Clinical Review

The Management of Non–insulin-dependent Diabetes Mellitus in the Elderly

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More than 8 million Americans are afflicted with non–insulin-dependent diabetes mellitus (NIDDM), a complex disease process characterized by insulin resistance and impaired insulin secretion. Diet and exercise continue to be the cornerstones of treatment. Most patients, however, require the addition of an oral sulfonylurea agent to achieve adequate glucose control. The second-generation sulfonylureas, glyburide and glipizide, are effective at lower doses and may have fewer adverse effects and drug interactions than the older, first-generation agents. For these reasons the second-generation sulfonylureas are preferred. Insulin therapy is required in patients with hyperosmolar state, infection, or other forms of stress, or in those who fail to respond to treatment with oral sulfonylurea. Some patients may benefit from the concurrent administration of insulin and an oral agent. Hypoglycemia is the greatest risk of drug therapy in elderly patients with NIDDM. This is especially true in elderly patients who are exquisitely sensitive to the effects of sulfonylureas and insulin. Treatment should, therefore, be initiated at very low doses and gradually adjusted.

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Non–insulin-dependent diabetes mellitus (NIDDM, type II diabetes mellitus) is the most common form of diabetes, afflicting 8 to 11 million people in the United States alone.[1–4] Lifestyle, other underlying diseases, and longevity all play key roles in the development of glucose intolerance and NIDDM.[5,6] Rather than the traditional complaints of polyuria, polyphagia, and polydypsia, elderly patients with NIDDM often present with signs, symptoms, and complications that may be difficult to distinguish from changes commonly associated with aging, such as weight loss and fatigue (Table 1).[5]

The prevalence of NIDDM in those 30 to 50 years of age is 3% to 5%.[3] The prevalence of NIDDM, however, is greater among older age groups, increasing to 10% to 15% among those over the age of 60 years.[6] The implications of these prevalence data are staggering when one considers the aging of the US population. Currently, 11% of our population is 65 years of age or older, and by 2020, approximately 20% of our population will be in this age group.[7]

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Pathogenesis and Diagnosis of NIDDM

In nondiabetic patients, postprandial hyperglycemia stimulates insulin secretion by the pancreas. This combination promotes glucose uptake by splanchnic and peripheral tissues and suppresses hepatic glucose production.[8] Non–insulin-dependent diabetes mellitus is a heterogeneous disorder that is characterized by impaired insulin secretion and decreased tissue sensitivity to insulin (ie, insulin resistance). In patients with NIDDM, insulin resistance is manifested by inefficient peripheral glucose utilization in muscle and adipose tissue and accelerated rates of hepatic glucose production.[5,8,9]

Patients with clinical disease have fasting hyperglycemia and defects both in insulin secretion and insulin uptake. The sequence of development of insulin resistance and impaired insulin secretion in patients with NIDDM is not known. It is hypothesized that diabetes in the lean person begins with impaired insulin secretion, whereas disease in the obese patient begins with impaired tissue sensitivity to insulin.[8] Eriksson and colleagues,[9] however, report that insulin resistance precedes β-cell dysfunction in NIDDM. Regardless of which occurs first, development of one deficiency is followed by the development of the other, and only after both insulin

Table 1. The Diagnosis of Diabetes in Nonpregnant Adults Is Based on the Presence of One of the Following Criteria

- Random plasma glucose ≥200 mg/dL (11.1 mmol/L) *plus* classic symptoms of diabetes mellitus (eg, polydipsia, polyuria, polyphagia, weight loss)
- Fasting plasma glucose level ≥140 mg/dL (7.8 mmol/L) on ≥2 occasions
- Fasting plasma glucose level <140 mg/dL (7.8 mmol/L) *plus* sustained elevated plasma glucose levels during ≥2 oral glucose tolerance tests. The 2-hour sample and at least one other between 0 and 2 hours after 75-gram glucose dose should be ≥200 mg/dL (11.1 mmol/L). Oral glucose tolerance testing not necessary if fasting plasma glucose level ≥140 mg/dL

Adapted from Lebovitz.[14]

secretion and insulin action are present does NIDDM develop.[8,9]

Both fasting and postprandial hyperglycemia are seen in patients with NIDDM.[8,9] Fasting hyperglycemia is caused by an abnormally high basal hepatic glucose production. Postprandial hyperglycemia is caused by peripheral insulin resistance as demonstrated by impaired glucose uptake by peripheral tissues.[8]

