AN ANTHOLOGY OF DIABETES

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ABSTRACT

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia; associated with abnormalities in carbohydrate, fat and protein metabolism; and resulting in chronic complications including microvascular and neuropathic. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. The present work is a collection of different aspects of the disease.

Key word: Diabetes mellitus, metabolic disorders, hyperglycemia

INTRODUCTION

If left untreated, diabetes can cause many complications. Acute complications can include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death. Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, and damage to the eyes. Diabetes is due to either the pancreas not producing enough insulin or the cells of types of diabetes mellitus:

Fig. 1: universal symbol for diabetes

The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease.

Several pathogenetic processes are involved in the development of diabetes. These include processes which destroy the beta cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin.

Classification

Mainly two types

- Type 1 (insulin dependent dm = iddm)
- Type 2 (non insulin dependent dm = niddm)

Gestational diabetes

Type 1 dm results from the pancreas's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (iddm) or "juvenile diabetes". The cause is unknown. Type 2 dm begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (niddm) or "adult-onset diabetes". The most common cause is excessive body weight and insufficient exercise.

Gestational diabetes is the third main form, and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels.

Etiology

Type 1 dm is mainly associated with organ specific auto immune disease. Circulating islet cell antibodies (icas) are present in more than 70% of type 1 patients. It may also be caused by sudden stress such as an infection when the mass of β-cells of pancreas falls below 5 – 10%. Genetic susceptibility and environmental factors may also load to dm1.

Type 2 has a much stronger genetics relationship than type 1. Identical twins have a concordance rate approaching 100% if a parent has type 2. The risk of child eventually developing type 2 is 5 – 10 of compared with 1 – 2 to for type 1.

The major cause of type 2 is obesity. Obesity is associated with hyperinsulinemia & marked insulin insensitivity and a decrease in the number of insulin receptors. There is a selective defect in the beta ill secretory mechanism that prevents it from responding normally to glucose.

Pathogenesis

Type 1 dm: type 1 dm is characterised by an absolute deficiency of insulin. This may be due to an autoimmune mediated destruction of pancreatic β cells or may be idiopathic.

The autoimmune process is mediated by microphages and t-lymphocytes with circulating antibodies to various β cell antigens. The most commonly detected antibody associated with type 1 is islet cell antibody. Others include insulin auto antibodies; antibodies direct against glutamic and decarboxylase; antibodies against islet tyrosine phosphate (ia1 & ia2β) organ specific auto immune disorder such as graves disease; addisons disease and thyroiditis.

Type 2 dm

Type 2 dm may be due to both insulin resistance and relative insulin deficiency or β cell dysfunction. Insulin resistance manifest by an increase in lipolysis and free fatty and production, increase in hepatic glucose production and decrease in skeletal muscle uptake of glucose. Free fatty and indirectly leads to the hyperglycemia by stimulating hepatic glucose production.

In type 2 patients the pancreatic β-cell, are genetically vulnerable to injury, leading too accelerated cell tumor and premature aging, and ultimately to a modest reduction in β –cell mass. Chronic hyperglycemia may enhance the ability of β-cell to function as a consequence of persistent β-cell stimulation.
Pathophysiology

Many tissues contain insulin receptors to which insulin binds reversibly. The biological response of insulin can be altered by either a change in receptor affinity for insulin or a change in the total number of receptors. Changes in the receptors can occur due to obesity and chronic exposure to high insulin levels. Both lead to an increase in the number of receptors, down regulation. Acute deficiency of insulin leads to unstrained hepatic glycogenolysis and gluconeogenesis with a consequent increase in hepatic glucose output. Glucose uptake is decreased in insulin-sensitive tissues and hyperglycemia ensures.

Type 1 Diabetes

Lowered plasma volume produces dizziness and weakness due to postural hypotension. Diabetic ketoacidosis may also occur due to total body potassium loss and general catabolism of muscle protein further contribute to the weakness. Other symptoms are anorexia, nausea & vomiting. The patient's breath may have the familiar odor of acetone.

Type 2 Diabetes

The most common clinical manifestation is chronic skin infections. In women, pruritis and symptoms of vaginitis are common. Retinopathy or the combination of neuropathy, peripheral vascular disease and infections may manifest as foot ulceration or gangrene.

