IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Pharmacotherapy Of Diabetes

[1]Nikita Durgadas Ambhore, [2]Dr. Harshal Anwane, [3]Dr. Shivshankar Mhaske, [4] Karan Dnyanba Gavhane, [5]Kapil Pandurangji Bhagat.

[1]Student, [2]Professor, [3]Principal, [4] Student, [5]Student.
[1]Pharmacy,
[1]Satyajeet College of Pharmacy, Mehkar, India.

Abstract: This chapter provides: Information to assess the need for services for people with diabetes and its complications. Criteria to assess the success of programmes for the care and early detection of this group of disorders. The chapter does not aim to provide a systematic review of the literature on diabetes epidemiology and health care. There are a number of systematic reviews available in the Cochrane Library and other sources. Instead, the chapter highlights the most recent important studies in these areas and suggests issues, particularly in the domain of health services research, where more information is needed. Considerable documentation and a large measure of agreement exist on the aims of diabetes care and how these might be achieved. The most important consensus documents on the subject are listed in Appendix II and some feature as specific references in the text. (Further explanation and relevant references for the statements made below are included in subsequent sections.)

Index Terms **- diabetes,insulin, hyperglycemic, albuminuria.**

INTRODUCTION

BEFORE THE DISCOVERY OF INSULIN, TYPE 1 DIABETES – WHERE INSULIN EFFICIENCY CAN LEAD TO KETOACIDOSIS – WAS INVARIABLY FATAL. SINCE THE INTRODUCTION OF INSULIN, THE THERAPEUTIC FOCUS HAS BROADENED FROM TREATING AND PREVENTING DIABETIC KETOACIDOSIS TO PREVENTING LONG-TERM VASCULAR COMPLICATIONS. TYPE 2 DIABETES – WHERE INSULIN RESISTANCE AND A RELATIVE LACK OF INSULIN LEAD TO HYPERGLYCAEMIA – NOT ONLY CAUSES SYMPTOMS RELATED DIRECTLY TO HYPERGLYCAEMIA (POLYURIA, POLYDIPSIA AND BLURRED VISION – SEE BELOW), BUT IS ALSO A VERY POWERFUL RISK FACTOR FOR ATHEROMATOUS DISEASE. GLUCOSE INTOLERANCE AND DIABETES MELLITUS ARE INCREASINGLY PREVALENT IN AFFLUENT AND DEVELOPING COUNTRIES, AND REPRESENT A MAJOR PUBLIC HEALTH CHALLENGE. ADDRESSING RISK FACTORS DISTINCT FROM BLOOD GLUCOSE, ESPECIALLY HYPERTENSION, IS OF PARAMOUNT IMPORTANCE AND IS COVERED ELSEWHERE .IN THIS CHAPTER, WE FOCUS MAINLY ON THE TYPES OF INSULIN AND ORAL HYPOGLYCAEMIC AGENTS.

Diabetes mellitus is a group of metabolic diseases characterized by elevated blood glucose levels (hyperglycemia) resulting from defects in insulin secretion, insulin action or both. Insulin is a hormone manufactured by the beta cells of the pancreas, which is required to utilize glucose from digested food as an energy source. Chronic hyperglycemia is associated with microvascular and macrovascular complications that can lead to visual impairment, blindness, kidney disease, nerve damage, amputations, heart disease, and stroke. In 1997 an estimated 4.5% of the US population had diabetes. Direct and indirect health care expenses were estimated at $98 billion.

In type 1 diabetes, the body does not produce insulin, and daily insulin injections are required. Over 700,000 people in the United States have type 1 diabetes; this is 5-10% of all cases of diabetes mellitus. Type 1 diabetes is usually diagnosed during childhood or early adolescence and it affects about 1 in every 600 children.Type 2 diabetes is the result of failure to produce sufficient insulin and insulin resistance. Elevated blood glucose levels are managed with reduced food intake, increased physical activity, and eventually oral medications or insulin. Type 2 diabetes is believed to affect more than 15 million adult Americans, 50% of whom are undiagnosed. It is typically diagnosed during adulthood. However with the increasing incidence of childhood obesity and concurrent insulin resistance, the number of children diagnosed with type 2 diabetes has also increased worldwide