NIDDM or type II diabetes can be subclassified as *nonobese NIDDM* or *obese NIDDM*. Terminology for NIDDM that is no longer used includes *adult-onset* diabetes, *maturity-onset* diabetes (MOD), *ketosis-resistant* diabetes, and *stable* diabetes.[10]

NIDDM is frequently detected in the elderly patient by routine blood glucose testing or by routine ophthalmologic examination that reveals diabetic retinopathy.[7] The elderly person with NIDDM rarely presents with the classic symptoms of polyuria, polyphagia, and polydypsia. Instead, symptoms of weight loss and fatigue, or one of the complications of diabetes, is a more common presentation.[5]

Complications associated with diabetes mellitus are both macrovascular (coronary artery disease, claudication, and stroke) and microvascular (retinopathy, neuropathy, and nephropathy), with macrovascular complications being the major cause of death.[5] It is currently believed that glucose control is a critical factor in the prevention of these complications.[1,11]

In addition to changes in glucose metabolism, patients with NIDDM frequently exhibit defects in lipid metabolism, as evidenced by increased triglyceride concentrations and atherosclerosis.[12] There may be an association between atherosclerosis and hyperinsulinemia.[13] It is not uncommon to find hyperinsulinemia in patients with insulin resistance and in patients with NIDDM. In addition, the elderly, even in the absence of NIDDM, are prone to hyperlipidemia[5]; thus, NIDDM in the elderly compounds their preexisting risk of macrovascular disease. Improved glycemic control achieved by a controlled diet, exercise, sulfonylureas therapy, and/or insulin therapy may decrease plasma triglyceride concentrations.[12]

A firm diagnosis of diabetes can be based on a fasting plasma glucose level above 140 mg/dL (7.8 mmol/L) on at least two occasions.[14] Since this level has been set somewhat high, more false-negative results should be expected than false-positives. If there is a high clinical suspicion of diabetes despite a normal fasting glucose (ie, 140 mg/dL [<7.8 mmol/L]), the diagnosis can be confirmed through the use of the oral glucose tolerance test (Table 1).[5,14]

