transaminase levels returned to normal when therapy was discontinued. Acarbose was well tolerated and effective in the management of NIDDM.	Good to fair	
	EFFICACY				
1	Salvatore T; Giugliano D (1996) Pharmacokinetic-pharmacodynamic relationships of acarbose.	Review article	Acarbose represents a new pharmacological approach to achieving the metabolic benefits of a slower carbohydrate absorption in diabetes, acting as a potent, competitive inhibitor of intestinal alpha-glucosidases. Apart from attenuation of	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Clin Pharmacokinet Feb; 30(2): 94-106		postprandial increases in blood glucose levels, other effects include a decreased beta-pancreatic response to meals, and influences on gut hormone secretion and plasma lipid levels. Acarbose can be used as first line therapy in patients with type 2 diabetes poorly controlled by diet alone, and help control type 1 diabetes in patients with 'brittle diabetes'. The lack of body weight gain or hypoglycemic effects may be advantageous for obese or elderly patients.		
2	Coniff RF; Shapiro JA; Seaton TB; Bray GA (1995) Multicenter placebo controlled trial comparing acarbose with placebo, tolbutamide & tolbutamide-plus-acarbose in NIDDM Am J Med May; 98(5): 443-51	RCT 290 pts 30 wks	All active H/S were superior to placebo in reducing postprandial hyperglycemia and Hb A1c levels. The ranking in order of efficacy was: acarbose-plus-tolbutamide (85 mg/dL), tolbutamide (71), acarbose(56) and placebo (13). Tolbutamide was associated with increases in body weight & postprandial insulin levels when taken alone, but these were ameliorated when tolbutamide was taken in combination with acarbose. Acarbose was effective in the treatment of NIDDM. Controol of glycemia was siggnificantly better with acarbose compared with diet alone. Acarbose-plus-tolbutamide was superior to tolbutamide alone.	Good to fair	
3	Yee HS; Fong NT (1996) A review of the safety and efficacy of acarbose in diabetes	Review article	Potential advantages of acarbose include greater effectiveness in controlling postpradial plasma glucose levels and overall decrease in the glycosylated	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	mellitus. Pharmacotherapy Sep-Oct; 16(5): 792-805		hemoglobin by 0.5-1.0%. Acarbose also offers a lower risk of hypoglycemia, and a possible delay in initiating insulin therapy.		
4	Campbell LK; White JR; Campbell RK (1996) Acarbose: its role in the treatment of diabetes mellitus. Ann Pharmacother Nov; 30(11): 1255-62	Review article	Acarbose is effective in reducing postprandial hyperglycemia, does not stimulate endogenous insulin secretion and, therefore, will not cause hypoglycaemia when used as monotherapy. The enhanced glycaemic control achieved with acarbose is additive to that of sulphonylureas. It lowers postprandial serum glucose and insulin concentrations and does not promote weight gain. Acarbose can be used as first line therapy with diet and exercise, or it can be used in combination with sulphonylureas to lower HbA1c concentrations at additional 0.5-0.9%. Acarbose, through its unique mechanism of action, appear to be a safe and effective adjunctive agent to diet/exercise therapy or sulphonylurea therapy for treatment of NIDDM.	Good to fair	
5	Deerochanawong C; Serirat S; Kornthong P (1996) Efficacy of acarbose as monotherapy in NIDDM patients. J Med Assoc Thai Feb; 79(2): 69-75	Open study	Acarbose (100 mg three times a day for 12 weeks) significantly decreased fasting and postprandial plasma glucose. HbA1c also significantly decreased from the baseline. The results indicate that treatment with acarbose is safe and effective in adjunct to dietary therapy for the treatment of NIDDM.	Good to fair	
6	Soonthornpun S, Rattarasarn C,	RCT	Acarbose was effective in lowering of 1-	Good to	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Thamprasit A, Leetanaporn K (1998) Effect of acarbose in treatment of type II diabetes mellitus: a double-blind, crossover, placebo-controlled trial. J Med Assoc Thai Mar; 81(3): 195-200	15 pts 12 wks	hour and 2-hour postprandial plasma glucose. Fasting plasma glucose was slightly decreased but without significant change. Overall glycemic control tended to improve during the study period as indicated by the falling of HbA1c levels from 7.7 +/- 0.4 to 7.0 +/- 0.2 per cent (p=0.05). Serum C-peptide both fasting and postprandial as well as serum lipid were not affected by acarbose. Almost half of the patients treated with acarbose had mild and tolerable gastro intestinal adverse effects. In conclusion, acarbose, as combined therapy with other oral hypoglycemic agents, was effective in improvement of glycemic control particularly postprandial hyperglycemia in fairly, well controlled NIDDM patients with mild and acceptable adverse effects.	fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
7	Sieradzki J; Soszynski P (1999) Evaluation of acarbose efficacy and safety for treatment of diabetes mellitus. Testing of observations under general health care conditions. Przegl Lek 56(5): 335-41	RCT 480 pts (the whole pts population consisted of 600 pts) 8 wks	Significant weight and BMI loss was observed in the whole studied group. Fasting and 2 hours postprandial glycaemia was markedly improved in the whole studied population, and particularly in those who was initially qualified into the group of bad diabetes control. The most favourable effect on glycaemia was observed for acarbose monotherapy when compared to combined treatment. No difference was found in the glycaemic response refered to the initial body mass index. Tested lipid parameters improved during 8-week observation: serum cholesterol level decreased but did not reached presumed statistical significance. Significant improvement was noted in triglyceride levels.	Good	Fasting blood glucose was the criteria of inclusion into the analysis
8	Holman RR; Cull CA; Turner RC (1999) A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (UK Prospective Diabetes Study 44). Diabetes Care Jun; 22(6): 960-4	RCT 1,946 pts 3 years	Analysis by intention to treat showed that patients allocated to acarbose, compared with placebo, had 0.2% significantly lower median HbA1c at 3 years. In patients remaining on their allocated therapy, the HbA1c difference at 3 years (309 acarbose, 470 placebo) was 0.5% lower median HbA1c. Acarbose appeared to be equally efficacious when given in addition to diet alone; in addition to monotherapy with a sulphonylurea, metformin, or insulin; or in combination with more complex treatment regimens. No significant differences were seen in fasting plasma glucose, body	Good	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			weight, incidence of hypoglycemia, or frequency of major clinical events. Conclusion: Acarbose significantly improved glycemic control over 3 years in patients with established type 2 diabetes, irrespective of concomittent therapy for diabetes.		
9	Fischer S, Hanefeld M, Spengler M, Boheme K, Temelkova-Kurktschiev T (1998) European study on dose-response relationship of acarbose as first-line drug in non-insulin-dependent diabetes mellitus: efficacy and safety of low and high doses. Acta Diabetolo Apr; 35(1): 34-40	RCT 495 pts 24 wks	Even a low dosage of 25 mg t.i.d. acarbose was found to reduce fasting and postprandial blood glucose levels (1 h postprandial –11.6%; 2 h post prandial –11.3%). Acarbose in a dosage of 200 mg t.i.d. had the greatest effect on these parameters. In the placebo group the mean 2 h postprandial area under the curve (AUC) value for blood glucose was 22.6 mmol/l after 24 weeks' therapy. The mean 2 h postprandial AUC values in the patients given acarbose at doses of 25, 50, 100 and 200 mg t.i.d. were found to be 21.2, 19.6, 20.3 and 18.5 mmol/l, respectively. The corresponding HbA1c values for the placebo and acarbose groups were 7.83%, 7.3%, 7.08%, 6.98% and 6.79%. There was a plateau of blood glucose level at a dosage of 50-100 mg t.i.d.	Good	
10	Ozgen AG; Hamulu F; Bayraktar F; Cetinkalp S; Yilmaz C; Tuzun M; Kabalak T (1998)	RCT 21 pts	Before treatment, 18 pts had hypoglycemic symptoms during oral glucose tolerance test (OGTT). Following 3 months of acarbose treatment, the lowest plasma glucose levels	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Long term treatment with acarbose for the treatment of reactive hypoglycemia. Eat Weight Disord Sep; 3(3): 136-40	3 months	at the 3rd and 4th hours increased and plasma insulin and c-peptide levels were reduced. Plasma glucose levels were significantly increased during the last 3 hours. Frequency of hypoglycemic attacks was reduced from 4 times a week to 1. C-peptide levels in 24-hour urine collection did not change significantly. These results confirm that acarbose may be of value in preventing reactive hypoglycemia by reducing the early hyperglycemic stimulus to insulin secretion, and in the treatment of reactive hypoglycemia.		
11	Meneilly GS; Ryan EA; Radziuk J; Lau DC; Yale JF; Morais J; Chiasson JL; Rabasa-Lhoret R; Maheux P; Tessier D; Wolever T; Josse RG; Elahi D (2000) Effect of acarbose on insulin sensitivity in elderly patients with diabetes. Diabetes Care Aug; 23(8): 1162-7	RCT 23 pts in placebo group, 22 pts in acarbose group 12 month	There was significant difference in the change in fasting plasma glucose levels and in incremental postprandial glucose values between groups. There was a significant difference in the change in HbA(1c) values in response to treatment. The change in fasting insulin in response to treatment and incremental postprandial insulin responses was also significantly different between groups. During the hyperglycemic clamps, glucose and insulin values were similar in both groups before and after therapy. However, there was a significant difference in the change in insulin sensitivity in response to treatment between the placebo and the acarbose groups. In conclusion, acarbose increases insulin sensitivity but not insulin release in elderly	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			patients with diabetes.		
12	Costa B, Pinol C. Acarbose in ambulatory treatment of non-insulin-dependent diabetes mellitus associated to imminent sulphonylurea failure: randomized-multicentric trial in primary health-care. Diabetes and Acarbose Research Group. Diabetes Res Clin Pract 1997 Oct; 38(1): 33-40	RCT 65 pts 6 months	Acarbose-treated patients significantly reduced HbA1c levels (9.0/7.9 vs 8.8/8.5%; P<0.01), based upon a marked decrease but statistically not significant, in mean post prandial plasma glucose levels (11.9/9.6 vs 12.4/11.1 mmol/l). No significant differences between fasting plasma glucose and lipid profile were detected.	Good to fair	
13	Rosentock J, Brown A, Fisher J, Jain A, Littlejohn T, Nadeau D, Sussman A, Taylor T, Krol A, Magner J (1998) Efficacy and safety of acarbose in metformin-treated patients with type 2 diabetes. Diabetes Care Dec; 21(12): 2050-5	RCT -31 wks	The addition of acarbose to patients on background metformin and diet therapy showed a statistically significant reductions in HbA1c and fasting and postprandial plasma glucose and serum insulin levels compared with placebo.	Good to fair	
14	Hotta N; Kakuta H; Sano T; Matsumae H; Yamada H; Kitazawa S; Sakamoto N (1993) Long-term effect of acarbose on glycaemic control in non-insulin-dependent diabetes mellitus: a placebo-controlled	24 wks	In the acarbose group, the 2 h postprandial blood glucose and haemoglobin A1 levels decreased significantly. In the placebo group, the 2 h postprandial blood glucose and the haemoglobin A1 level showed no significant changes. A 75 g oral glucose tolerance test was performed before and after the study, the difference not being significant in either the acarbose group or	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	double-blind study. Diabet Med Mar; 10(2): 134-8		the placebo group.		
15	Rodger NW; Chiasson JL; Josse RG; Hunt JA; Palmason C; Ross SA; Ryan EA; Tan MH; Wolever TM (1995) Clinical experience with acarbose: results of a Canadian multicentre study. Clin Invest Med Aug; 18(4): 318-24	RCT 1 year	The addition of acarbose in all 4 treatment groups (those managed by diet only, diet and sulphonylurea, diet and biguanide, and diet and insulin) resulted in significant reductions in postprandial blood glucose levels. HbA1C was significantly lower after 12 months of acarbose therapy, cxompared with placebo, in all groups except the diet and insulin group.	Good to fair	
16	Coniff R; Krol A (1997) Acarbose: a review of US clinical experience. Clin Ther Jan-Feb; 19(1): 16-26; discussion 2-3	Review article	Acarbose in doses up to 100 mg three times daily for periods up to 16 weeks, was significantly superior to placebo with respect to mean reduction in HbA1c levels and mean 1-hour postprandial glucose levels.	Good to fair	
17	Hoffman J; Spengler M (1997) Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II Study. Am J Med Dec; 103(6): 483-90	RCT 96 pts 24 wks	Both acarbose and metformin showed the same improvement of efficacy criteria compared with placebo. For fasting and 1 hour postprandial blood glucose, acarbose vs placebo and metformin versus placebo were statistically significant, but not acarbose vs metformin. No effect on fasting insulin could be observed. Relative postprandial insulin increase was statistically significant for	Good to fair	Only 94 patients were valid for efficacy evaluation

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			acarbose vs placebo and metformin vs placebo, but not acarbose vs metformin. With respect to lipid profile, acarbose was superior to metformin; acarbose vs placebo and acarbose vs metformin were statistically significant, but not metformin vs placebo.		
18	Rosliakova LV; Roijtman AP; Ametov AS; Dolgov VV (2000) Acarbose (glucobai) effects on lipid metabolism in patients with non-insulin dependent diabetes mellitus. Ter Arkh 72(8): 54-6	RCT 63 pts 6 months	Glucobai has improved glycemic profiles, reduced insulinemia and body mass index, trigliserides, total cholesterol, artherogenic index. Blood levels of HDLP cholesterol elevated by 62%. In conclusion, long term intake of acarbose improves carbohydrate metabolism and produces a hypolipidemic effect.	Abs?	