HISTORY

Diabetes was one of the first diseases described,with an Egyptian manuscript from c. 1500 BCE mentioning "too great emptying of the urine".The first described cases are believed to be of type 1 diabetes. Indian physicians around the same time identified the disease and classified it as madhumeha or "honey urine", noting the urine would attract ants.The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Apollonius of Memphis.The disease was considered rare during the time of the Roman empire, with Galen commenting he had only seen two cases during his career.This is possibly due to the diet and life-style of the ancient people, or because the clinical symptoms were observed during the advanced stage of the disease. Galen named the disease "diarrhea of the urine" (diarrheaurinosa). The earliest surviving work with a detailed reference to diabetes is that of Aretaeus of Cappadocia (2nd or early 3rd century CE). He described the symptoms and the course of the disease, which he attributed to the moisture and coldness, reflecting the beliefs of the "Pneumatic School". He hypothesized a correlation of diabetes with other diseases and he discussed differential diagnosis from the snakebite which also provokes excessive thirst. His work remained unknown in the West until the middle of the 16th century when, in 1552, the first Latin edition was published in Venice.

Type 1 and type 2 diabetes were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400-500 CE with type 1 associated with youth and type 2 with being overweight.The term "mellitus" or "from honey" was added by the Briton John Rolle in the late 1700s to separate the condition from diabetes insipidus, which is also associated with frequent urination.Effective treatment was not developed until the early part of the 20th century, when Canadians Frederick Banting and Charles Herbert Best isolated and purified insulin in 1921 and 1922.This was followed by the development of the longacting insulin NPH in the 1940s.[2]

DEFINATION:-

DIABETES MELLITUS:-

1. Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period
2. Diabetes mellitus is a serious disease in which the body cannot properly control the amount of sugar in your blood because it does not have enough insulin
3. Diabetes mellitus (DM) is a group of metabolic disorders characterized by a chronichyperglycemic condition resulting from defects in insulin secretion, insulin action or both.

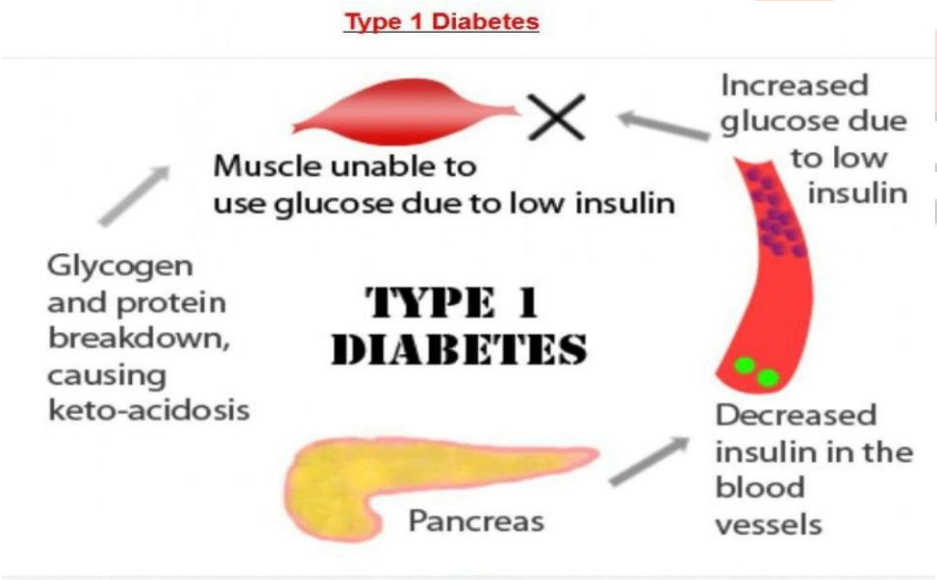
	Type 1 diabetes	Type 2 diabetes
General blood glucose target ranges	4–6mmol/L before meals Less than 10mmol/L after meals*	6–8mmol/L before meals 6–10mmol/L after meals*

THERE ARE THREE MAIN TYPES OF DIABETES MELLITUS:-

1. TYPE 1: DIABETES MELLITUS

This used to be called insulin dependent diabetes or juvenile diabetes. However this was confusing as many people with type 2 diabetes also need insulin to manage their diabetes.