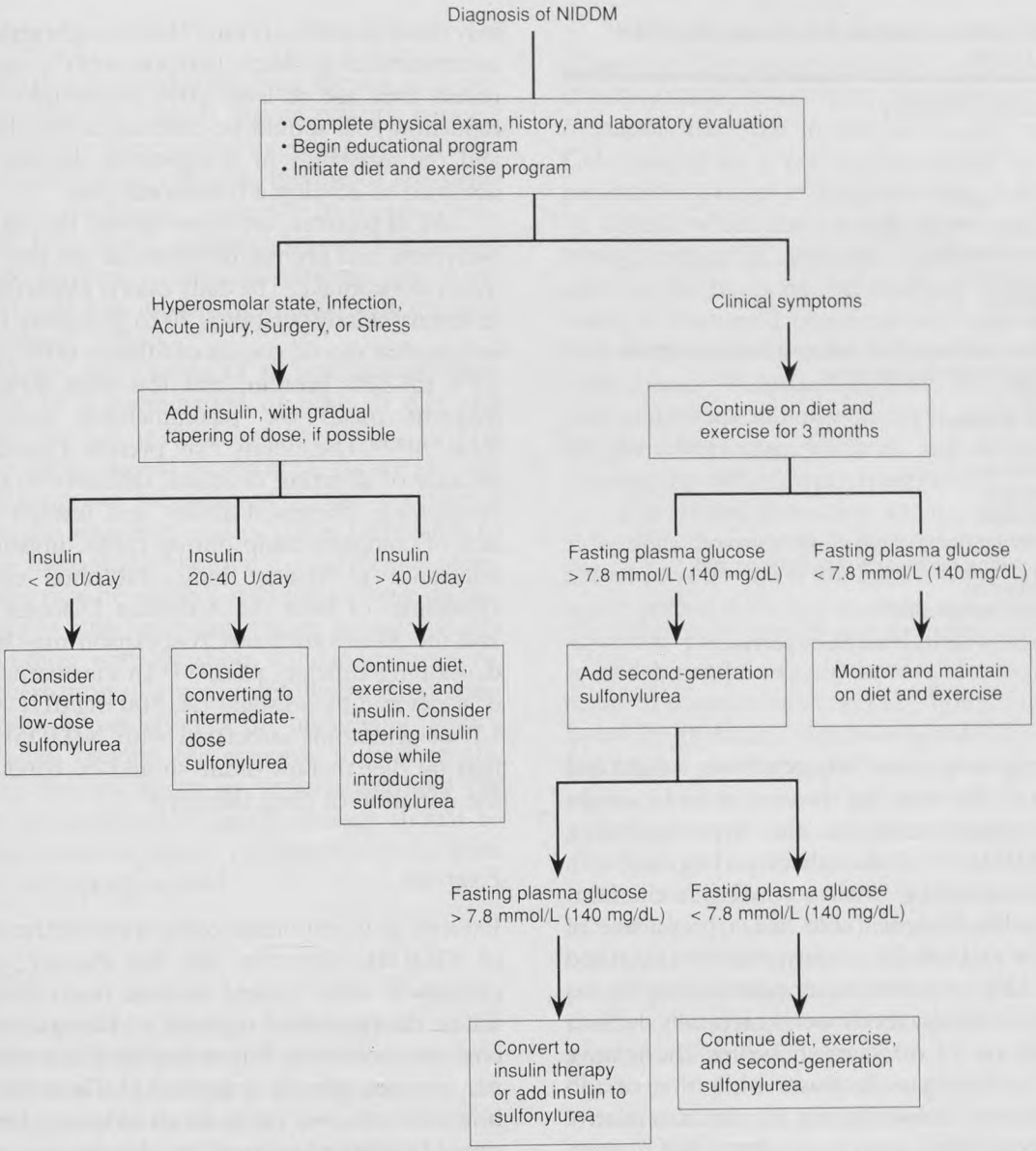
Management of NIDDM

The cornerstones of therapy for patients with NIDDM are diet, exercise, oral sulfonylureas, and insulin. Patient education also is critical if therapy is to be successful. An algorithm has been developed to demonstrate an approach to the use of these treatment modalities in the elderly patient (Figure). The goals of therapy in elderly patients with NIDDM are to control hyperglycemia, prevent the development or progression of acute and chronic complications, and avoid hypoglycemia. Elderly patients tolerate hypoglycemia poorly, and those with impaired cerebral and cardiac circulation are at risk of tissue damage during a severe episode of hypoglycemia.[7,15]

The first step in providing optimal therapy for the patient with NIDDM is a complete physical and laboratory evaluation (Table 2) that will provide baseline information to begin treatment. Elderly patients often suffer from several chronic conditions that are being treated with multiple drugs. Persons in the 8th decade of life often have three or four chronic diseases,[7] some of which can exacerbate hyperglycemia. In addition, many drugs can either increase or decrease glucose concentrations. For example, diuretics and β-blockers may contribute to poor blood glucose control in some patients (Table 1). Knowledge of the impact of prolonged drug therapy for chronic conditions is critical to the optimal control of hyperglycemia. Moreover, because many acute and chronic diseases may themselves exacerbate hyperglycemia, the control of diabetes is possible only when concurrent conditions are corrected or stabilized.

Education

Although education is a necessary component in the successful management of NIDDM, it is often given a lower priority than other aspects of diabetes care. Both the patient and family members or the primary caregiver



Algorithm for the management of NIDDM in the elderly.

must be included in the educational process. Physicians' perceptions of information given to patients may differ substantially from what patients remember. For example, one study demonstrated a discrepancy rate between physician and patient recollections of instructions for weight loss and blood glucose goals of 57% and 43%, respectively.[16]

Patient referral to a diabetes education team is a logical approach for physicians who, because of time constraints, cannot provide the scope of counseling that is needed for elderly patients and their families.[17] Patients and caregivers must understand the disease process, expected complications, and treatment alternatives. In addition, patients must be willing participants in dietary changes and a routine exercise program. They must appreciate the necessity for strict adherence to medication regimens and know the proper actions to take in the case of acute illness. Although the necessity for routine blood glucose monitoring in elderly patients with NIDDM is controversial,[18–21] patients who are suitable candidates for self-monitoring of blood glucose may be taught by a certified diabetes educator.

Patients who are well educated are better partners in the management of the disease. The educational process must be ongoing, with continuous reinforcement. Written instructions reinforce individual and group counseling efforts. Compliance is likely to be better in patients who understand the implications of their therapy.