Complications

Persistent hyperglycemia and hyper tension are the two major controllable factors that influence the development of diabetic complication. These can be divided into those caused by micro vascular disease and those secondary to macro vascular disease.

Renal failure due to severe micro vascular nephropathy is the major cause of death in type 1, where as macrovascular disease is the leading cause type 2. Blindness may occur in both type 1 and type 2.

Although neuropathy is common in both types, severe autonomic neuropathy is much more common type 1. Peripheral vascular disease causing ulceration or gangrene in the lower limbs is the major cause of hospital bed occupancy by patients with diabetes. Some of these chronic complications are discussed below.

Eye disease

Blurring of vision is usually a benign occurrence associated with rapid changes in blood control. Open angle glaucoma is more common in patients with diabetes. Cataracts are also common in patients with diabetes, past middle age.

In any population of adults with diabetes, retinopathy will be present in between 10% and 50%. In the early stages retinopathy may not interfere with the patient’s vision.

Diseases of the urinary tract

Nephropathy is one of the potentially life-threatening complications of diabetes. Poor control of diabetes is associated with enlargement of kidney and in high glomerular filtration rate. Patients who go on to develop micro albuminuria are at risk of developing frank albuminuria and renal failure in later years.

Nerve damage

Neuropathy can affect patients with diabetes in many different ways. Peripheral neuropathy is the most common complication seen in type 2 dm patients. Paresthesias, numbness or pain may be predominant symptom. The feet are involved for more often than hands. It is the most prevalent in
elderly patients with type 2, but may be found with any type of diabetes, at any age beyond childhood.

Painful diabetic neuropathy is a cause of considerable morbidity.

In diabetic proximal motor neuropathy, there is rapid onset of weakness and wasting, principally of the thigh muscle. Pain is common.

Autonomic neuropathy may affect any part of the sympathetic or parasympathetic nervous system. The commonest manifestation is diabetic impotence. Bladder dysfunction usually takes the form of loss of bladder tone with a large increase in volume. Diabetic diarrhoea may occur at night.

Gastro paresis may cause delayed gastrointestinal transit and variable food absorption causing difficulty in the insulin – treated patients, or it may cause vomiting. Postural hypotension may also occur.

Cardio vascular disease

myocardial infarction is the major cause of death in diabetes. Peripheral vascular disease is associated with foot problems. Cerebrovascular events may also occur.

Hypotension occurs in association with both macrovascular and microvascular disease. A further risk factor for cardio vascular disease is dyslipidaemia.

Diabetic foot

Foot problems in diabetes cause more inpatient bed occupancy. Foor ulcer can be divided in to 3 categories.

Classical neuropathic ulceration occurs on the sole of the foot. The values can be deep but are usually painless. Ischaemic ulcers are classically painful, usually occur on the distal end of the toes, and are associated with signs of peripheral vascular disease and ischaemia. The most common lessons are infected foot ulcers.

Diabetes mellitus and physiological effects of insulin

Virtually all forms of dm are caused by a decrease in the circulating concentration of insulin (insulin deficiency) and a decrease in response of peripheral tissues to insulin (insulin resistance). Insulin lowers the concentration of glucose in blood by inhibiting hepatic glucose production and by stimulating the uptake and metabolism of glucose by muscle and adipose tissue. Insulin inhibits the lipolysis, stimulate fatty and synthesis and also stimulate amino acid uptake and protein synthesis. In diabetic patients the insulin deficiency lead to enhanced rate of gluconeogenesis.

Therapy

Dietary therapy

Diet and excurse are the first treatment of choice for patients with type 2 dm. 'Diabetic foods' are not recommended as they are often expensive and their nutritional content is not always compatible with healthy eating advice.

Dietary advice for people with diabetes is given below:

- Use high fat dietary foods eg: -skimmed milk, low fat yoghurt etc.
- Use grill, steam or oven bake foods.
- Eat at least 5 portions of fruits and vegetables.
- Mono unnatural fats such as olive oil are preferred.