19	Kendrup H; Bongers H; Spengler M: Kusenbach G: Skopnik H (1999) Efficacy and safety of acarbose min patients with cystic fibrosis and impaired glucose tolerance. Eur J Pediatr Jun; 158(6): 455-9	RCT 12 pts 2 wks	Treatment with acarbose was associated with significant reductions in the mean value, mean peak values and the area under the curve of plasma glucose, insulin and C-peptide, compared to respective baseline values and placebo. Conclusion: Acarbose has a positive therapeutic effect on glucose tolerance in cystic fibrosis patients, as shown by attenuation of postprandial plasma glucose increase and a significant decrease in insulin secretion response.	Good to fair	
20	Sels JP; Verdonk HE; Wolffenbuttel BH (1998) Effects of acarbose (Glucobay) in persons with type 1 diabetes:	RCT 62 pts	During the placebo run-in period, HbA1c levels tended to decrease from 8.9 +/- 1.1 to 8.5 +/- 0.9%. After 8 and 16 weeks of acarbose treatment, the mean level had decreased further to 8.1 +/- 0.9 and 8.2 +/-	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	a multicentre study. Diabetes Res Clin Pract Aug; 139-45	16 weeks	0.9%, respectively. After stopping acarbose HbA1c levels increased again to mean level of 8.6 +/- 0.9%. None of these changes over time reached statistical significance except for a significant drop during acarbose treatment of the time-point 90 min after lunch. After stopping acarbose treatment, values returned to pre-study levels. Conclusion: Acarbose up to 3 x 100 mg/day can be a valuable adjunct to insulin in improving metabolic control in persons with type 1 diabetes.		
21	Lam KS; Tiu SC; Tsang MW; Dp TP; Tam SC (1998) Acarbose in NIDDM patients with poor control on conventional oral agents. A 24 week placebo-controlled study. Diabetes Care July; 21(7): 1154-8	RCT 90 patients 24 wks	Acarbose treatment was associated with significantly greater reductions in HbA1c (-0.5+/- 0.2% vs. placebo 0.1+/- 0.2%), 1-h postprandial glucose (-2.3+/- 0.4 mmol/l vs. placebo 0.7+/-0.4mmol/l) and body weight (-0.54+/-0.32kg vs.placebo 0.42+/-0.29kg). There was no significant difference between the 2 gps regarding changes in FPG and lipids or fasting and postprandial insulin levels. In NIDDM pts inadequately controlled on conventional oral agents, acarbose in moderate doses resulted in beneficial effects on glycemic control esp. postprandial glycemia & mean body wt. Additional use of acarbose can be considered as a useful alternative in such pts if they are reluctant to accept insulin therapy.	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	REPAGLINIDE-SAFETY				
1	Goldberg RB, Einhorn D, Lucas CP, Rendell MS, Damsbo P, Huang WC, Strange P, Brodows RG (1998) A randomized placebo-controlled trial of repaglinide in the treatment of type 2 diabetes. Diabetes Care Nov;21(11):1897-903	99 patients RCT	repaglinide was well tolerated	Abs	
2	Wolffenbuttel BH; Landgraf R (1999) A 1-year multi center randomized double blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. Dutch & German Repaglinide Study Gp. Diabetes Care Mar; 22(3); 463-7	RCT 424 pts 12 mths	15% of the repaglinide treated and 13% of glyburide treated subjects withdrew due to adverse events mostly hyperglycaemia. No difference in adverse events between both drugs were reported. There were no differences in incidences of hypoglycaemia. Repaglinide is a safe oral blood glucose lowering agent with a potency similar to that of glyburide.	Good to fair	
3	Landgraf R; Bilo HJ; Muller PG (1999) A comparison of repaglinide and glibenclamide in the treatment of type 2 diabetic pts previously treated with	RCT 195 pts 14 weeks	Repaglinide and glibenclamide were both well tolerated. No significant differences were observed between the 2 treatment gps with respect to adverse events, including hypoglycaemic episodes and weight change. No accumulation of repaglinide was apparent during the maintainence	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	sulphonylureas. Eur J Clin Pharmacol May; 55(3): 165-71		period. Repaglinide is well tolerated as glibenclamide & is equally effective in the management of type 2 DM.		
4	Marbury T, Huang WC, Strange P, Lebovitz H (1999) Repaglinide versus glyburide: a one-year comparison trial. Diabetes Res Clin Pract Mar;43(3):155-66	RCT prospective, 1-year, multicenter, double-blind, 576 patients	Repaglinide, at doses of 0.5-4.0 mg administered three times preprandially, was well tolerated and provided safe and consistently effectiveglycemic control during this 1-year study. Patients using repaglinide received the same therapeutic benefits as those using glyburide, and may have received additional benefits.	Abs	
5	Strange P, Schwartz SL, Graf RJ, Polvino W, Weston I, Marbury TC, Huang WC, Goldberg RB (1999) Pharmacokinetics, pharmaco-dynamics, and dose-response relationship of repaglinide in type 2 diabetes. Diabetes Technol Ther Fall;1(3):247-56	143 patients. RCT	Repaglinide was well tolerated in patients with type 2 diabetes.	Abs	
6	Jovanovic L, Dailey G 3rd, Huang WC, Strange P, Goldstein BJ (2000)	361 patients having type 2 diabetes	Repaglinide was well tolerated in a preprandial fixed-dose regimen of 1 mg or 4 mg, assigned without adjustment for	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Repaglinide in type 2 diabetes: a 24-week, fixed-dose efficacy and safety study. J Clin Pharmacol Jan;40(1):49-57	RCT multicenter study	clinical parameters.		
7	Schatz H (1999) Preclinical and clinical studies on safety and tolerability of repaglinide. Exp Clin Endocrinol Diabetes 107 Suppl 4:S144-8	Review. A total of five active-controlled, long-term trials of identical design have been carried out (with 12 months of maintenance on a fixed, pretitrated dose), including 1228 patients on repaglinide and 597 on sulphonylureas, 417 of whom were on glibenclamide.	The most common adverse event in the phase II studies was hypoglycaemia. The frequency of hypoglycaemia was identical for repaglinide and sulphonylureas; however, fewer nocturnal hypoglycaemic events were observed with repaglinide and no increase in the frequency of hypoglycaemic events occurred in elderly patients (> 65 years) compared with younger patients. Severe reactions (assistance required) were approximately twice as frequent in the comparator group. During these studies, two serious hypoglycaemic reactions were reported (coma, seizure or hospitalization), both occurring in patients on glibenclamide. The frequency of serious adverse events and serious cardiovascular events was comparable between repaglinide and sulphonylureas.	Abs	
	REPAGLINIDE –EFFICACY				
1	Jovanovic L, Dailey G 3rd, Huang WC, Strange P,	361 patients having type 2 diabetes RCT	Repaglinide 1 mg or 4 mg treatment decreased mean fasting plasma glucose	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Goldstein BJ (2000) Repaglinide in type 2 diabetes: a 24-week, fixed-dose efficacy and safety study. J Clin Pharmacol Jan;40(1):49-57	multicenter study	(FPG) values (by -47 mg/dL or -49 mg/dL) while the placebo group had increased FPG values (by 19 mg/dL). For the repaglinide treatment groups at the end of the study, changes in HbA1c from baseline values ranged from 1.8 to 1.9 percentage points lower than the placebo group.		
2	Strange P, Schwartz SL, Graf RJ, Polvino W, Weston I, Marbury TC, Huang WC, Goldberg RB (1999) Pharmacokinetics, pharmaco-dynamics, and dose-response relationship of repaglinide in type 2 diabetes. Diabetes Technol Ther Fall;1(3):247-56	143 patients. RCT	Blood concentrations of repaglinide were proportional to the dose administered. INS mean values increased in all repaglinide treatment groups (by 6.7 to 12.9 microU/mL). All doses of repaglinide significantly decreased values of BG mean and FSG as compared with the placebo group. BG mean values stabilized between the second and third week of repaglinide treatment. A well-defined dose-response relationship was observed for BG mean and FSG values. All doses of repaglinide were well tolerated, and there were no serious adverse events. CONCLUSIONS: the therapeutic reduction of serum glucose levels produced by repaglinide is dose-dependent for the 0.25- to 4-mg dose range. All doses of repaglinide tested were effective in patients with type 2 diabetes.	Abs	
3	Landgraf R; Bilo HJ; Muller PG (1999) A comparison of repaglinide and glibenclamide in the treatment of type 2 diabetic pts	RCT 195 pts 14 weeks	By the end of the study, the 2-hr postprandial blood glucose values were lower in the repaglinide group (8.1 mmol/l) than in the glibenclamide gp (9.1 mmol/l). Baseline HbA1c values had decreased to the same degree in both. There are no	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	previously treated with sulphonylureas. Eur J Clin Pharmacol May; 55(3): 165-71		significant differences between both the gps in the levels of fasting blood glucose, fructosamine, fasting-c-peptide, insulin & proinsulin. Repaglinide is equally effective as glibenclamide in the management of type 2 diabetes. Repaglinide may however offer an improvement in PPG compared with glibenclamide thereby helping to reduce the relative long-term risk of diabetic complications.		
4	Van Gaal LF, Van Acker KL, De Leeuw IH (2001) Repaglinide improves blood glucose control in sulphonylurea-naive type 2 diabetes. Diabetes Res Clin Pract Sept;53(3):141-8	25 patients RCT	Repaglinide associated with a decrease in HbA(1c) of 2.3%Hb relative to the placebo group P=0.018). Repaglinide also associated with a decrease in fructosamine, by 0.88 mmol/l, relative to placebo (P<0.001), with a 20% decrease (from 3.80 to 3.04 mmol/l) within the repaglinide group (P<0.001). Fasting and postprandial blood glucose concentrations decreased in association with repaglinide by 3.6 and 6.4 mmol/l, respectively, relative to placebo (P<0.001 in each case). Within the repaglinide group fasting and postprandial blood glucose decreased by 3.9 and 6.2 mmol/l, respectively (P<0.001 in each case). The number of patients reporting hypoglycaemia in the repaglinide group was similar to placebo (15 vs. 20, respectively; NS). Test meal assessments confirmed repaglinide effectively controls glucose levels by stimulating mealtime insulin secretion. Fasting serum insulin concentration not raised compared to	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			baseline or placebo during repaglinide therapy, albeit that fasting glucose levels were decreased by repaglinide. Concl:,Twice-daily meal-related insulin secretagogue therapy with repaglinide, a new short and rapid-acting prandial glucose regulator, is capable of improving all measures of glycaemic control without increased hypoglycaemia or fasting hyperinsulinaemia		
5	Madsbad S, Kilhovd B, Lager I, Mustajoki P, Dejgaard A; Scandinavian Repaglinide Group (2001) Comparison between repaglinide and glipizide in Type 2 diabetes mellitus: a 1-year multicentre study. Diabet Med May;18(5):395-401	RCT	Fasting blood glucose decreased in the repaglinide group by 2.4 mmol/l and increased in the glipizide group by 1.0 mmol/l ($P < 0.05$ between groups). In the study population as a whole, repaglinide was able to maintain glycaemic control (HbA1c level) during the 1-year study period, whereas control deteriorated significantly with glipizide. Change in HbA1c from baseline was significantly better with repaglinide than with glipizide after 12 months ($P < 0.05$). In addition, FBG deteriorated significantly in the glipizide group than repaglinide group ($P < 0.05$). No patients in either group experienced major hypoglycaemic event; the number of patients experiencing minor hypoglycaemia was similar in the repaglinide and glipizide groups (15% and 19%, respectively). CONCLUSIONS: Repaglinide, given as a prandial glucose regulator, is shown to be effective treatment of patients with Type 2 diabetes, and better than glipizide in controlling HbA1c and	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			FBG levels, overall, and in OHA-naïve patients.		