Table 2. Special Considerations in the Assessment of the Patient with NIDDM

- Physical examination and history
  - Dietary habits
  - Weight loss
  - Blood pressure
  - Chills
  - Fever with activity
  - Gastrointestinal function
  - Special sense function
  - Coexistent diseases
  - Drug therapy
  - Integrity of the musculoskeletal and integumentary systems
  - Mental status and cognitive function
  - Social situation
  - Knowledge of diabetes
- Laboratory evaluation
  - Electrocardiogram
  - Lipid measurement
  - Measures of the functional status of major organs
  - Urinalysis (including microscopic examination and microalbuminuria)
  - Ophthalmologic examination

Based on data from Goldberg and Coon[5] and Morley and Perry.[15]

Diet

There is a strong association between body weight and the prevalence of diabetes. An increase in body weight may promote insulin resistance and hyperinsulinism, leading to NIDDM.[7,11] Framingham participants with relative weights exceeding 140% according to the Metropolitan Desirable Weight Table had a prevalence of diabetes of 17% to 19%. In contrast, diabetes occurred in only 8% to 12% of persons with relative weights less than 119%.[6] Interestingly, body weight typically declines slowly after the age of 60 years; however, the relative proportion of muscle mass decreases while that of adipose tissue increases.[7] It is unknown whether this relative increase in adipose tissue, even in the absence of obesity, places the elderly patient at higher risk of developing NIDDM.

Because obesity is a major risk factor in the development of NIDDM, dietary modification is the first line of treatment. The risk of diabetes more than doubles with every 20% increase over an individual's ideal body weight.[5] Obesity provokes insulin resistance, inducing a compensatory increase in insulin secretion. Basal insulin levels are elevated in relation to the degree of obesity. Weight reduction can improve glucose tolerance and decrease insulin resistance.[22] Unfortunately, the dietary approach to controlling NIDDM is successful in only a minority of patients, largely because of the difficulty the patient encounters in changing lifelong eating habits and adhering to a hypocaloric diet.[7,23]

Some elderly patients are not obese when NIDDM is diagnosed. Severe caloric restriction in these patients may result in malnutrition. Thus, weight reduction is not recommended in elderly persons over the age of 70 years unless they are at least 20% overweight.[15] A weight reduction goal should be established for obese patients, and the assistance of a registered dietician should be obtained to develop a nutritional plan.

In all patients, attention should be paid to the carbohydrate and fiber composition of the diet as well as to total caloric intake. The daily caloric requirement of most sedentary elderly persons is 20 to 25 kcal/kg of ideal body weight that should consist of 50% to 60% carbohydrate, 15% to 20% protein, and less than 30% fat. Small, frequent meals are recommended over one large meal.[14,15,18] The elderly may present a special challenge because of ill-fitting dentures, difficulty in chewing and swallowing, decreased ability and interest in cooking, lack of companionship during meals, impaired taste, or reluctance to change long-established eating habits. Guidelines of both the American Diabetes Association and the American Heart Association may be helpful in developing a dietary plan.[14,24] In the absence of a markedly elevated blood sugar (ie, 200 mg/dL [>11.1 mmol/L]) or symptoms associated with NIDDM, a 3-month trial on diet therapy alone should be conducted before the initiation of drug therapy.[22]

Exercise

Exercise is an important component of the management of NIDDM. However, like diet therapy, success with exercise is often limited because many patients fail to follow the prescribed regimen.[1,7] Exercise improves glucose metabolism by improving insulin sensitivity, and it may increase glucose tolerance.[1,5] These improvements, however, may not occur in all elderly patients.[15] Additional benefits of exercise are weight loss, stress reduction, reduction of cholesterol levels, and improvements in cardiac status.[1,5]

Exercise may be difficult for the elderly person because of fear of injury, poor vision, arthritis, cardiovascular disease, Parkinson's disease, or other chronic illnesses. Patients who are capable of undertaking an exercise regimen should begin with stretching and flexibility exercises followed by 20 to 30 minutes of low-impact, aerobic exercise (eg, walking, swimming, or bicycling) at a pace that is strenuous enough to increase the heart rate to 100 to 120 beats per minute. Swimming may be especially well suited for arthritic patients. In addition, the selection of proper exercise shoes and attention to foot care are critical in the elderly patient with diabetes.[14,15,18] Elderly patients must be closely evaluated before the institution of an exercise program and closely monitored following its initiation.