When the diet and exercise do not achieve adequate blood glucose control, initiation with oral anti-diabetic is advocated.

Insulin therapy

insulin is the mainstay of treatment for patients with type1 diabetes, insulin is also important in type 2 diabetes when blood glucose levels can not be controlled by diet, weight loss, exercise and oral medications.

The common used insulin types are,

- Humlog and novolog / very short acting
- Regular / short acting
- Nph / intermediate acting

- Lente / inter mediate acting.
- Ultralente / long acting
- Lanctus
- Combinations – 75 / 25, 70/30, 50/50.

Different methods of insulin delivery are,

- Prefilled insulin pens
- Insulin pump
- Intranasal, transdermal, or inhalation.

Pharmacotherapy

Type 2 diabetes is a common fast growing disease that affects about 5% of the population worldwide. This disease is complicated by specific cardiovascular events and mortality rate. Pharmacological treatment is needed in greater than 80% of type 2 diabetes subjects. (8)

There have been a tradition for many years to use only one antibiotic drug at a time and most patients are still treated with either insulin secretagogues or insulin alone. Both these have only a minor effect on cardio vascular events and mortality rate. Normalization of hba1c results in declination of complication and mortality rate. (6)

The three pathophysiological components which leads to development of hyper glycaemia in obese adults are peripheral insulin resistant (reduced insulin mediated glucose uptake in skeletal muscle) insulin resistance in the liver (resulting in inappropriate glucose production) and impared of insulin response to glucose.

Oral hypoglycemic agents

- Sulfonyl ureas
  - i generation
    - Tolbutamide
  - ii generation
    - Glibenclamide
    - Glipizide
    - Glitazone
    - Glimepiride
  - Biguanides
    - Metformin
  - Non sulfonyl urea insulintropic
    - Repaglinide
    - Netaglinide
  - Thiazolidine diones
    - Rosiglitazone

Pioglitazone

Sulfonyl ureas

Sulfonyl urea derivatives are a class of anti diabetic drugs that are used in the management of dm type 2. They act by increasing insulin release from the beta cells in the pancreas.

Mode of action

Sulfonyl urea bind to an ap – dependent k+ channel on the cell membrane of pancreatic beta cells. This inhibits a tonic, hyperpolarizing outflux of potassium, which causes the electric potential over the membrane to become more positive. This depolarization opens voltage – gated ca++ channels. The rise in intracellular ca++ leads to increased fusion of insulin granules with the cell membrane, and therefore increased secretion of insulin.

There is some evidence that sulfonyl urea also sensitize beta cells to glucose, that they limit glucose production in the liver, that they decrease lipolysis (break down and release of fatty acids by adipose tissue) and decrease clearance of insulin by the liver.

Uses

Sulfonyl urea are used almost exclusively in dm type 2. In about 10% of patients, sulfonyl urea alone are ineffective in controlling blood glucose levels. Addition of metformin or a thiazolidine dione may be necessary, or
(ultimately) insulin. Triple therapy of sulfonyl urea a biguanide (merformin) and a thiazolidinedione is also used.

Biguanides

Mode of action
The mechanism of action of biguanides is poorly understood. This include reduced gastro intestinal absorption of carbohydrate; inhibition of hepatic gluconeogenesis; stimulation of tissue uptake of glucose; and increased insulin receptor binding. Of these the most important is the effect on hepatic gluconeogenesis.

The major advantage of metformin over sulfonyl urea is that it does not cause either hypoglycaemia or weight gain.

Use
Metformin is used in the obese patients with diabetes as it does not cause weight gain.

As it has a different mode of action to the sulfonyl urea, repaglinide or the thiazolidinediones, it can be valuable when prescribed in combination.

Repaglinide

Mode of action
Repaglinide acts by mediating the closure of atp – sensitive K⁺ channels in the pancreatic beta cells, which causes subsequent depolarization, thereby stimulating the release of insulin from beta cells.

Use
Repaglinide is an effective first line therapy in type 2 diabetes and may be used in combination with metformin to produce a synergistic effect. It is indicated in type 2 patients who are not controlled on diet alone or on metformin alone. Repaglinide lowers fasting and post-prandial blood glucose by approximately 4 m mol/l and 7m mol/l respectively.