6	Wolffenbuttel BH; Landgraf R (1999) A 1-year multi center randomized double blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. Dutch & German Repaglinide Study Gp. Diabetes Care Mar; 22(3); 463-7	RCT 424 pts 12 mths	The trial was completed by 320 subjects, 211 (74%) in the repaglinide and 109 (78%) in the glyburide gp. HbA1c initially decreased in both gps and then increased during the second half year of the maintainence period to a similar extent in the repaglinide and glybunide subjects (0.58 & 0.45% vs. at screening; respectively). In the small gp of subjects who previously controlled their condition with diet only (n=37) a sustained improvement of metabolic control could be observed with both drugs, which slightly better with glyburide than repaglinide. Same trends were seen with FPG. Repaglinide is a efficacious oral blood glucose-lowering agent with a potency similar to that of glyburide.	Good to fair	15 % of the repaglinide-treated & 13% of glyburide-treated subjects withdrew due to adverse events, mostly hyperglycaemia
7	Marbury T, Huang WC, Strange P, Lebovitz H (1999) Repaglinide versus glyburide: a one-year comparison trial. Diabetes Res Clin Pract Mar;43(3):155-66	RCT prospective, 1-year, multicenter, double-blind, 576 patients	Repaglinide provided glycemic control -at least as effective and potentially safer than that provided by glyburide. The glucose-lowering effect of repaglinide was most pronounced in pharmacotherapy-naive patients, who showed rapid and marked decreases in mean glycosylated hemoglobin levels from baseline (9.4%) to month 3 (7.6%) and month 12 (7.9%). Mean FPG levels also decreased overall in this group, from 222 mg/dl at baseline, to 175 mg/dl at month 3,	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			to 188 mg/dl at month 12. At endpoint, morning C-peptide levels increased significantly in glyburide-treated patients compared with those treated with repaglinide, but morning fasting insulin levels did not differ significantly between the two groups. Repaglinide efficacy was sustained over 1 year and not influenced by age or sex		
8	Goldberg RB, Einhorn D, Lucas CP, Rendell MS, Damsbo P, Huang WC, Strange P,Brodows RG (1998) A randomized placebo-controlled trial of repaglinide in the treatment of type 2 diabetes. Diabetes Care Nov;21(11):1897-903	99 patients RCT	Mean HbA1c decreased from 8.5 to 7.8% in patients treated with repaglinide and increased from 8.1 to 9.3% in patients receiving placebo, with a statistically significant difference of - 1.7% ($P < 0.0001$) between treatment groups at the last visit. Mean fasting plasma glucose and postprandial glucose increased in patients receiving placebo and decreased in patients treated with repaglinide, with statistically significant ($P < 0.01$) differences between groups at the last visit. Concentrations of fasting and postprandial insulin and C-peptide were lower at the last visit compared with baseline for patients treated with placebo and higher for patients treated with repaglinide, and the differences between groups were statistically significant ($P < 0.05$). CONCLUSIONS: This study demonstrated that repaglinide was efficacious in lowering blood glucose concentrations.	Abs	
	ROSIGLITAZONE-SAFETY				

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
1	Lebovitz HE, Dole JF, Patwardhan R, Rappaport EB, Freed MI (2001) Rosiglitazone monotherapy is effective in patients with type 2 diabetes. J Clin Endocrinol Metab Jan; 86 (1) : 280-8	RCT patients 26 weeks	Urinary albumin excretion decreased significantly in the rosiglitazone (4 mg bd) group. There was no increase in adverse events with rosiglitazone. In the short-term, rosiglitazone is an insulin sensitizer that is safe as monotherapy in patients with type 2 diabetes who are inadequately controlled by lifestyle interventions.	Good to fair	
2	Raskin Rappaport EB, Cole ST, Yan Y , Patwardhan R, Freed MI (2000) Rosiglitazone short term monotherapy lowers fasting and postprandial glucose in patients with type 2 diabetes. Diabetologia Mar; 43 (3) :273-84	RCT 303 pts 8 weeks	Total LDL & HDL cholesterol were increased significantly in the rosiglitazone treatment groups but the total cholesterol/HDL ratios did not change significantly. The proportion of patients with one or more adverse events was similar in all 4 treatment groups. No pt showed evidence of hepatotoxicity. Rosiglitazone given twice daily was safe and well tolerated in patients with type 2 diabetes.	Good	
3	Nolan JJ; Jones NP; Patwardhan R; Deacon LF (2000) Rosiglitazone taken once daily provides effective glycaemic control in pts with type 2 DM. Diabet Med Apr; 17(4) : 287-94	RCT 369 pts 8 weeks	The overall incidence of adverse experiences was similar in all treatment groups including placebo with no evidence of hypoglycaemia or hepatotoxicity. Rosiglitazone is well tolerated at doses up to and including 12 mg.	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
4	Phillips LS, Grunberger G, Miller E, Patwardhan R, Rappaport EB, Salzman A (2001) Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. Diabetes Care Feb;24(2): 303-15	RCT patients 26 weeks.	The proportion of patients with at least one adverse event were comparable among the rosiglitazone and placebo groups. There was no evidence of hepatotxicity in any treatment group. There were statistically significant increases in weight and serum lipids in all rosiglitazone treatment groups compared with placebo. For LDL and HDL cholesterol, the observed increase appeared to be dose related. Rosiglitazone at total daily doses of 4 and 8 mg significantly improved glycemic control in patients with type 2 diabetes and was well tolerated.	Good	
	ROSIGLITAZONE-EFFICACY				
1	Nolan JJ; Jones NP; Patwardhan R; Deacon LF (2000) Rosiglitazone taken once daily provides effective glycaemic control in pts with type 2 DM. Diabet Med Apr; 17(4) : 287-94	RCT 369 pts 8 weeks	At 8 wks, FPG decreased significantly in the rosiglitazone 4mg, 8mg & 12 mg gps (-0.9, -2.0 & -1.7 mmol/l) compared with placebo (+0.4 mmol/l). The improvements in FPG were dose ordered for 4 & 8 mg/day. The 12 mg/day dose produced no additional improvement. Rosiglitazone improves glycaemic control when given once daily to treat type 2 DM.	Good to fair	
2	Phillips LS, Grunberger G, Miller E, Patwardhan R, Rappaport EB, Salzman A (2001)	RCT patients	Rosiglitazone produced dosage-dependent reductions in HbA1c of 0.8, 0.9, 1.1, and 1.5% in the 4 mg o.d, 2 mg b.i.d, 8 mg o.d., and 4 mg b.i.d groups, respectively, compared with placebo.	Good	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. Diabetes Care Feb;24(2): 303-15	weeks.	Approximately 33% of drug –naïve patients treat with rosiglitazone achieved HbA1c < or =7% at study end. Rosiglitazone at total daily doses of 4 and 8 mg significantly improved glycemic control in patients with type 2 diabetes		
3	Raskin Rappaport EB, Cole ST, Yan Y , Patwardhan R, Freed MI (2000) Rosiglitazone short-term monotherapy lowers fasting and postprandial glucose in patients with type 2 diabetes. Diabetologia Mar; 43 (3) : 273-84	RCT 303 pts 8 weeks	All rosiglitazone doses (2,4 or 6 mg twice daily) significantly reduced FPG compared with baseline. All rosiglitazone treatment gps showed significantly reduced peak postprandial glucose concentration compared with baseline and with placebo. Rosiglitazone given twice daily significantly reduced fasting and postprandial glucose concentration in type 2 diabetes pts. The glucose lowering effect of the 4 mg twice daily dose was similar to that of 6mg twice daily, suggesting that 4mg twice daily should be the max clinical dose.	Good to fair	
	COMBINATION THERAPY- SAFETY				
1	Wolffenbuttel BH, Gomis R, Squatrite S, Jones NP, Patwardhan RN (2000) Addition of low dose rosiglitazone to sulphonylurea therapy improves glycaemic control in type 2 diabetic patients.	RCT 574 pts 26 weeks	The overall incidence of adverse experiences was similar in all three treatment gps with no significant cardiac events, hypoglycaemia or hepatotoxicity. The combination of gliclazide and rosiglitazone was safe & well tolerated in pts with type 2 diabetes.	Good	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Diabet Med Jan; 17(1) : 40-7				
2	Standl E, Schernthaner G, Rybka J, Hanefeld M, Raptis SA, Naditch (2001) Improved glycaemic control with miglitol in inadequately-controlled type 2 diabetics. Diabetes Res Clin Pract Mar; 51(3): 205-13	RCT 154 pts 24 wks	Flatulence and diarrhea were reported by statistically, significantly more patients receiving miglitol than placebo, but adverse events overall were reported by only 10 more patients in the miglitol group. No cases of hypoglycaemia were reported. Conclusion: Miglitol can be safely added to long-term combination therapy in people with Type 2 diabetes inadequately controlled with glibenclamide plus metformin.	Good	
3	Coniff RF; Shapiro JA; Seaton TB; Bray GA (1995) Multicenter placebo controlled trial comparing acarbose with placebo, tolbutamide & tolbutamide-plus-acarbose in NIDDM Am J Med May; 98(5): 443-51	RCT 290 pts 30 wks	Acarbose alone or in combination with tolbutamide caused significantly more gastrointestinal adverse events (mainly flatulence & soft stools or diarrhoea) than tolbutamide or placebo, but these are generally well tolerated. Clinically significant elevations in hepatic transaminase levels occurred in 3 patients in the acarbose group and 2 in the acarbose-plus-tolbutamide group. Transaminase levels returned to normal when therapy was discontinued. Acarbose was well tolerated and effective in the management of NIDDM.	Good	
	COMBINATION THERAPY - EFFICACY				
1	F. Gregorio; F. Ambrosit; S. Manfrini; M. Velussi, F. Carle; R. Testa; D. Merante; P.	RCT 174 patients	Similar improvements in glycemic levels were observed with both treatment (Sulphonylurea increased up to max. and	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Filipponi Poorly Controlled Elderly Type 2 Diabetic Patients: The Effects of Increasing Sulphonylurea Dosages or adding Metformin. Diabetic Medicine;16:1016-1024	18 months	sulphonylurea + metformin) within the first month. Similar decrease HbA_{1c} within third month. Glycemic control no further changed. In first group; fasting glucose decrease from 14.21 to 9.88, average day long glucose from 14.87 to 10.69 and HbA_{1c} from 1.32% to 8.66%. In 2 group; fasting glucose decreased from 14.59 to 9.05, average day long glucose from 15.09 to10.32 and HbA_{1c} from 10.33 to 8.77 (for all $P<0.0005$). In this 2nd group a decrease in LDL-cholesterol ($P<0.05$) and increase in HDL-cholesterol levels ($P<0.02$). 1st group, anthrombin III activity increase significantly ($P<0.01$). In 2nd group significant reduction in marker of platelete function ($P<0.01$), thrombin generation ($P<0.01$) and fibrinolysis inhibition ($P<0.001$). Increase in some fibrinolytic activation markers ($P<0.010$). fasting lactate concentration were unchanged in metformin treated group. Either high sulphonylurea dosage or a therapy combining lower sulphonylurea dosages with metformin are effective.and safe in an aged but healthy population. Metformin provides additional benefits countracting several cardiovascular risk factors but must be administered with caution, bearing in mind the general contraindication for drug but not age alone.		
2	Standl E, Schernthaner G, Rybka J, Hanefeld M, Raptis SA, Naditch (2001)	RCT 154 pts	Addition of miglitol to sulphonylureas and metformin produced a statistically, significantly greater reduction in HbA1c	Good	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Improved glycaemic control with miglitol in inadequately-controlled type 2 diabetics. Diabetes Res Clin Pract Mar; 51(3): 205-13	24 wks	and postprandial glucose. Reduction in fasting blood glucose was greater with miglitol than placebo, and there was possible difference in favor of miglitol for fasting and postprandial triglyceride levels, but these did not reach statistical significance. Conclusion: Miglitol can effectively be added to long-term combination therapy in people with Type 2 diabetes inadequately controlled with glibenclamide plus metformin.		
3	Wolffenbuttel BH, Gomis R, Squatrite S, Jones NP, Patwardhan RN (2000) Addition of low dose rosiglitazone to sulphonylurea therapy improves glycaemic control in type 2 diabetic patients. Diabet Med Jan; 17(1) : 40-7	RCT 574 pts 26 weeks	Mean baseline HbA1c was 9.2% & FPG was 11.4 mmol/l. Gliclazide plus rosiglitazone produced significant decrease compared with gliclazide plus placebo in HbA1c and FPG. The combination of gliclazide and rosiglitazone was effective in pts with type 2 diabetes.	Good	
4	Fonseca V; Rosenstock J; Patwardhan R; Salzman A (2000) Effect of metformin & rosiglitazone combination therapy in pts with type 2 DM, a RCT. JAMA Apr 5; 283(13): 1695-702	RCT 348 pts 26 wks	Glycosylated hemoglobin levels, FPG levels, insulin sensitivity & beta-cell function improved significantly with metformin-rosiglitazone therapy in a dose-dependent manner. Dose-dependent increases in body weight. Combination treatment with once-daily metformin-rosiglitazone improves glycaemic control, insulin sensitivity and beta-cell function more effectively than	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			treatment with metformin alone.		
5	Prof Robert Turner, UKPDS Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) The Lancet Vol. 352:83753 Sept.	RCT 3867 pts 10 years	There was an 11% reduction in HbA1c level in the intensive group compared with the conventional group. Compared with the conventional group, the risk in the intensive group was 12% lower for any diabetes-related endpoint; 10% lower for any diabetes-related death; and 6% lower for all-cause mortality. Most of the risk reduction in any diabetes-related end-point aggregate endpoint was due to a 25% risk reduction in microvascular endpoints, including the need for retinal photocoagulation. There was no difference for any of the three intensive agents (chlorpropamide, glibenclamide, or insulin).	Abs	
6	Prof Robert Turner,UKPDS Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) The Lancet Vol. 352:85465 Sept.	RCT	In patients with type 2 diabetes, intensive blood glucose control decreases progression of microvascular disease and may reduce the risk of heart attacks. 4075 patients in 15 centres and 1074 of them are overweight.	Abs	
7	Coniff RF; Shapiro JA; Seaton TB; Bray GA (1995) Multicenter placebo controlled trial comparing acarbose with	RCT 290 pts 30 wks	All active H/S were superior to placebo in reducing postprandial hyperglycemia and Hb A1c levels.The ranking in order of efficacy was: acarbose-plus-tolbutamide (85 mg/dL), tolbutamide (71), acarbose(56) and placebo (13). Tolbutamide was	Good	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	placebo, tolbutamide & tolbutamide-plus-acarbose in NIDDM Am J Med May; 98(5): 443-51		associated with increases in body weight & postprandial insulin levels when taken alone, but these were ameliorated when tolbutamide was taken in combination with acarbose. Acarbose was effective in the treatment of NIDDM. Control of glycemia was siggnificantly better with acarbose compared with diet alone. Acarbose-plus-tolbutamide was superior to tolbutamide alone.		
	INSULIN INSULIN ASPART- SAFETY				
1.	Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L (2000) Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. Diabetes Care May;23(5):583-8	RCT A multicenter randomized open-label 6-month study (882 subjects) with a 6-month extension period (714 subjects) that enrolled subjects with type 1 diabetes.HbA1c and post prandial glucose were measured at 0, 6 and 12 mth.	The study showed that insulin aspart (IAsp) provided significantly improved post prandial glycemic control compared with Human Insulin (HI) when used as the mealtime insulin in a multiple injection regimen. IAsp allowed mealtime injection without compromising standard safety parameters or otherwise bringing about an increase in hypoglycemic episodes or adverse events.	Good	
2	Bode BW, Strange P (2001) Efficacy, safety, and pump compatibility of insulin aspart used in continuous subcutaneous insulin infusion therapy in patients with type 1 diabetes. Diabetes Care Jan;24(1):69-72	A single-center randomized open-label study. Patients received continuos subcutaneous insulin infusion (CSII therapy) with insulin aspart (n = 19) or buffered regular human insulin (n = 10) for 7 weeks. 28 complete	Patients receiving insulin aspart had fewer hypoglycemic events per patient (2.9) than those patients receiving buffered regular human insulin (6.2). There were no differences between the two insulins in the occurrence of hyperglycemic events (blood glucose >19 mmol/l) or in the number and type of adverse events. CONCLUSIONS: Insulin aspart and buffered regular human insulin were both	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
		study , 1 from aspart withdrew and lost to f/up.	well tolerated, and suitable to be used with an external pump in CSII therapy.		