Drug Therapy

The greatest risk associated with drug therapy is hypoglycemia, to which the elderly are particularly prone.[5] Because of concern about avoiding hypoglycemic episodes, some investigators advocate the use of less stringent goals for blood glucose control.[19] In contrast, others maintain that strict maintenance of euglycemia prevents hyperglycemic coma and chronic and acute complications, and is as important in older patients as in younger persons.[15,21,25]

Drug therapy may consist of an oral hypoglycemic agent, insulin, or a combination of both. If diet and exercise alone do not control hyperglycemia, an oral hypoglycemic agent should be initiated. As weight loss and exercise programs are adhered to and a resultant increase in insulin sensitivity occurs, it may be possible to taper or even discontinue the oral hypoglycemic agent. Insulin therapy may be needed in patients whose disease progresses, those with secondary failure to sulfonylurea therapy, or in those with infection, acute injury, surgery, stress, or exacerbation of intercurrent illness. Resolution of the infection or correction of the underlying physiologic stress often restores the response to oral agents, thus allowing the oral agent to be reinstated and the insulin to be discontinued.[14] Insulin therapy should be initiated with caution in elderly patients because of their susceptibility to hypoglycemia.[5]

Sulfonylureas

A key factor in a patient's response to sulfonylureas is the stage of the disease at initiation of therapy. Patients tend to respond better when therapy is initiated early in the course of the disease, before the development of excessive insulin resistance and reduced β-cell function.[1,26] In general, patients who are most likely to respond well to sulfonylurea therapy are (1) those diagnosed with NIDDM after the age of 40 years, (2) those having NIDDM for less than 5 years, (3) those who are not overweight or only moderately so, and (4) those requiring no insulin or less than 40 units of insulin daily.[14] Approximately 85% of patients treated with sulfonylureas can achieve normal or greatly improved glucose control.[7]

The mechanism of action of sulfonylureas has not been fully elucidated. Their effects on the pancreas and on other tissues can be summarized as follows: (1) inhibition of hepatic glucose production; (2) enhancement of insulin secretion; (3) improvement in uptake and metabolism of glucose by peripheral tissues; and (4) increase in binding of insulin to insulin receptors.[1,7,11,26,27]

Sulfonylureas are classified as either first or second generation. The first generation of agents, which consists of tolbutamide, tolazamide, chlorpropamide, and acetohexamide, has been in clinical use for several decades. Chlorpropamide is not recommended for use in elderly patients because of its long duration of action (ie, 24 to 72 hours), which may predispose patients to prolonged hypoglycemia. In addition, a high incidence of disulfiram-like reactions (eg, flushing, headache) when alcohol is consumed concomitantly and water retention with hyponatremia make chlorpropamide a less than ideal therapy.[23] All sulfonylureas are highly bound to plasma proteins and may be displaced from binding sites by phenylbutazone, warfarin, and salicylates, thus increasing the risk of hypoglycemia.[23,28]

The second-generation agents, glyburide and glipizide, differ from the first-generation agents in that they are effective in lower milligram doses and may have a lower potential for hyponatremia and drug interactions involving protein-binding-site displacement.[1,23,28] The second-generation sulfonylureas differ from each other in terms of duration of action (24 hours for glyburide; 12 hours for glipizide), metabolism and excretion (renal and hepatic for glyburide; primarily renal for glipizide), administration with food (glipizide should not be given with meals), and effect on glucose concentrations.[29,30]

Both glyburide and glipizide are appropriate treatments for the elderly patient with diabetes and effectively reduce plasma glucose concentrations in patients with NIDDM.[30,31] However, glyburide reduces fasting plasma glucose concentrations more than glipizide, and postprandial glucose concentrations are lowered more by glipizide. Glyburide decreases basal hepatic glucose production more effectively than glipizide.[30] This greater reduction in hepatic glucose production correlates with a drop in fasting plasma glucose (and fasting insulin concentrations) and may account for the greater suppression of fasting plasma glucose during glyburide as compared with glipizide therapy. The more profound effect of glipizide on postprandial glucose concentrations may be related to the more rapid absorption and elimination of glipizide than occurs with glyburide.[30,31]

Both glyburide and glipizide can be initially administered once daily.[11,27] Glyburide is usually effective when administered as a single daily dose of less than 10 mg. Some patients, especially those receiving more than 10 mg of glyburide per day, may have a more satisfactory response if the total dose is divided and administered twice daily. Glipizide is effective in many patients when administered in a total daily dose of at least 15 to 20 mg; however, the daily dose of glipizide should be divided for patients needing more than 15 mg per day.[32–36] Glipizide should not be administered with meals, as absorption

may be delayed. The absorption of glyburide, however, is not affected by food.[27] These differences in dosages, dosing intervals, and administration schedules may have implications for the cost of therapy and patient compliance.