Thiazolidinediones

Mode of action
They act by enhancing insulin action and promoting glucose utilization in peripheral tissues, possibly by stimulating non – oxidative glucose metabolism in muscle and suppressing gluconeogenesis in liver. They also have an effect on reducing insulin resistance.

They act most effectively in combination with other oral antidiabetic agents including sulfonyl urea and metformin.

Use
Thiazolidinediones improves glycaemic control in patients with insulin resistance by reducing hba1c levels upto 1.5%. The combination of thiazolidinediones with metformin is preferred to combination with sulfonyl urea, especially in obese patients.

Glycemic control with monotherapy
First line monotherapy typically begins with sulfonyl urea (an insulin secretagogue) or metformin (which inhibit hepatic gluconeogenesis).

Metformin is after used in over weight or obese subject, unless contra indicated or not tolerated and sulfonyl ureas (sus) are prescribed in leaner subjects, subjects seemingly more insulinopenic, or those who can't receive or tolerate metformin.

Studies have reported decrease in basal and post prandial plasma glucose (pppg) levels of ~ 3 to 5 m mol/l following 3 to 6 months of treatment sulfonyl ureas. Glycated haemoglobin has also been demonstrated to decrease by 20%. Clinical studies have reported significant reduction in fasting plasma glucose concentration (fpg) (22 to 26% of pretreatment levels) and glycated haemoglobin levels (12 to 17% of pretreatment levels) with metformin monotherapy.

For patients with type 2 diabetes, oral mono therapy may be initially effective for controlling blood glucose. But it is associated with a high secondary failure rate.(primary failure is frequent only in patients with high base line blood glucose at the time of beginning mono therapy, where as secondary failure is to be expected in the course of disease).

Glycemic control with combination therapy
A major problem in the management of type 2 diabetes is that glycemic control with diet and / or drug treatment declines as the disease progresses. Various anti diabetic combination therapies have been established to overcome this and should be introduced as soon as diet or drug monotherapy fail.

The combination therapy can improve insulin insensitivity β-cell function or both. The different classes of oral agents used to treat type 2 diabetes have complementary mechanism of action, and their use in combination often results in blood glucose reduction. That are significantly greater than those obtained with maximal dose of any single drug.

Once "secondary failure" to monotherapy occurs combinations therapy is introduced, usually metaformen and sulfonyl urea; or a thiazolodene dione + sulfonyl urea or metformin. Thiazolidinediones stimulate increased peripheral in the muscle, liver and adipose tissue. Met forming inhibits glucose genesis.

Combination therapy with thiazolidinedione and a biguanide (met forming) offers the additional benefit of complementary mechanism of action without increasing the risk of hypoglycemia.thiazolidine diones and metformin lower cardiac rule factors, as well as lowering serum glucose are there for the best choice. For initial therapy of type 2 dm.

If combination therapy with met forming and sulfonyl urea fails to produce acceptable glycemic control, several option are available:

2addition of bed time neutral protamine hage dorn (nph) insulin while maintaining therapy with oral agents.

- Institution of a regimen consisting of multiple insulin injections
- Addition of troglitazone or acarbose to a regimen of sulfonyl urea plus metformin.
- The basic principal of combination therapy is that small doses of 2 drugs, there is greater efficiency and fewer side effects than with a large dose of either drug used as mono therapy.

The choice of add on thiazolidinedione or insulin therapy when 2 oral agents are sufficient to control glycaemia in patients with type 2 diabetes necessitates balancing the risks and benefits of each drug beyond their anti diabetic action. Because the addition of a third oral agent is unlikely to decrease hba1c levels by >1.5-1.7%, insulin is often the only means of lowering hba1c to target levels when the base line is >8.5-9.0% the introduction of triple agent combination at lower base line hba1c levels, (ie, earlier in the disease course) could potentially increase the percentage of patients attending hba1c -7%. In addition longer term studies beyond 24 weeks may demonstrate that more patients can attain and sustain these glycemic targets.