3	Amiel S, Home PD, Jacobsen JL, et al (2001) Insulin aspart safe for long-term treatment. Program and abstracts of the 37th Annual Meeting of the European Association for the Study of Diabetes (EASD); September 9-13,	753 patients with type 1 diabetes treated with either regular insulin or insulin aspart.	The frequency of major hypoglycemic events was similar in both groups, but there was a 24% increase in frequency of minor hypoglycemia, and a slower rate of increase in HbA1c in patients treated with insulin aspart. At 2.5 years, HbA1c was 0.2% lower in patients receiving insulin aspart	Abs	
4	Colagiuri S, Heller S, Vaaler S, et al (2001) Insulin aspart reduces the frequency of nocturnal hypoglycaemia in patients with type 1 diabetes. Program and abstracts of the 37th Annual Meeting of the European Association for the Study of Diabetes (EASD); September 9-13,	A 16-week crossover study of 155 patients with type 1 diabetes	Mild hypoglycemia in 38% of those treated with regular insulin vs 35% of patients treated with insulin aspart; severe nocturnal hypoglycemia was detected at a rate of 0.7 vs 0.2 episodes/year with regular insulin and insulin aspart, respectively. Hemoglobin A1c levels did not change from 7.7% with either insulin.	Abs	
5	Lyness W, Tyler J, Lawrence (2001) Pharmacokinetics of the rapid-acting insulin analog, insulin aspart, in subjects with impaired hepatic or renal function.		The pharmacokinetics of insulin aspart was similar in patients with or without renal dysfunction (not requiring dialysis) or hepatic dysfunction, suggesting that there should be comparable safety profiles in spite of these conditions.	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Program and abstracts of the 37th Annual Meeting of the European Association for the Study of Diabetes (EASD); September 9-13,				
	INSULIN ASPART - EFFECTIVENESS				
1	Bode BW, Strange P (2001) Efficacy, safety, and pump compatibility of insulin aspart used in continuous subcutaneous insulin infusion therapy in patients with type 1 diabetes. Diabetes Care Jan;24(1):69-72	This was a single-center randomized open-label study Patients received continuos subcutaneous insulin infusion (CSII therapy) with insulin aspart (n = 19) or buffered regular human insulin (n = 10) for 7 weeks.	Insulin aspart and buffered regular human insulin were both effective in controlling average daily blood glucose levels (8.2 +/- 1.9 and 8.5 +/- 2.1 mmol/l, respectively) (mean +/- SD) and maintaining serum fructosamine (343 +/- 25.7 and 336 +/- 27.4 micromol/l) and HbA1c (6.9 +/- 0.6 and 7.1 +/- 0.6%) levels. Similar numbers of patients experienced hypoglycemia (blood glucose <2.5 mmol/l): 14 (74%) insulin aspart patients versus 6 (60%) buffered regular human insulin patients.	Good to fair	
2	Setter SM, Corbett CF, Campbell RK, White JR (2000) Insulin aspart: a new rapid-acting insulin analog. Ann Pharmacother Dec;34(12):1423-31	Review	Insulin aspart is a convenient premeal insulin for use by patients requiring mealtime insulin. Furthermore, due to favorable pharmacokinetics, insulin aspart controls postprandial blood glucose concentrations at least as well as regular human insulin and contributes to improved quality of life.	Abs	
3	Brunner GA, Hirschberger S, Sendlhofer G, Wutte A,	RCT 20 Type 1 diabetic	With regard to prandial glycaemia IAsp(+15min) is as effective as HI(-5min)	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Ellmerer M, Balent B, Schaupp L, Krejs GJ, Pieber TR (2000) Post-prandial administration of the insulin analogue insulin aspart in patients with Type 1 diabetes mellitus. Diabet Med May;17(5):371-5	patients	and superior to HI(0min). Thus, post-prandial dosing of the insulin analogue IAsp offers an attractive and feasible therapeutic option for well-controlled patients with Type 1 diabetes mellitus		
4	Rosenfalck AM, Thorsby P, Kjems L, Birkeland K, Dejgaard A, Hanssen KF, Madsbad S (2000) Improved postprandial glycaemic control with insulin Aspart in type 2 diabetic patients treated with insulin. Acta Diabetol Mar;37(1):41-6	The effect on postprandial blood glucose control of immediately pre-meal injection of rapid acting insulin analogue Aspart (IAsp) compared with human insulin Actrapid injected immediately or 30 minutes before a test meal in insulin-treated type 2 diabetic patients with residual beta-cell function 22 patients	A significantly improved postprandial glucose control was demonstrated with IAsp as compared to Act0, based on a significantly smaller postprandial blood glucose. These results indicate that the improved glucose control previously demonstrated with insulin Aspart compared to human insulin in healthy subjects and type 1 diabetic patients also applies to insulin-treated type 2 diabetic patients.	Abs	
5	Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L (2000) Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes.	RCT This was a multicenter randomized open-label 6-month study (882 subjects) with a 6-month extension period (714 subjects) that enrolled subjects with type 1 diabetes	Postprandial glycemic control was significantly better with IAsp compared with HI after 6 and 12 months of treatment. HbA1c was slightly, but significantly, lower for IAsp compared with HI at 6 and 12 months.	Good	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Diabetes Care May;23(5):583-8				
6	DeVries JH, Lindholm A, Heine RJ, et al (2001) A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in type 1 diabetes. Program and abstracts of the 37th Annual Meeting of the European Association for the Study of Diabetes (EASD); September 9-13,	a 64-week study of 227 patients with type 1 diabetes treated with 1 daily injection of either regular insulin or insulin aspart	Levels of HbA1c showed a trend to be lower by 0.1% to 0.2% with insulin aspart, and hypoglycemia occurred with similar frequency in the 2 groups.	Abs	
	INSULIN DETEMIR - EFFECTIVENESS				
1	Kaku K (2001) [Insulin detemir(NN-304)] Insulin detemir (103 2 relevant)1: Nippon Rinsho Nov;59(11):2151-6	Review	To normalize blood glucose in diabetic patients who require insulin treatment, a tailoring the time-action profile of injected insulin is needed. B29Lys-myristoyl. des-B30 human insulin(NN-304), which metabolic action is prolonged by association of the fatty acid residue to albumin in the blood and peripheral tissues, belongs to a new class of soluble long-acting insulin analogs. The aim of clinical development of NN-304 is to reduce the disadvantages of currently available long-acting insulin formulations. NN-304 might offer advantages in clinical use such as reproducing physiological basal insulin action derived from a flatter time-action profile.	Abs	
2	Selam JL, Skeie S, Vaugue P, et	425 patients with type	Although patients in both groups showed	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	al (2001) Promising results of 6 months treatment with insulin detemir in type 1 diabetic patients. Program and abstracts of the 37th Annual Meeting of the European Association for the Study of Diabetes (EASD); September 9-13,	1 diabetes with either insulin detemir or NPH for 6 months.	similar HbA1c levels, patients in the insulin detemir group had lower fasting glucose levels (9.3 vs 11.1 mM/L); lower intraindividual variation in fasting glucose (3.6 vs 3.9 mM/L); and a 21% reduction in hypoglycemic episodes		
3	Roberts A, Standl E, Bayer T, et al (2001) Efficacy and safety of 6-month treatment with insulin detemir in type 1 diabetic patients on a basal-bolus regimen. Program and abstracts of the 37th Annual Meeting of the European Association for the Study of Diabetes (EASD); September 9-13,	460 patients with type 1 diabetes on a basal-bolus regimen of either NPH or insulin detemir twice daily and regular insulin	Glycemic end points were similar in the NPH and insulin detemir groups, respectively (HbA1c 7.6 vs 7.7%, fasting glucose 10.7 vs 10.6 mM/L, intraindividual variation in fasting glucose 3.1 vs 2.9 mM/L, symptomatic hypoglycemia 62% vs 61%).	Abs	
4	Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M (2001) Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus	RCT of 59 type 1 diabetic subjects comprised a 2-week run-in period on a basal-bolus regimen with NPH insulin once daily, followed by two 6-week periods of optimized basal-bolus	Insulin detemir was as effective as NPH in maintaining glycemic control when administered at a higher molar dose.	Good to Fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	therapy. Diabetes Care Feb;24(2):296-301	therapy with either once-daily insulin detemir or NPH insulin			
	INSULIN DETEMIR- SAFETY				
1	Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M (2001) Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: a randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. Diabetes Care Feb;24(2):296-301	RCT of 59 type 1 diabetic - a 2-week run-in period on a basal-bolus regimen with NPH insulin once daily, followed by two 6-week periods optimized basal-bolus therapy with either once-daily insulin detemir or NPH insulin	The results indicate that insulin detemir may provide more predictable fasting blood glucose with lower intrasubject variation and reduced risk of hypoglycemia compared with NPH.	Good to Fair	
	INSULIN GLARGINE - SAFETY				
1	Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T (2000) A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes Care Nov;23(11):1666-71	Randomised Control Trial. n = 310 on Basal analog; n = 309 on NPH human insulin. 31 withdrew. Primary study end point- last available measurement on treatment. Variables – GHb, FBG, FBG, occurrence of hypoglycemia.	Insulin glargine appears to be as safe as NPH insulin. None of the treatment related adverse events in the study , apart from hypoglycemic reactions were considered serious.	Good	
2	Rosenstock J, Park G, Zimmerman J; U.S. Insulin	Randomised Controlled Trial,	CONCLUSIONS: Both formulations of insulin glargine (30ug	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Glargine (HOE 901) Type 1 (2000) Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. Diabetes Investigator Diabetes Care Aug;23(8):1137-42.	a 4-week trial, 256 patients with type 1 diabetes. Primary end point – FPG.	or 80 ug of Zinc Chloride) were well tolerated, similar to NPH insulin. No differences in adverse events were observed for both treatment.		
3	Fonseca V, Bell D, Mecca T. Less symptomatic hypoglycemia with insulin glargine compared to NPH in patients with type 2 diabetes. Program and abstracts of the 37th Annual Meeting of the European Association for the Study of Diabetes (EASD); September 9-13, 2001; Glasgow, United Kingdom.	100 patients with type 2 diabetes randomized to either insulin glargine or NPH	Compared with the NPH group, a smaller proportion of patients taking insulin glargine reported at least 1 hypoglycemic episode (46% vs 60%), hypoglycemia with glucose levels <50 mg/dL (17% vs 31%), and nocturnal hypoglycemia (15% vs 31%).	Abs	
4	Rosenstock J, Schwartz SL, Clark CM Jr, Park GD, Donley DW, Edwards MB (2001) Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care Apr;24(4):631-6	518 subjects with type 2 diabetes were randomised to received insulin glargine and insulin NPH.	Insulin glargine have the advantage of significantly reducing nocturnal hypoglycemia - 25%, with a safety profile similar to NPH insulin.	Good to fair	
5	Forjanic-Klapproth J, Home PD (2001)	4 phase 3 studies of 1104 patients treated with insulin glargine	Approximately half of all patients in the 4 trials had type 1 diabetes. Of the 2 studies of patients with type 2 diabetes, the United	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Progression of retinopathy with insulin glargine or NPH insulin. Program and abstracts of the 37th Annual Meeting of the European Association for the Study of Diabetes (EASD); September 9-13, Glasgow, United Kingdom.	and 1103 treated with NPH	States study showed more and the European study showed less retinopathy progression with NPH than with glargine by at least 3 steps on fundus photography. In addition, the European study showed greater development of macular edema on photography but less progression to nonproliferative retinopathy on clinical examination.		
6	Ciaraldi TP, Carter L, Seipke G, Mudaliar S, Henry RR (2001) Effects of the long-acting insulin analog insulin glargine on cultured human skeletal muscle cells: comparisons to insulin and IGF-I. J Clin Endocrinol Metab Dec;86(12):5838-47	Studies performed using human insulin and IGF-I as reference compound; cells both from type II diabetic and nondiabetics were treated with the test and reference compounds and examined for metabolic and mitogenic effects. 17 healthy subjects and 16 diabetic patients participated.	In human skeletal muscle cells, insulin glargine is equivalent to human insulin for metabolic responses and does not display augmented mitogenic effects.	Abs	
	INSULIN GLARGINE- EFFECTIVENESS				
1.	Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T (2000) A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin	RCT of 619 patients. Type 1 diabetes patients receiving basal-bolus insulin treatment with NPH human insulin and insulin lispro were randomized to receive	Compared with all NPH insulin patients, insulin glargine patients had significant decreases in fasting blood glucose More patients in the insulin glargine group (29.6%) than in the NPH group (16.8%) reached a target fasting blood glucose of 119 mg/dl (< 6.6 mmol/l). However, there were no differences	Good	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	lispro in patients with type 1 diabetes. Diabetes Care Nov;23(11):1666-71	insulin glargine (HOE 901), a long-acting basal insulin analog, once a day (n = 310) or NPH human insulin (n = 309). Final n= 588.	between the groups with respect to change in GHb. Insulin glargine treatment was also associated with a significant decrease in the variability of fasting blood glucose values (P = 0.0124).		
2	Rosenstock J, Park G, Zimmerman J; U.S. Insulin Glargine (HOE 901) Type 1Diabetes Investigator Group (2000) Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. Diabetes Care Aug;23(8):1137-42	RCT a 4-week trial, 256 patients with type 1 diabetes received either NPH insulin or insulin glargine containing 30 microg/ml zinc (insulin glargine[30]) or 80 microg/ml zinc (insulin glargine[80]).	Insulin glargine was superior to NPH insulin in reducing FPG levels in patients who had previously received NPH insulin twice daily but not in patients who had previously received NPH once daily. FPG levels were more stable in patients using insulin glargine than in patients using NPH insulin.	Good to fair	
3	Pieber TR, Eugene-Jolchine I, Derobert E (2000) Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European Study Group of HOE 901 in type 1 diabetes. Diabetes Care Feb;23(2):157-62.	RCT 333 type 1 diabetic patients. Patients were randomised to 3 groups – HOE 901 (30 ug Zinc Chloride), HOE 901 (80ug Zinc Chloride) and NPH insulin.	In conclusion, HOE 901 (both formulations) administered once daily at bedtime as a basal insulin in patient with type I diabetes was more effective than NPH insulin once or twice daily and was generally at least as safe as NPH insulin.	Good to fair	
4	Gillies PS, Figgitt DP, Lamb HM (2000)	Review	Four large clinical trials of up to 28 weeks' duration have shown that a single bedtime dose of insulin glargine, in combination	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Insulin glargine. Drugs Feb;59(2):253-60; discussion 261-2		with preprandial short-acting insulin, is as effective or more effective than once or twice daily NPH plus short-acting insulin in improving glycaemic control in patients with type 1 diabetes mellitus. In 3 large comparative trials, insulin glargine decreased glycosylated haemoglobin and/or fasting blood glucose levels to a similar extent to that seen with NPH insulin in patients with insulin-dependent or non-insulin-dependent type 2 diabetes mellitus, either as monotherapy or in combination with oral hypoglycaemic agents. Insulin glargine appears to be well tolerated. A lower incidence of hypoglycaemia, especially at night, was reported in most trials with insulin glargine when compared with NPH insulin.		