The second-generation sulfonylureas are extensively metabolized. Glipizide is metabolized to inactive metabolites and is excreted primarily renally. Glyburide has essentially inactive metabolites that are excreted in both the urine and bile.[27] Most drugs that are eliminated primarily by the kidneys show an age-related decrease in elimination. The property of dual clearance of glyburide may lower the risk of drug accumulation and hypoglycemia in the elderly patient with impaired renal function.[5,37] Initiating therapy with a low dose of glyburide (1.25 mg) or glipizide (2.5 mg), and gradually increasing the dose according to glycemic control, is recommended to avoid hypoglycemia in the elderly.[5,37,38]

Concurrent Sulfonylurea and Insulin

Combination therapy with an oral sulfonylurea and insulin in the patient with NIDDM is an option for which there is currently no clear consensus. Patients with NIDDM who are candidates for combined insulin and sulfonylurea therapy are those who are inadequately controlled by diet plus sulfonylureas or a daily regimen of two injections of mixed intermediate-acting and regular insulin alone.[14] In addition, patients who are likely to respond to combination therapy may be characterized as being mildly to moderately obese, having NIDDM for a short time, and having preserved pancreatic function.[39–41]

Combination insulin and oral sulfonylurea therapy may reduce total insulin requirements by as much as 50% in patients with NIDDM.[42] Gutniak and coworkers[43] conducted a study of glyburide and insulin in patients in whom oral sulfonylurea treatment had been ineffective. Combination therapy decreased insulin requirements by nearly one half and improved metabolic control, as evidenced by a reduction in hemoglobin A_{1c} (HbA_{1c}) from an average of 11.1% on day 3 to 9.1% on day 325. These patients, however, demonstrated significant weight gain despite their lower insulin dose.

Insulin

Even in patients in whom diabetes was initially well controlled by oral hypoglycemic therapy, the disease may ultimately worsen because of secondary failure. There are two types of secondary failure. The first is caused by progression of the disease, resulting in insulinopenia or increased insulin resistance. The second type is a reversible secondary failure that results from acute illness, stress, or weight gain.[1,11] Patients with NIDDM who experience an acutely stressful situation may present in a nonketotic, hyperglycemic, hyperosmolar state that is characterized by confusion or coma, severe dehydration, shallow respiration, and excessive thirst. This acute and potentially life-threatening complication of NIDDM requires immediate treatment with fluid, insulin, and potassium.[14] Reversible secondary failure may require the temporary administration of insulin (eg, a bedtime dose of 5 or 10 units); return to sulfonylurea therapy is generally possible after the secondary condition has been brought under control.

Insulin therapy should be administered with care, especially in elderly patients. Because of the exquisite sensitivity of the elderly to drug therapy, these patients should be given small doses of insulin initially. Daily doses may range from as low as 4 units of intermediate-acting insulin to a high of generally not more than 30 units (Figure). A mixture of short-acting and intermediate-acting insulins generally yields a good response.[5,7,14] Hyperinsulinemia has been implicated as a potential risk factor for atherosclerosis in those patients requiring very large doses of insulin.[11]

Conclusions

Management of NIDDM in the elderly is a challenge. Many of the signs, symptoms, and complications of the disease parallel those commonly found in elderly persons without diabetes mellitus. Diet and exercise remain the cornerstones of management. Elevated serum glucose is brought under control in most patients, however, only after the addition of either a sulfonylurea agent or insulin.

Patients with NIDDM who do not have significant clinical symptoms should be started on a 3-month program of diet and exercise. If this fails to control fasting plasma glucose at a level of 140 mg/dL (7.8 mmol/L) or less, the addition of an oral sulfonylurea agent is warranted. The use of the second-generation sulfonylureas, glyburide and glipizide, may be preferred over that of the older, first-generation agents. The second-generation sulfonylureas offer the advantages of lower doses and lower risk of drug interactions and hyponatremia.

Insulin is required in patients with diabetes mellitus who have significant clinical symptoms and in those who present in a hyperosmolar state or who have an infection or other physiologic stressor. After bringing the acute condition under control, it may be possible to convert the patient to oral therapy. Therapy must be tailored to

individual response, which may have considerable interpatient variability. It is recommended that individual patients be maintained on the lowest effective dose of insulin. Patients who are controlled on less than 20 units of insulin per day may be switched directly to low doses of oral sulfonylureas. Patients requiring higher daily doses of insulin may be switched to oral sulfonylurea therapy by either first converting to an intermediate dose of the oral agent (in patients needing 20 to 40 U/day) or by tapering the insulin dose while initiating oral sulfonylurea therapy (in patients needing >40 units insulin/day).

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