A higher incidence of confirmed overall and nocturnal hypoglycemic events occurred in the insulin glargine group. However, compared with rosiglitazone, insulin glargine was associated with fewer adverse effects, less weight gain, and no edema, where as 12.5% of patients receiving rosiglitazone reported adema, a common side effects associated with these agents. Although insulin therapy produce modest weight gain, rosiglitazone led to twice as much weight gain (3kg) as insulin glargine(1.6). Thus patients treated with insulin glargine resulted in a significantly improved serum lipid profice compared with those treated with rosiglitazone.

In summary, both low dose insulin glargine and maximin dose rosiglitazone effectively. Lowered hba1c levels in triple therapy regimens, with glargine conferring lower fpg levels over all and greater improvements in patients with higher baseline hba1c levels. Compared with rosiglitazone, insulin glargine was associated with more hypoglycemia but fewer adverse reactions, no edema, less weight gain and salutary lipid changes at a lower cost of therapy. These results provides solid clinical to select a third antidiabetic agent when dual therapy is deemed. Inadequate in the complex setting of worsening type 2 diabetes.
Combination therapy with oral agent

When a maximal dose of metformin or sulfonyl urea is used as mono therapy, about 25% of patients with type 2 diabetes with a starting fasting plasma glucose levels 12.2 –13.3 mmol/L will achieve an acceptable level of glycemic control accordingly to american diabetes association guidelines (fasting plasma glucose level < 7.8 mmol/L and hba1c values < 8.0%, however because the hypoglycemic effect of troglitazone can anticipate that a smaller percentage of patients will reach the desired therapeutic goal. An even smaller percentage of patients with type 2 diabetes will achieve acceptable glycemic control with acarbose therapy. There for most patients with type 2 diabetes will require combination therapy to reach an acceptable level of glycemic control. Moreover, because type 2 diabetes mellitus is a progressive disease, even patients with a good initial response to oral agents eventually will require a second (or third) medication.

The most commonly used combination therapy is metformin + a sulfonyl urea. Addition of met forming to sulfonyl urea therapy gives an additive glucose- lowering effect. It also gives an additive response both with respect to glucose lowering and lipid lowering effects. Numerous studied have shown that addition of acarbose to sulfonyl urea or to met forming therapy provides an additive effect.

When insulin is used as mono therapy large doses (>80 to 100 v/d) are required to achieve normoglycemia, and significant weight gain commonly occurs. Because combination therapy with bed time insulin and oral agents effectively reduces elevated plasma glucose levels, requires considerably less insulin (therapy minimizing, weight gain) and often allows for fewer insulin injections per day.

Combination therapy with bedtime insulin plus oral agents the effectiveness of bedtime insulin therapy in patients with type 2 diabetes in whom acceptable glycemic control does not occur with oral agents alone or in combination is well documented. In such patients, the elevated fasting plasma glucose level is caused by incomplete suppression of basal hepatic glucose production by sulfonyl urea or met forming. Bed time insulin takes advantage of the differential sensitivity of hepatic compared with peripheral tissues to insulin. Low doses of insulin effectively suppress hepatic glucose production and have a much smaller effect on stimulation muscle glucose uptake. By giving a modest dose of intermediate – acting insulin( such as nph insulin) at bed time, the elevated basal rate of hepatic glucose production can be reduced to normal, and the likelihood of hypoglycemia will decrease because glucose uptake is only minimally stimulated.

A meta- analysis of 16 randomized, place bed controlled trials comparing sulfonyl urea plus insulin with place plus insulin showed significantly lower fasting plasma glucose and hba1c values, a lower daily insulin dose, and absence of eight gain in patients who received bed time insulin plus day time sulfonyl urea.

In patients with type 2 diabetes that was inadequately controlled with metformin alone, addition of bed time nph insulin compared with switching to a multiple insulin injection regimen produced equivalent glycemic control. However, the group that revived metformin plus bed time nph insulin required 50% less insulin and experienced no weight gain.

In diabetic patients receiving sulfonyl urea plus metformin in whom the desired therapeutic goal in not reached, option include addition of a third oral agent (troglitazone or acarbose), addition of bed time nph insulin or switching to a multiple insulin injection regimen.