5	Rosenstock J, Schwartz SL, Clark CM Jr, Park GD, Donley DW, Edwards MB (2001) Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care, Apr;24(4):631-6	518 subjects with type 2 diabetes	In patients with type 2 diabetes, once-daily bedtime insulin glargine is as effective as once- or twice-daily NPH in improving and maintaining glycemic control. The insulin glargine and NPH groups showed similat significant decreases in HbA1c.	Good to fair	
6	Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T (2000) Time-action profile of the long-	RCT 15 healthy male volunteers (aged 27 +/- 4 years, BMI 22.2 +/- 1.8 kg/m2) received	Long-acting insulin analog HOE901 induces a smoother metabolic effect than NPH insulin. This observation suggest that HOE 901 is a promising candidate for a once a day basal insulin substitution.	Good to fair OR poor	Small sample RCT, short duration.

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care May;23(5):644-9	single subcutaneous injections of 0.4 U/kg body wt of HOE901, NPH insulin, or placebo on 3 study days in a randomized order.			
7	Ciaraldi TP, Carter L, Seipke G, Mudaliar S, Henry RR (2001) Effects of the long-acting insulin analog insulin glargine on cultured human skeletal muscle cells: comparisons to insulin and IGF-I. J Clin Endocrinol Metab Dec;86(12):5838-47	Studies performed using human insulin and IGF-I as reference compound; cells both from type II diabetic and nondiabetics were treated with the test and reference compounds and examined for metabolic and mitogenic effects. 17 healthy subjects and 16 diabetic patients participated.	In human skeletal muscle cells, insulin glargine is equivalent to human insulin for metabolic responses and does not display augmented mitogenic effects.		? study design.
	INSULIN LISPRO – SAFETY				
1.	Schmauss S, Konig A, Landgraf R (1998) Human insulin analogue [LYS(B28), PRO(B29)]: the ideal pump insulin? Diabet Med Mar;15(3):247-9	RCT 11 Type 1 patients	There was no significant difference with respect to hypoglycaemic or other adverse events. It can be concluded that lispro in CSII therapy is safe and may improve postprandial glucose excursions	Abs	
2.	Heller SR, Amiel SA, Mansell P (1999) Effect of the fast-acting insulin	RCT 165 subjects with type 1 diabetes, randomised to receive insulin lispro	The use of a fast-acting insulin analog, insulin lispro, as part of a basal bolus regimen reduces nocturnal hypoglycemia by threefold in patients with type 1 diabetes	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. U.K. Lispro Study Group. Diabetes Care Oct;22(10):1607-11	4 months and followed by regular insulin for 4 months OR regular insulin for 4 month followed by insulin lispro for 4 months. The main outcome measures- number of hypoglycemic episodes and HbA1c level.	who maintain tight glycemic control during intensive insulin therapy.		
3	Bastyr EJ 3rd, Huang Y, Brunelle RL, Vignati L, Cox DJ, Kotsanos JG (2000) Factors associated with nocturnal hypoglycaemia among patients with type 2 diabetes new to insulin therapy: experience with insulin lispro. Diabetes Obes Metab Jan;2(1):39-46	RCT Three hundred and sixty-five type 2 diabetic patients	Type 2 diabetic patients new to insulin therapy demonstrated lower risk of nocturnal hypoglycaemia with insulin lispro.	Abs	
4	Raskin P, Holcombe JH, Tamborlane WV, Malone JI, Strowig S, Ahern JA, Lavent F.J (2001) A comparison of insulin lispro and buffered regular human insulin administered via continuous subcutaneous insulin infusion pump. Diabetes Complications Nov-	RCT, 58 patients	No differences between treatments were observed in basal or bolus insulin doses, weight gain, or the incidence and rate of hypoglycemia, hyperglycemia, or pump occlusions. When used in external pumps, insulin lispro provides better glycemic control than buffered regular human insulin with a similar adverse event profile.	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Dec;15(6):295-300.				
5	Renner R, Pfutzner A, Trautmann M, Harzer O, Sauter K, Landgraf R (1999) Use of insulin lispro in continuous subcutaneous insulin infusion treatment. Results of a multicenter trial. German Humalog-CSII Study Group. Diabetes Care May;22(5):784-8	Randomised Controlled Trial. 113 type 1 patients (60 male, 53 female). Observation parameters are HbA1c, post prandial blood glucose. Adverseevents-hypoglycemic/hyperglycemic episodes, number of catheter obstruction and treatment satisfaction.	No significant differences were reported for the rate of hypoglycemia. No severe case of ketoacidosis was seen during insulin lispro treatment, whereas one case was reported during therapy with regular human insulin. Treatment satisfaction was better when patients were treated with insulin lispro. Its safety profile does not differ from that of regular human insulin.	Good to fair	
6	Cheta D, Strachinariu R, Trifan E, Nicolau A, Ionescu-Tirgoviste C, Georgescu M, Ghenof M, Mincu I, Uta D, Ristic S (1998) Safety and efficacy of insulin lispro in patients with diabetes mellitus. Rom J Intern Med Jan-Jun;36(1-2):85-96	Clinical trial 19 IDDM patients	There has been reported only one serious adverse event during the study: a ketoacidosis due to a technical dosing error. Ten patients have reported mild hypoglycemic episodes. The outcomes of clinical study and of Quality of Life Lispro--the first human insulin analogue used in humans--is effective, safe, and it is broadening beneficially the spectrum of insulins.	Abs	
7	Glazer NB, Zalani S, Anderson JH Jr, Bastyr EJ 3rd (1999)	Ten clinical trials of 3634 patients with type 1 and type 2 diabetes	There were no clinically or statistically significant differences in the frequency of treatment-emergent	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Safety of insulin lispro: pooled data from clinical trials. Am J Health Syst Pharm Mar 15;56(6):542-7	mellitus	adverse events or progression of retinopathy, neuropathy, or cardiovascular disease reported with each therapy. There was no difference between insulin lispro and Humulin R in the occurrence and progression of kidney disease as measured by changes in serum creatinine levels.		
	INSULIN LISPRO - EFFECTIVENESS				
1.	Garg SK, Anderson JH, Perry SV, Mackenzie T, Keith P, Jennings MK, Hansen MM, Chase HP (1999) Long-term efficacy of humalog in subjects with Type 1 diabetes mellitus. .Diabet Med May;16(5):384-7	RCT 20 subjects with Type 1 diabetes mellitus	Humalog insulin is effective in lowering postprandial glucose excursions even after up to 5.4 years of treatment.	Abs	
2.	Valle D, Santoro D, Bates P, Scarpa L; Italian Multicentre Lispro Study Group (2001) Italian multicentre study of intensive therapy with insulin lispro in 1184 patients with Type 1 diabetes. Diabetes Nutr Metab Jun;14(3):126-32	RCT 1184 Italian patients with Type 1 diabetes, randomised to insulin lispro (n=586) or regular human insulin (n=598) as pre-meal bolus for 3 months	Post-prandial blood glucose levels were lower with insulin lispro after breakfast ($p<0.001$), lunch ($p<0.005$) and dinner ($p<0.001$). The HbA1c level was decreased from baseline by both insulins, but the percent increase in patients with acceptable (<8%) HbA1c was greater with insulin lispro. Thus, compared with regular human insulin, improved glycaemic control was achieved with insulin lispro	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
3.	Raskin P, Holcombe JH, Tamborlane WV, Malone JI, Strowig S, Ahern JA, Lavent F (2001) A comparison of insulin lispro and buffered regular human insulin administered via continuous subcutaneous insulin infusion pump. J Diabetes Complications Nov-Dec;15(6):295-300	RCT, 58 patients	Insulin lispro use was associated with a significantly lower HbA(1c) than was buffered regular human insulin (7.41+/-0.97 vs. 7.65+/-0.85 mmol/l; P=.004). Fasting serum glucose values before the test meal were similar between the two therapies. The 1-h (11.16+/-4.29 vs. 13.20+/-4.68 mmol/l; P=.012) and 2-h (9.64+/-4.10 vs. 12.53+/-4.64 mmol/l; P=.001) postprandial glucose concentrations were significantly lower during treatment with insulin lispro.	Abs	
4.	Renner R, Pfutzner A, Trautmann M, Harzer O, Sauter K, Landgraf R (1999) Use of insulin lispro in continuous subcutaneous insulin infusion treatment. Results of a multicenter trial. German Humalog-CSII Study Group. Diabetes Care May;22(5):784-8	RCT 113 type 1 patients (60 male, 53 female)	HbA1c decreased in both treatment periods, but it was better during insulin lispro treatment . In addition, the 1-h and 2-h postprandial rises in blood glucose were significantly lower ($P < 0.001$ for each meal) with insulin lispro, resulting in smoother daily glucose profiles as compared with regular human insulin. CONCLUSIONS: Insulin lispro may result in an improvement of long-term glucose control during CSII treatment.	Good to fair	
5.	Travaglini MT, Garg SK, Chase HP (1998) Use of insulin lispro in the	A prospective study, telephone records of 75 children treated for ketonuria were	Doses of supplemental insulin used to treat patients with both moderate and large urine ketone values were similar (P>.05) in the insulin lispro and regular insulin groups.	Good to Fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	outpatient management of ketonuria. Arch Pediatr Adolesc Med Jul;152(7):672-5.	analyzed. The outcome number of succesful home treatment, the amount of insulin the patients needed, and the time to resolution of ketonuria.	Likewise, the time to resolution of moderate or large ketonuria was not statistically different (P>.05) between the 2 groups. Insulin lispro is an effective option for the outpatient management of ketonuria.		
	INHALED AND ORAL INSULIN- SAFETY				
1.	Laube BL, Georgopoulos A, Adams GK 3rd (1993) Preliminary study of the efficacy of insulin aerosol delivered by oral inhalation in diabetic patients. JAMA Apr 28;269(16):2106-9	Nonrandomized, placebo-controlled trial, 6 patients with NIDDM	No side effects were reported following insulin or placebo aerosol inhalation	Abs	
2.	Klonoff DC (1999) Inhaled insulin. Diabetes Technol Ther Fall;1(3):307-13	Review	Pulmonary toxicity due to inhaled insulin has not been reported, but no chronic use studies have been conducted.	Abs	
3.	Laube BL (2001) Treating diabetes with aerosolized insulin. Chest Sep;120(3 Suppl):99S-106S	Review	Aerosolized insulin is well-tolerated, and there is no evidence of irritation, hypoglycemia, or changes in pulmonary function when administered over short periods	Good	
4.	Skyler JS, Cefalu WT, Kourides	RCT	Inhaled insulin was well tolerated and had	Good	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	IA, Landschulz WH, Balagtas CC, Cheng SL, Gelfand RA (2001) Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. Lancet Feb 3;357(9253):331-5	73 patients with type 1 diabetes mellitus	no effect on pulmonary function (ie, spirometry, lung volumes, diffusion capacity, and oxygen saturation).		
5.	Cefalu WT, Skyler JS, Kourides IA, Landschulz WH, Balagtas CC, Cheng S, Gelfand RA; Inhaled Insulin Study Group (2001) Inhaled human insulin treatment in patients with type 2 diabetes mellitus. Ann Intern Med Feb 6;134(3):203-7	Randomized, open-label, 3-month study consisting of a screening visit, a 4-week baseline lead-in phase, and a 12-week treatment phase. 26 patients (16 men, 10 women) with type 2 diabetes	Patients experienced an average of 0.83 mild to moderate hypoglycemic event per month; no severe events were recorded. Patients showed no significant weight gain or change in pulmonary function compared with baseline. . CONCLUSIONS: Pulmonary delivery of insulin in type 2 diabetic patients who require insulin was well tolerated, and demonstrated no adverse pulmonary effects.	Good to fair	
6.	Henry R, Mudaliar S, Howland W, et al Pulmonary delivery of insulin using the *AERx* insulin diabetes management system in healthy and asthmatic subjects. Program and abstracts of the 37th Annual Meeting of the European Association for the	To assess the effect of respiratory function on the safety and efficacy of inhaled insulin - Using *AERx* iDMS (insulin diabetes management system) to deliver a liquid aerosol of human insulin for inhalation. 28 healthy and 17	No adverse effects were observed on airway reactivity, although information was not given regarding the appearance of clinical symptoms such as cough in patients with asthma.	Abstract	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Study of Diabetes (EASD); September 9-13, 2001; Glasgow, United Kingdom.	asthmatic individuals without diabetes none of whom were cigarette smokers			
	INHALED INSULIN - EFFECTIVENESS				
1.	Laube BL, Georgopoulos A, Adams GK 3rd (1993) Preliminary study of the efficacy of insulin aerosol delivered by oral inhalation in diabetic patients. JAMA Apr 8;269(16):2106-9	Nonrandomized, placebo-controlled trial, 6 patients with NIDDM	These preliminary results indicate that a dose of approximately 1.0 U of aerosolized insulin per kilogram of body weight, delivered by oral inhalation and deposited predominantly within the lungs, can effectively normalize plasma glucose levels in patients with NIDDM.	Abs	
2.	Klonoff DC (1999) Inhaled insulin. Diabetes Technol Ther Fall;1(3):307-13	Review	Studies comparing sequentially administered subcutaneous and inhaled regular insulins have demonstrated significantly reproducible glucose-lowering effects of inhaled insulin. In type 1 and insulin-treated type 2 patients, substitution of premeal inhaled insulin for subcutaneous insulin has resulted in no significant change in control. In a series of patients with type 2 diabetes failing oral agents, addition of premeal inhaled insulin resulted in significantly improved control.	Abs	
3.	Cefalu WT, Skyler JS, Kourides IA, Landschulz WH, Balagtas CC, Cheng S, Gelfand RA; Inhaled Insulin Study Group (2001)	Randomized, open-label, 3-month study consisting of a screening visit, a 4-week baseline lead-in phase, and a 12-week	Inhaled insulin treatment for 3 months significantly improved glycemic control compared with baseline: Mean hemoglobin A(1c) levels decreased by 0.0071 +/- 0.0072 (0.71% +/- 0.72%).	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Inhaled human insulin treatment in patients with type 2 diabetes mellitus. Ann Intern Med Feb 6;134(3):203-7	treatment phase. 26 patients (16 men, 10 women) with type 2 diabetes			
4.	Laube BL (2001) Treating diabetes with aerosolized insulin. Chest Sep;120(3 Suppl):99S-106S	Review	Aerosolized insulin is effectively delivered to the alveolar region of the lung, absorption rates and decreases in glucose levels are similar to those achieved with SC-delivered insulin during the fasting state. Other human trials have shown that inhaled insulin also effectively controls postprandial glucose levels.. It is likely that the treatment of diabetes with aerosolized insulin will provide an effective alternative means for controlling plasma glucose levels in diabetic individuals.	Good	
5.	Gerber RA, Cappelleri JC, Kourides IA, Gelfand RA (2001) Treatment satisfaction with inhaled insulin in patients with type 1 diabetes: a randomized controlled trial. Diabetes Care Sep;24(9):1556-9	RCT 69 Type I diabetes patients	Inhaled insulin may offer the first practical, non invasive alternative to insulin injections. For patients with type 1 diabetes, inhaled insulin maintains glycemic control and provides greater overall satisfaction and convenience/ease of use than subcutaneous insulin.	Good to fair	
6.	Heinemann L, Traut T, Heise T (1997)	RCT- To compare the pharmacodynamics of insulin after inhalation	Onset of action, assessed as glucose infusion rate, after insulin inhalation was substantially more rapid than after	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Time-action profile of inhaled insulin. Diabet Med Jan;14(1):63-72	of 99 U microcrystalline solid insulin and subcutaneous injection of 10 U regular insulin and intravenous injection of 5 U regular insulin 11 healthy volunteers	subcutaneous injection and half-maximal action was reached earlier (31 +/- 17 vs 54 +/- 12 min; $p < 0.001$).		
7.	Farr SJ, McElduff A, Mather LE, Okikawa J, Ward ME, Gonda I, Licko V, Rubsamen RM. Pulmonary insulin administration using the AERx system: physiological and physicochemical factors influencing insulin effectiveness in healthy fasting subjects. Diabetes Technol Ther 2000 Summer;2(2):185-97	This study evaluated the influence of formulation pH and concentration and different respiratory maneuvers on pharmacokinetic and pharmacodynamic properties of inhaled insulin 23 healthy subjects	Pulmonary delivery of aqueous bolus aerosols of insulin in healthy subjects resulted in rapid absorption with an associated hypoglycemic effect quicker than is achieved after subcutaneous dosing of regular insulin. Inhaled insulin pharmacokinetics and pharmacodynamics were independent of formulation variables (pH, concentration) but affected by certain respiratory	Abs	
8.	Heinemann L, Pfutzner A, Heise T. Alternative routes of administration as an approach to improve insulin therapy:update on dermal, oral, nasal and pulmonary insulin delivery.	Review	The pharmaco dynamic effects of insulin formulations administered via lung are comparable to, or even faster than, those of s.c. injected regular insulin or rapid-acting insulin analogues. Relative biopotency of inhaled insulin in most cases is approximately 10%, i.e., the dose of insulin administered must be 10-fold higher than with s.c. application. Metabolic control is comparable to that of s.c. insulin therapy.	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Curr Pharm Des 2001 Sep;7(14):1327-51		To date no serious side effects have been reported from these human trials. In summary, it appear that after several decades of research, for the first time a feasible alternative route for insulin administration is within reach		
9.	Henry R, Mudaliar S, Howland W, et al. Pulmonary delivery of insulin using the *AERx* insulin diabetes management system in healthy and asthmatic subjects. Program and abstracts of the 37th Annual Meeting of the European Association for the Study of Diabetes (EASD); September 9-13, 2001; Glasgow, United Kingdom.	To assess the effect of respiratory function on the safety and efficacy of inhaled insulin. Using *AERx* iDMS (insulin diabetes management system) to deliver a liquid aerosol of human insulin for inhalation 28 healthy and 17 asthmatic individuals without diabetes none of whom were cigarette smokers	Compared with the patients with asthma, there was 27% greater insulin absorption and 44% more glucose-lowering effect in the healthy group. No adverse effects were observed on airway reactivity, although information was not given regarding the appearance of clinical symptoms such as cough in patients with asthma.	Abstract	
10.	Brunner GA, Balent B, Ellmerer M, Schaupp L, Siebenhofer A, Jendle JH, Okikawa J, Pieber TR (2001) Dose-response relation of liquid aerosol inhaled insulin in type I diabetic patients. Diabetologia Mar;44(3):305-8	RCT In total, 18 C-peptide negative patients with Type I (insulin-dependent) diabetes mellitus participated in this randomised, open-label, 5-period crossover trial	The inhalation of soluble human insulin using the AERx iDMS is feasible and provides a clear dose response. Further long-term studies are required to investigate safety aspects, HbA1c values, incidence of hypoglycaemic events and the quality of life.	Abs	
11.	Harsch IA, Hahn EG, Konturek PC (2001)	Review	The therapeutic efficacy and safety of the inhaled insulin- comparable to the usual subcutaneous insulin treatment regimens.	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Syringe, pen, inhaler - the evolution of insulin therapy. Med Sci Monit Jul-Aug;7(4):833-6		Most important advantage - enhanced therapeutic comfort of the patient no need to inject insulin for meal time glucose control. Generally, in terms of glycemic control, inhalable insulin offers no advantages in type 1 diabetics in comparison to an intensified conventional insulin therapy. No available clinical data concerning the efficiency of the inhaled insulin in patients with pulmonary diseases which may cause problems in absorption of inhaled insulin due to the smaller cumulative alveolar surface. In smokers without pulmonary disease the inhaled insulin act stronger and faster. Larger doses of insulin compared to subcutaneous insulin to achieve the same systemic effect, the costs to be clarified.		
12.	Skyler JS, Cefalu WT, Kourides IA, Landschulz WH, Balagtas CC, Cheng SL, Gelfand RA (2001) Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. Lancet Feb 3;357(9253):331-5	RCT 73 patients with type 1 diabetes mellitus	The study shows that preprandial insulin can be given by inhalation in individuals with insulin-deficient type 1 diabetes as a less invasive alternative to conventional preprandial insulin injections	Good	

EVIDENCE TABLE FOR MONITORING OF DIABETES MELLITUS

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Self monitoring in Type I DM				
1	Coster, S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R (2000) Monitoring blood glucose control in diabetes mellitus: a systematic review Health Technology Assessment. Vol 4: No 12 (Executive summary)	Meta-analysis	**Self monitoring in Type 1 DM** 24 papers retrieved, 8 controlled trials & 16 non-controlled trials. Among the controlled trials, only 1 suggested a benefit of blood testing for GHb. The remaining showed no difference between blood or urine testing or different frequencies of blood testing. A meta-analysis of data from studies that compared blood monitoring with urine monitoring in children or adults with Type 1 DM suggested a mean difference in GHb of approximately -0.567% (95% CI, -1.073 to –0.061). Blood testing noted to be more costly than urine testing.	Good	
	Self monitoring in type II DM				
1.	Coster, S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R (2000) Monitoring blood glucose control in diabetes mellitus: a systematic review Health Technology Assessment.	Meta-analysis	**Self monitoring in type 2 DM** 18 papers retrieved, (8RCT & 10 non-randomised studies) After excluding 2 RCTS, 6 studies included in meta-analysis. A random effects meta-analysis, using data from 4 studies, showed the mean difference in GHb between groups of patients performing blood or urine self-monitoring	Good	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Vol 4: No 12		& those not was -0.25% (95% CI-0.61-0.10). Meta-analysis of data from 3 studies showed that the difference in GHb for those performing self-monitoring of blood glucose compared with those performing urine testing was -0.03% (95% CI, -0.52-0.47). Blood testing was > costly than urine testing.		
2.	Faas A, Schellevis FG and Van Eijk JTM (1997) The Efficacy of Self- Monitoring of Blood Glucose in NIDDM Subjects Diabetes Care Sept ; 20(9) : 1482-1486.	Review article	Main conclusion: The efficacy of SMBG in NIDDM patients is still questionable. High quality randomised controlled trial was suggested to prove it.	Poor	
3.	Karter AJ, Ackerson, LM, Darbinian JA, D'Agostino RB Jr, Ferrara A, Liu J, Selby JV (2001) Self monitoring of blood glucose levels and glycaemic control: the Northern California Kaiser Permanente Diabetes registry.	Cohort study Study sample 24,312 adults patients with diabetes.	Self-monitoring among patients with Type 1 diabetes (> or = 3 times daily) & pharmacological treated type 2 diabetes (at least daily) associated with lower HbAIC levels (1.0 percentage points lower in type 1 diabetes & 0.6 points lower in type 2 diabetes) than was less frequent monitoring (p< 0.0001). Those who practiced self-monitoring (at any frequency) had 0.4 point lower HbAIc level than those not practising at all.	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Am J Med Jul; 111 (1): 1-9		Conclusion Frequent self monitoring of blood glucose levels associated with clinically & statistically better glycaemic control regardless of diabetes type or therapy.		
4.	Harris MI, National Health and Nutrition Examination Survey (NHANES III) (2001) Frequency of blood glucose monitoring in relation to glycaemic control in patients with type 2 diabetes. Diabetes care Jun; 24 (6): 979-82	Cross sectional survey of 1,480 patients with type 2 diabetes in the third National Health & Nutrition Examination Survey from September 1988 to October 1994. Data on therapy for diabetes, frequency of self monitoring of blood glucose and HbA1c were obtained from structured questionnaires and by clinical and lab assessments.	29% patients treated with insulin, 65% treated with oral agents & 80% treated with diet alone had never monitored their blood glucose or monitored it less than once per months. Self-monitoring (at least once per day) practiced by 39% of those taking insulin,, 5-6% of those treated with oral agents or diet alone., Conclusions: The data for all patients combined indicate that self monitoring of blood glucose is more common as HbA1c increases, suggesting that patients with poor glycemic control have a greater tendency to self monitor.	Fair	
5.	BT Allen, ER DeLong and JR Feussner (1990) Impact of glucose self-	The goal of this study was to compare the relative efficacy and cost of self-monitoring of blood glucose (SMBG) with routine	In patients with type II diabetes mellitus not treated with insulin, SMBG is no more effective, but is 8-12 times more expensive, than urine testing in facilitating improved glycemic control. Our results do not support widespread use of SMBG in diabetic	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	monitoring on non-insulin-treated patients with type II diabetes mellitus. Randomized controlled trial comparing blood and urine testing Diabetes Care, Vol 13, Issue 10 1044-1050 Oct	urine testing in the management of patients with type II (non-insulin-dependent) diabetes mellitus not treated with insulin . .RCT 54 patients with type II diabetes mellitus	patients not treated with insulin.		
	Laboratory and near patient testing				
1.	Coster, S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R Monitoring blood glucose control in diabetes mellitus: a systematic review Health Technology Assessment 2000. Vol 4: No 12	Meta-analysis	**Laboratory and near-patient testing**Results from the Diabetes Control & Complications Trial (DCCT) in Type 1 DM & The UK Prospective Study in Type 2 DM demonstrated clinical effectiveness of using GHb estimations to monitor blood glucose control. Data from DCCT suggest the overall package of intervention would have acceptable cost-effectiveness. No unconfounded studies have addressed the optimal testing frequency for GHb, current guidelines suggest from 4 tests per year in subjects with Type 1 DM to 2 tests per year in subjects with stable type 2 DM. Fructosamine estimations, which measure glycaemic control over shorter intervals, have not been shown to be better than GHb. Fructosamine assays are less costly than GHB.	Good	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
2.	Carter AW, Borchardt N, Cooney M, Greene D Dual test diabetes screening project: screening for poor glycaemic control in a large workplace population Diabetes Technol Ther 2000 Winter; 2 (4): 529-36	100 males & 177 females age between 22-71. (12 males & 22 females have diabetes)	A total of 31 subjects tested positive for blood glucose, 39 tested positive for fructosamine, indicating 15.1% ($p< 0.005$) improvement in detection chances with fructosamine. Cost per subject –including equipment, supplies & labour was $ 18.13. Conclusion: The addition of fructosamine test improves screening accuracy, ease of use & affordability.	Abs	
3.	Carter AW, Borchardt N, Cooney M, Greene D Dual test monitoring of hypoglycaemia using daily glucose and weekly fructosamine. Diabetes Technol Ther 2001 Fall; 3 (3): 399-403	A clinical trial of 48 subjects with a fasting blood glucose value of > or=126 mg/dL, casual blood glucose value of > or = 140 mg/dL, and/or blood fructosamine value of > or =310 micromol/L. Perform daily self test for 90 days Outcome: achieve / maintained FBG < or	Assess the impact of this test in assisting individuals having poor glycaemic control to achieve value closer to normal. The study indicates that the addition of weekly fructosamine values to daily blood glucose values provides both the patient and clinician valuable information to evaluate the impact of dietary, exercise, and medication therapy changes on glycaemic control by bridging the existing gap between daily blood glucose values and quarterly HbA1c confirmation of intervention results	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
		=110 mg/dL, casula BG of < or = 140 mg/dL and blood fructosamine level < or= 310 micromol/L.			