Triple drug therapy

Triple drug oral anti diabetic therapy

Triple drug oral anti diabetic therapy is an effective long term treatment for a substantial proportion of patients with type 2 diabetes.

Beneficial effects of triple drug combination of rosiglitazone with glibenclamide and metformin in type2 diabetes mellitus patients on insulin therapy consecutive type 2 diabetes patients who were been treated with insulin were selected. They were switched on to triple drug combination of glibenclamide 5 mg tid, metformin 500 tid, and rosiglitazone 4mg o.d along with insulin only. Subjects with duration of type 2 diabetes mellitus of at least 5 year duration and who were being treated with insulin were including in the study. Patients with any cardiac abnormality, including history of symptomatic angina; cardiac myocardial infarction or an abnormal ecg were excluded. Once the patients was off insulin, and continual to show a fall in plasma glucose leads, glibenclamide was periodically reduced. The rosiglitazone and metformin was continued in fill doses except in a few patients who could not to treat full doses of metformin.

RESULTS

Mean values for hemoglobin a1c (hba1c), fasting and postprandial glucose and insulin requirement decreased significantly form baseline during the occur of therapy for 6 months. The combination therapy at the end of 6 months significantly increased the proportion of patients achieving treat –

target hemoglobin a1c (hba1c) levels compared to earlier therapy.

Effect of triple drug combination on fasting and post prandial glucose, hba1c and insulin usage.

Table: Effect of triple drug combination on fasting and post prandial glucose, hba1c and insulin usage

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<th>Fasting blood glucose mg /dl</th>
<th>Post prandial blood glucose mg / dl</th>
<th>Hba1c %</th>
<th>Insulin dose Unit /day</th>
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<td>256.24 + 41.36</td>
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<tr>
<td>To 124.06 + 26.14</td>
<td>162.32 + 14.33</td>
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DISCUSSION

The triple drug combination could work synergistically in reducing insulin resistance, thereby reducing the requirements of insulin significantly. This study suggest that the triple drug therapy is quit effective in improving insulin – mediated glucose utilization through increased insulin sensitivity.

This study shows that a triple drug combination of rosiglitazone, glibenclamide and metformin is effective and well tolerated and can be safely used in type 2 diabetes patients receiving insulin with significantly improved metabolic control. With this combination it is possible to significantly reduced the insulin dose or discontinue insulin therapy in a large number of patients. The addition of rosiglitazone also offers an alternative to patients with inadequate glycemic control despite treatment with full doses of sulfonyl urea and metformin. The triple drug combination could help a good population of patients to reach target levels of hba1c and allow postponement of insulin therapy.

Long term efficacy of triple oral therapy for type 2 dm

A study was conducted in 35 patients. Out of these 26 patients (group a) had well controlled blood glucose levels on triple oral therapy with a mean glycated hemoglobin value of 6.9+/- 0.3%. In the 9 other patients (group b) triple oral therapy failed. The only difference found between these 2 groups was a significant increase in the stimulated c-peptide levels (from 3.6+/- 0.9 ng/ml to 5.2+/- 1.1 ng/ml; p=0.002) during follow – up in the group that had good glycemic control with triple oral therapy in comparison with non significant increase (3.7+/- 0.8 ng/ml to 4.2+/- 0.4 ng/ml; p= 0.46) in the group that failed to maintain glycemic control with triple oral therapy.

Research

Inhalable insulin has been developed which the original products were withdrawn due to side effects. The new inhalable insulin, affreza, under development by the pharmaceuticals company minutek corporation, was approved by the fda for general sale in june 2014. Inhaled insulin is that it may be more convenient and easy to use.

Transdermal insulin in the form of a cream has been developed and trials are being conducted on people with type 2 diabetes.
CONCLUSION

Triple oral anti diabetic therapy is an effective long term treatment for a substantial proportion of patients with type 2 diabetes who initially achieve glycemic control with triple oral therapy, particularly those in whom production of endogenous insulin is increased when thiazolidine diones is added.

In summary, a rational approach t therapy in patients with type 2 diabetes is to begin therapy with a sulfonyl urea or met forming and add another oral agent if the designed glycemic control is not achieved. If additional therapy is required, bed time nph insulion or a third oral agent can be added.

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