4.	Cefalu WT, Wang Z, Redmon E, Bell-Farrow AD, McBride D, King T Clinical validity of a self-test fructosamine in outpatient diabetic management. Diabetes Technol Ther 1999, Winter ; 1 (4) : 435-41	51 subjects (18 control, 33 diabetes) participated in cross sectional study & 20 subjects participated in a prospective, 6 week study with clinical intervention with glipizide gits or metformine in mono & combination therapy.	Fingerstick fructosamine corrrelate highly to laboratory fructosamine (r=0.80, p< 0.001) & glycated hemoglobin (r=0.81, p<0.001). In intervention study, significant decreases in fasting glucose (p<0.001), laboratory fructosamine (p< 0.0001) and fingerstick fructosamine (p<0.001) cpmpared to baseline. Conclusions: Fingersticks fructosamine correlates well to laboratory assessment of fructosamine & glycated Hb. Patient self-test fructosamine provides same clinical information as laboratory assessment.	Abs	
5.	Petiti DB, Contreras R, Dudl, J (2001) Randomized trial of	Randomized control trial 140 adults patients with HbA1C values of 8% or greater	No significant different between these 2 grps, in the mean absolute decrease of HbA1C levels at 3 months. (0.5% in fructosamine grps) vs 0.8% in control grps. & the difference favoured the control grps at 6/12 (0.7% fructosamine vs 1.2% control;	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	fructosamine home monitoring in patients with diabetes Eff Clin Pract Jan-Feb; 4 (1): 18-23	Intervention: Weekly Home Fructosamine monitoring in addition to daily glucose monitoring. Control only monitored daily glucose.	p=0.04) Conclusions: Addition of Home fructosamine monitoring to routine glucose monitoring did not improve glycaemic control.		
6.	Chen HS, Chen RL, Chang ZY, Li HD (2002) A comparison of fructosamine and HbA1c for home self monitoring blood glucose leveles in type 2 diabetes. Zhonghua Yi Xue Za Zhi (Taipei) Apr;65 : 151-155.	25 patients with type 2 diabetes were studied at 4 weeks intervals. Fasting, preprandial and postprandial blood glucose level were checked by glucometer twice a week for 16 weeks. Correlation of fructosamine and HbA1c with self monitoring of blood glucose (SMBG) values were calculated.	Both fructosamine and HbA1c were significantly correlated with SMBG values fom 1 week to 16 weeks prior to measurements. Conclusion: In type 2 diabetes serum fructosamine assay can better reflect average blood glucose concentration over the previous 3-6 weeks and HbA1c assay is better reflective over the previous 8-10 weeks. HbA1c measurement correlates more significantly with home capillary blood glucose level than the fructosamine assay, even over the previous 2 – 3 weeks.	Abs	
	COST EFFECTIVENESS OF GLYCAEMIC CONTROL				
1.	Gray A, Raiku M, McGuire A, Fenn P, Stevens R, Cull C, Stratton I, Adler A, Holman R, Turner R (2000)	23 UK hospital clinic based study centres, 3867 newly diagnosed type 2 diabetic patients. Comparing	Results: Intensive glucose control increased trial treatment costs by 695 pounds per patient but reduced the cost of complications by	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Cost effectiveness analysis of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). United Kingdom Prospective Diabetes Study Group. BMJ May 20;320 (7246) : 1373-8	conventional glucose control policy (mainly diet) with intensive glucose control policy with sulphonylurea or insulin. Main outcome measures: incremental cost per event-free year gained within the trial period.	957 pounds and increased the time free of complication (0.6 years) and lifetime gained of 1.14 years compared with conventional.		
2.	Wake N, Hisashige A, Katayama T, Kishikawa H, Ohkubo Yang, Sakai M, Araki E, Schihiri M (2000) Cost effectiveness of insulin therapy for type 2 diabetes: a 10 year follow up of the Kumamoto study. Diabetes Res Clin Pract Jun;48(3):201-210.	Economic evaluation based on a randomised controlled trial of 110 type 2 diabetic patients. Subjects were assigned into 2 groups- multiple injection therapy (MIT) and Conventional Insulin injection therapy (CIT). Outcomes measures- frequency of complications eg retinopathy, nephropathy, neuropathy, macrovascular event	The results of the study showed that MIT is recommended for the treatment of type 2 diabetic patients who require insulin therapy as soon as possible from the perspective of both patients and health policy. The reduction of total cost in MIT over CIT was mainly due to the reduced costs for management of diabetic complications.	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
		and diabetes related death. For cost estimation, payer viewpoint (the National Health Insurance) was adopted. Direct medical costs associated with diabetes during 10 years calculated and evaluated.			
3.	Palmer AJ, Wiess C, Sendi PP, Neeser K, Brandt A, Singh G, Wenzel H, Spinas GA (2000) Cost effectiveness of different management strategies fo type 1 diabetes: a Swiss Perspective. Diabetologica 2000 Jan;43(1):13-26.	Seven complications of diabetes were computer-modeled. Transition probabilities and costs were taken from published literature. Life expectancy, cumulative incidences of complications, and mean expected total lifetime costs per patient were calculated under six different management strategies. Incremental Cost effectiveness ratio were calculated in term of costs per life year gained	Conclusion: Optimal maangement of type 1 diabetes patients, including secondary and tertiary prevention, leads to reduced complications and improved life expectancy, with the increased costs of prevention offset to varying degrees by cost savings due to complications avoided	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
		compared with conventional insulin alone.			

MANAGEMENT OF DIABETIC MELLITUS- NON DRUG – Diet and exercise

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
1.	Hensrud DD (2001) Dietary treatment and long-term weight loss and maintenance in type 2 diabetes. Obes Res Nov;9 Suppl 4:348S-353S	Review Various weight-loss strategies with follow-up for at least 1 year have been evaluated in people with diabetes with mixed results.	The initial results from studies using prepared meals and liquid meal replacements show that weight loss and glycemic control are comparable with conventional dietary treatment. Comprehensive lifestyle therapies, involving diet, exercise, and behavioral modification, can lead to weight losses of approximately 2 to 10 kg over 10 to 20 weeks, with regain over 1 year of one-third to one-half of weight initially lost. The net improvement on glycemic control is usually small 1 year after weight loss. Creative strategies using these and other modalities are needed to improve long-term weight loss, weight maintenance, and glycemic control in patients with type 2 diabetes. Greater efforts in primary prevention are also needed due to the increasing prevalence of obesity and type 2 diabetes.	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
2.	Yip I, Go VL, DeShields S, Saltsman P, Bellman M, Thames G, Murray S, Wang HJ, Elashoff R, Heber D (2001) Liquid meal replacements and glycemic control in obese type 2 diabetes patients. Obes Res Nov;9 Suppl 4:341S-347S	RCT of 75 subjects with type 2 diabetes, treated only with oral agents, recruited for this 12-week clinical study. Subjects were randomized into 3 groups:- MR (liquid meal replacement) containing lactose, fructose, and sucrose, MR in which fructose and sucrose were replaced with oligosaccharides (sugar-free Slim-Fast), Exchange diet plan (EDP) using the proportion of macronutrients recommended by the American Diabetes Association.	RESULTS: 57 patients (41 MR and 16 EDP) finished the study. None developed serious adverse effects, including major hypoglycemic reactions. Weight losses in the MR 1 and MR 2 groups were comparable (6.4% and 6.7%, respectively) and greater than the weight loss in the EDP group (4.9%). Fasting glucose level significantly reduced in the MR group compared with the EDP group ($p = 0.012$). There was a significant reduction in the MR group in total cholesterol and low-density lipoprotein cholesterol but not seen in the EDP group. DISCUSSION: liquid MRs are a safe and effective weight loss tool for obese subjects with type 2 diabetes, and can result in improvements in body weight, glucose, insulin, hemoglobin A1c and lipid levels.	Abs	
3.	Wallace AJ, Sutherland WH, Mann JI, Williams SM (2001)	A randomised cross-over study at Diabetes clinic and general practice. 14 patients (6 men and 8 women)	RESULTS: After TSOL, serum PON1 activity increased significantly in women compared with men. In women, the increase in serum PON1 activity after the TSOL meal was significantly different (13 (1.25)	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	The effect of meals rich in thermally stressed olive and safflower oils on postprandial serum paraoxonase activity in patients with diabetes. Eur J Clin Nutr Nov;55(11):951-8	with type 2 diabetes, aged 48-67 y, glycated haemoglobin <10% and fasting blood glucose <11 mmol/l were recruited. INTERVENTIONS: Patients received a milkshake rich in thermally stressed safflower (TSAF) or olive oil (TSOL) and at least a week later alternate milkshake. These fats contained high levels of lipid oxidation and degradation products. Fasting and 4 h Blood samples after consumption were tested for postprandial serum paraoxonase(PON1) arylesterase activity and low density lipoprotein (LDL) oxidation.	micromol/ml/min, P=0.04) compared with the corresponding change (-1 micromol/ml/min) after the TSAF meal. The lag time in LDL oxidation and indices of oxidative stress and antioxidant capacity did not vary significantly during the meals. CONCLUSIONS: Meals rich in TSOL may increase postprandial serum PON1 activity in middle-aged and older diabetic women. This change is potentially anti-atherogenic and may favour the use of olive oil over polyunsaturated fats in the diet of patients with type 2 diabetes.		
4.	Michael Lean (2001) Nutrition and Dietary advice in diabetes	Special report	Dietary advice is not just about nutrients. It is about foods and what people eat and also involves how, where and with whom they eat, and why they eat in a particular way. 3 convincing studies using different designs conclude that a modest weight loss in overweight	Poor	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	The Parctitioner, March, vol 245 : 231-238		patients with diabetes does increase life expectancy very substantially. A Scottish study - an increase survival of 3 to 4 months for every kilogram of weight loss achieved in the first year after diagnosis. 2 large American epidemiological studies indicated a 25% increase in life expectancy with 10 kgs weight loss. Detailed principle of weight management have been outlined in evidence based guidelines, both from SIGN and NIH. Reduce fat intake and increase physical activity. Carbohydrates suppress appetite and increase metabolic rate as well as improving insulin sensitivities.		
5.	Rebecca GS, Betsy B, Marion F, Janine F, Alberta H, et al (1997) Translation of the Diabetes Nutrition Recommendations for Health Care Institutions. Diabetes Care, Jan ; Vol 20(1) : 96-105.	Position statement	Suggested a nutrition prescription from ADA for diabetes patients and it should be based on; - An assessment of what and when the patients is currently eating, changes in patients need, and willingness to change - Individualized treatment goals for glucose and lipid values & body weight. - Modification of usual eating habits Adherence to a meal planning principles and metabolic control by sufficient nutrition education and self management training. Specific short term behavioral goals to guide change in usual eating and exercise patterns - Monitoring blood glucose, glycated hemoglobin, lipids, blood pressure, and body weight, as well as quality of life.	Poor	Poor
6.	Anonymous (2002)	Position statement	Goals for medical nutrition therapy in all diabetes patients: 1. Attain and maintain optimal metabolic	Poor	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Evidence-based nutrition Principles and Recommendations for the treatment and prevention of Diabetes and related complications Diabetes Care Jan ; 25 (1) : 202-212.		outcomes including 2. Prevent and treat the chronic complications of diabetes. Modify nutrient intake and lifestyle as appropriate for the prevention and treatment of obesity, dyslipidemia, cardiovascular disease, hypertension and nephropathy. 3. Improve health through healthy food choices and physical activity 4. Address individual nutritional needs taking into consideration personal and cultural preferences and lifestyle while respecting individual's wishes and willingness to change		
	EXERCISE				
7.	Wiesinger GF, Pleiner J, Quittan M, Fuchsjager-Mayrl G, Crevenna R, Nuhr MJ, Francesconi C, Seit HP, Francesconi M, Fialka-Moser V, Wolzt (Article in German) (2001) Health related quality of life (HRQOL)in patients with long-standing insulin dependent (type 1) diabetes mellitus: benefits of regular physical training. Wien Klin Wochenschr Sep	23 healthy patients with history of type 1 diabetes for 20 +/- 10 years were included. 15 patients (age: 41 +/- 2 years) participated in an aerobic physical training program over 4 months and 8 patients (33 +/- 11 years) served as a control group. HRQOL was assessed by a validated questionnaire. Tests were carried out at baseline and after 4 months.	RESULTS: Physical training increased peak oxygen uptake (VO2max) by 27 +/- 13% after 4 months ($p = 0.04$) in the training group. There was no significant change in hand or leg isometric muscle strength. All HRQOL scales improved in the training group with significantly higher ($p < 0.04$) Social Functioning and Vitality scores, respectively. Moreover, insulin requirements decreased during physical training program ($p < 0.05$). CONCLUSIONS: Data indicate that physical exercise training in patients with type I diabetes mellitus improves metabolic control and various aspects of HRQOL. Besides enhanced cardiorespiratory capacity, provide subjective benefit in patients with longstanding insulin dependent (type 1) DM.	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	17;113(17-18):670-5				
8.	Hamdy O, Good year LJ, Horton ES (2001) Diet and exercise in type 2 diabetes mellitus. Endocrinol Metab Clin North Am 2001 Dec;30(4): 883-907.	A review article	It is now clear that regular physical exercise is important in both the prevention and treatment of type 2 diabetes. Benefits of exercise - increased energy expenditure, which, combined with dietary restriction, decreased body fat, increased insulin sensitivity, improved long-term glycemic control, improved lipid profiles, lower blood pressure, and increased cardiovascular fitness. Before starting an exercise program, all patients with type 2 diabetes should have -complete history and physical examination, especially evaluation of cardiovascular disease, medications that may affect glycemic control during or after exercise, and diabetic complications including retinopathy, nephropathy, and neuropathy. Exercise programs should be designed to start slowly, build up gradually, and emphasize moderately intense exercise performed at least 3 times a week	abs	
9.	Schuster DP, Duvuuri V (2002) Diabetes mellitus. Clin Podiatr Med Surg Jan; 19(1) :79-107.	A review article.	DM- group of metabolic diseases characterised by hyperglycemia resulting from defects in insulin secretion , insulin action, or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction , and failure of various organs, especially eyes, kidneys, nerves, heart and blood vessels. The management of this disease is complicated. Good diabetic control depends on diligence blood glucose monitoring, frequent adjustment of medications, adherence to a regular diet and	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			exercise plan, and treatment of comorbid conditions such as hypertension and hyperlipidemia.		

EVIDENCE TABLE FOR SCREENING OF MICROALBUMINURIA IN DIABETIC PATIENTS

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
1.	WHO Technical report Series : recommendation in WHO Tech Report 844 Geneve: WHO 1994; 55-59	Technical report	Microalbuminuria is defined when: Urinary albumin Excreation rate (AER) : 20-200ug/min or 30-300mg/24 hours. Urine Albumin : Creatinine Ratio (ACR) : 30-300 mg/gm creatinine or 2.5-3.5 gm/mol creatinine Urine Albumin Concentration (ALB) : 20-200 mg/l in normal urine output Aim of screening for microalbuminuria: - The urine sampling must be convenient. - The test must have a good sensitivity (over 90%) and reasonable specificity. - Can be done at any district health center without additional major cost. -The test must have low variability.		

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			The target groups are: -Age more than 12 years old and all patients with NIDDM should screened for UAER at least once a year until age of 70 years old. Elevated albumin Microalbuminuria is infrequent before age of 14 years old or in IDDM, patient who have had diabetes for less than 5 years.		
2.	Consensus development conference on the diagnosis and management of nephropathy in patients with Diabetes. Diabetic Care Nov 1994: 17 (11) 1357-1361		Screening should be done in pts with IDDM duration of diabetes more than 5 years and In NIDDM, screening must be done at the time of diagnosis and in all individual who are younger than 70 years old. Because of the difficulty in dating the onset of NIDDM. Methods of urine sampling -Timed overnight urine collection 12 hours OR the preferred methods for screening are quantitative determination of urinary albumin in a timed urine collection or Albumin : creatinine Ratio in a random urine specimen	Poor	
3.	Peter H Bennet, Steven Haffner, Bertram L Kasiske, William F Keane, Carl Eric Mogensen, Hans-Henrik Parving, Michael W Steffes and Gary E Striker (1995) Screening and management of		All diabetic patients who are older than 12 years, should have their urine tested for albumin excretion at least once a year, optimally under stable metabolic control. The recommendation was all individuals with NIDDM who are younger than 70 years old and no overt renal disease must be screened for microalbuminuria. The screening procedure must be delay if patient has either one of the conditions	?	Recommendation to the NKF from Councill

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Microalbuminuria in Patients With Diabetes Mellitus: Recommendations to the Scientific Advisory Board of the National Kidney Foundation From an Ad Hoc Committee of the Council on Diabetes Mellitus of the National Kidney Foundation American Journal of Kidney Diseases 25(1):107-112.		listed below: Urinary tract infection Acute febrile illness Heart failure Heavy exertion Nonsteroidal antiinflamatory drugs & ACE inhibitor. It is acknowledge that a timed urinary albumin excreation rate, either a 24 hours or overnight (8-12 hours) collection is clearly the most sensitive assays.		
4.	Beatty OL, Ritchie CM, Bell PM, Hadden DR, Kennedy L, Atkinson AB (1995) Microalbuminuria as identified by a spot morning urine specimen in non insulin treated diabetes: an eight year follow up. Diabetic Med Mar; 12(3):261-266	Cohort of 8 years To determine whether spot morning urinary albumin can identify patients at risk of mortality and progression to nephropathy by follow up pts with microalbuminuria (MA) identified by the test.	Those with MA identified by spot urine albumin concentration – 46.8% died compared to those without MA – only 21.3%. It is a worthwhile and robust clinical test. Conclusion: Spot urinary albumin concentration is of value in identifying patients with an increased risk of mortality or progression to nephropathy, and is simple to obtain in clinics.	Fair	
5.	Hermans et al (1994)	Cross sectional study of 480DM patients, comparing three methods	Micral Test vs RIA : Sen: 93.2% Spec : 88.1%	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Detection of low range diabetic microalbuminuria : micral test revisited. Diabetic Medicine 11; 715-6	to detect microalbuminuria Micral test vs Albustix vs RIA on 24 hours urine collection.	NPV: 85.8% PPV: 94.4% Albustix vs RIA : Sen: 70.5% Spec : 79.0% NPV: 73% PPV: 76.9%		
6.	R E Gilbert, A Akdeniz, G Jerums. Semi-quantitative determination of microalbuminuria by urinary dipstick Aust NZ J Med 1992; 22	To assess usefulness of Micral test in the detection of microalbuminuria using 24 hours urine specimens, results compared with radioimmunoassay and immunoturbidimetry.	Compare with immunoturbidimetry - similar results to those of radioimmunoassay (RIA). Ability to detect UAC >/= 20 mg/l, Micral-test had a sensitivity, specificity and positive predicted value of 93.1%, 92.3% and 86.4% respectively. Timed urine collection are cumbersome and subjected to collection errors and poor patients compliance. Random spot urine or preferably an early morning urine, more convenient alternative because it is subject to less variability in AER. Together with the availability of the dipstick, the presence of microalbuminuria can be easily determined at sites without sophisticated laboratory facilities. However a positive Micral-Test to be confirmed by AER of timed urine	Good to fair	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			collection using established methodology and those with Micral test negative to be subjected to annual retesting.		
7.	Mogansen et al (1997) Multicenter evaluation of the Micral Test II test strip, an immunologic rapid test for the detection of microalbuminuria. Diabetes Care Nov;20(11) : 1642-6	Multicenter cross sectional study of 2228 urine samples of 111 diabetic patients	Micral Test II vs routine test: Sensitivity : 96.7% Specificity : 71% Neg Predictive value : 95% Pos Predictive value : 78% Interperson variability of colour interpretation showed 93% concordant reading. Drug interaction and condition : false increase in oxytetracycline , false decrease in temperature <10Celcius Colour stability after 2 weeks: Stable in 60% Shift by one colour block:36% Shift > than one colour block: 4%.	Good	Immediate and reliable semiquantitative determination of low albumin concentration in urine samples with an almost user-independent colour interpretation. Use urine albumin concentration rather than UAE rate in definition.
8.	Leong SO, Lui KF,Ng WY, Thai AC (1998) The use of semi-quantitative urine strip (Micral Test) for microalbuminuria screening in patients with diabetes mellitus. Singapore Med J Mar;39(3):101-3.	100 consecutive diabetic patients who were dipstick negative for proteinuria (Albustix) were enrolled for the study. Micral test performed on a paired morning and random urine specimens from the same patients. Results were compared with a timed 24 hours urinary albumin excretion using RIA.	18 specimens were positive by RIA metthod with a urinary albumin range of 32-177 mg/24 hours. With Micral test the following were obtained: First morning urine : Sensitivity was 66.7% Specificity was 97.6% PPV was 85.7%	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			NNV was 93.0% Random urine: Sensitivity was 77.8% Specificity was 91.5% PPV 66.7% NNV 94.9%		
9.	Zheng Y L (1999) Determination of sensitivity and specificity of the Micral Test II strip for detection of microalbuminuria in diabetic and non diabetic patient. Nephron 81:455	Case control study, urine sample of 22 NIDDM compared with 18 urine from non diabetic patients. Test for Micral test II compare with gold standard turbidimetric immunoassay. Excluded patients with overt proteinuria.	In diabetic : Sensitivity Micral test II was 88.9% Specificity Micral test II was 53.8% Variability Micral test II was 68.2% Non diabetic : Sensitivity Micral test II was 100% Specificity Micral test II was 92.3% Variability Micral test II was 83.3%	Good	Higher sensitivity is good for screening purposes but need second test for confirmation using turbidimetry immunoassay.

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			Incidence false positive in higher in diabetic vs non diabetic : 46.1% vs 21.4%.		
10.	Steve et al 1992		If facilities available for measurement of urine creatinine and urine for microalbuminuria by laboratory methods: A random single void (upright) urine collection can be used and measure the urine Albumin : Creatinine ratio. Random upright single sample urine collection give a sensitivity of 99% compare with 24 hours urine collection that both assessed by radioimmunoassay.		
11.	Shield JP., Hunt LP, Baum JD (1995) Penncock CA. Screening for diabetic microalbuminuria in routine clinical care: which method? Arch Dis Children Jun;72(6):524-5		The measurement of an albumin: creatinine ratio with a cut-off > 2.0 mg/mmol was found to be suitable with specificity of 93% and sensitivity : 97%, examination also done on spot urine sample.	Fair	
12.	Adries 1999		Determination of urine albumin concentration (UAC/ALB) is less sensitive and specific than that of Albumin: creatinine ratio as a screening procedure for microalbuminuria. Variability resulting from the creatinine assay		

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
			apparently has less consequence for A: C ratio than the effect of the variability of the urinary flow rate in albumin concentration measurement (Adries *et al*.,1999).		
13.	Watts GF et al (1996) Urinary tract infection and albumin secretion in IDDM: implication for the measurement of microalbuminuria . Diabetic Medicine Dec : 13:520-524.	Cross sectional study, to determine UTI using quantitative microbiology in 172 IDDM who were being tested for microalbuminuria on overnight collection, UAER & ACR.	The point prevalence of UTI at first screening for microalbuminuria was only 3%. Presence of UTI does not apparently affect the measurement of urinary albumin excretion unless pyuria is presence.	Good to fair	Examination of urine for infection (culture) is not necessary except examination for pyuria or symptomatic.
14.	Ng WY, Lui KF, Thai AC (2000) Evaluation of a rapid screening test for microalbuminuria with a spot measurement of urine albumin-creatine ratio. Ann Acad Med Singapore Jan;29(1):62-5.	The albumin and creatinine levels in the spot urine specimens were measured in a single rapid assay format using DCA 2000+ desktop and UEAR in the timed 24 hrs urine measured by the reference laboratory method.	The results - albumin creatinine ratio gave good performance characteristics for diagnosis of microalbuminuria. The DCA2000+ desktop system provides rapid and reliable method for measuring microalbuminuria in spot morning urine	Abs	
15.	Collins AC, Vincent J, Newall RG, Mitchell KM, Veberti GC (2001)	Compare performance of DCA 2000 microalbuminuria system for albumin and creatinine conc and albumin - creatinine ratio with lab	The DCA 2000 system - a safe substitutes for laboratory based measurements, ease of use and low cost making it suitable for screening and monitoring diabetes treatment. The system facilitates the used of random urines and may obviate the	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	An aid to the early detection and maangement of diabetic nephropathy: assessment of a new point of care microalbuminuria system in the diabetic clinic. Diabet Med Nov;18(11):928-32.	measurement 154 diabetic samples and 77 normal samples.	used of timed samples		
16.	Khawali C, Andriolo A, Ferreira SR (2002) Comparison of methods for urinary albumin determination in patients with type 1 diabetes. Braz J Med J Mar;35(3):337-43.	Compared Albumin/creatinine ratio determination using commercial kit DCA200 with conventional turbidimetric determination in the laboratory, and with overnight albumin excretion rate (reference method). 55 type 1 diabetic adolescents – collect first morning urine, and tested for albumin and creatinine with DCA2000 , later tested using lab analysis.	A/C ratio results of both methods strongly correlated. The study concluded that an early morning specimen should be used instead of timed overnight urine and the A/C ratio is an accurate, reliable and easily determined parameter for the screening of diabetic nephropathy. The immediate measurement of A/C ratio is feasible using the DCA 2000 kit	Abs	Micral test correctly detect diabetic microalbuminuria compared to RIA. It has high sensitivityand NPV when used in broad range microalbuminuria In lower range microalbuminuria (30- 99 mg/24 hrs) sensitivity reduced by 10%, thereby
17.	Le Floch JP, Marre M, Rodier M, Passa P (2001)	A prospective survey was carried out in 302 diabetic patients on sensitivity and	The results were compared with those observed in reference laboratory using same samples and showed good	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	Interest of Clinitek microalbumin in screening for microalbuminuria : results of multicentre study in 302 diabetes patients. Diabetes Metab Feb;27(1):36-9	specificity of screening microalbuminuria using Clinitek microalbumin.	agreement. The study found that Clinitek microalbumin is a good screening test for microalbuminuria and any positive result should be confirmed with reference assay.		
18.	Parikh CR, Gyamlani GG, Carvounis CP (2002) Screening for microalbuminuria simplified by urine specific gravity Am J Nephrol Jul-Aug;22(4):315-319.	Randomised 42 patients from primary clinic and 34 patients from diabetic clinic. Relationship between urine spesific gravity(Usg) and urine creatinine (Ucr) were determined.	The relationship between urine spesific gravity(Usg) and urine creatinine (Ucr) was determined so that Ucr can be derived from from Usg to correct for albumin concentration in the urine which is influenced by urine volume. Good correlation was found to exist between Usg and Ucr. Conclusion: By mesuring spot urine albumin and specific gravity by dipstick, easy and immediate and accurate results can be obtained in office settings.	Pubmed - In Process	
19.	Croal BL, Mutch WJ, Clark BM, Dickie A, Church J, Noble D, Ross IS (2001)	The Clinitek 50,is a urine chemistry point of care analyser for the semi quantitative measurement of albumin and creatinine, and calculation of	The Clinitek results agreed with the central lab results in 89% of diabetic samples and 80% of the ICU pts samples. Conclusion: Clinitek 50 provides useful, immediate clinical information regarding	Abs	

No	Author, Title, Journal, Year, Volume	Study design, sample size & Follow up	Outcome & Characteristic	Grade	Comment
	The clinical application of urine albumin:creatinine ratio point-of-care device. Clin Chim Acta May;307(1-2):15-21.	albumin:creatinine ratio (ACR). Samples taken from 252 consecutive patients attending city centre diabetic clinic and also from 40 patients admitted to ICU. Albumin and Creatinine measurements carried out using Clinitek 50 and also central lab.	microalbuminuria status for use in clinic setting or as potential immediate risk management tool in ICU.		