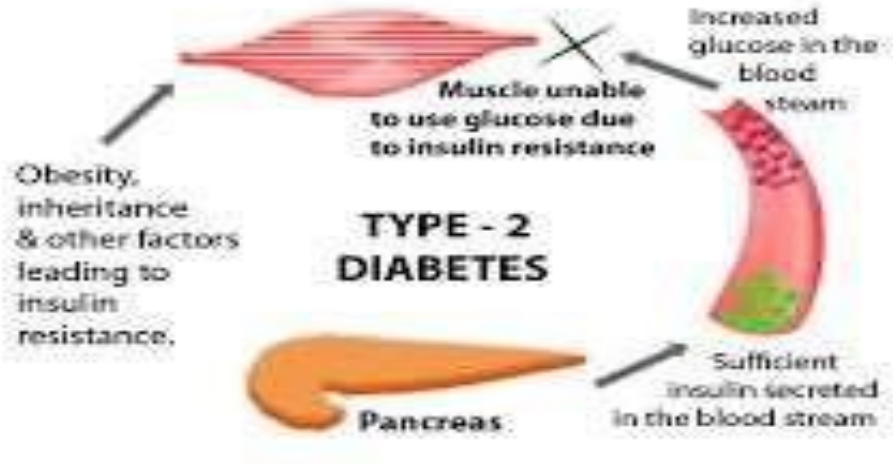
While type 1 diabetes can and does occur at any age, it's usually diagnosed in children and young adults. Type 1 diabetes is the less common form of diabetes, affecting just 10–15% of all people with diabetes.



In type 1 diabetes, the pancreas cannot produce enough insulin because the cells that make the insulin have been destroyed by the body's own immune system. This insulin must be replaced. Therefore people with type 1 diabetes must have insulin every day to live. At present insulin can only be given by injection or by infusion via an insulin pump, but other methods of getting it may be possible in the future.[3]

1.TYPE 2: DIABETES MELLITUS

This used to be called non-insulin dependent diabetes or mature-age onset diabetes.It is by far the most common form, occurring in 85–90% of all people with diabetes.While adults are usually affected, more and more younger people, even children, are now developing type 2 diabetes. Lifestyle choices can contribute to the development of type 2 diabetes. It is strongly associated with high blood pressure, abnormal blood fats and the classic 'apple shape' body where there is extra weight around the waist.



People with type 2 diabetes are usually insulin resistant. This means that their pancreas is making insulin but the insulin is not working as well as it should. The pancreas responds by working harder to make more insulin. Eventually it can't make enough to keep the glucose balance right and blood glucose levels rise.

Adopting a healthy lifestyle may delay the need for tablets and/or insulin. However it is important to know that if you do need tablets and/or insulin, this is just the natural progression of the condition. By taking tablets and/or insulin as soon as they are needed, the risk of developing complications caused by diabetes can be reduced.[3]

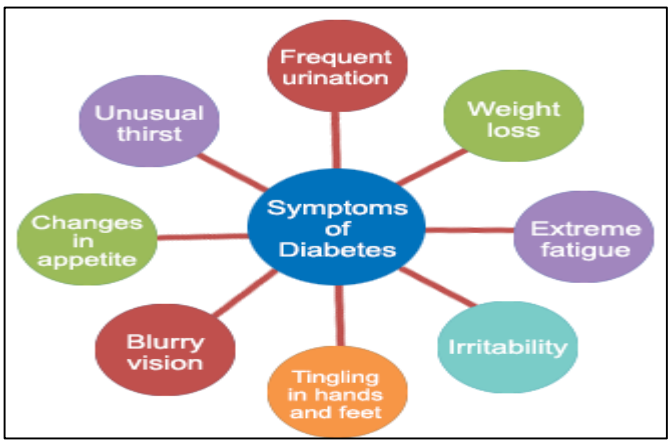
2.TYPE 3: GESTATIONAL DIABETES

Gestational diabetes can develop when a woman is pregnant. Pregnant women make hormones that can lead to insulin resistance. All women have insulin resistance late in their pregnancy. If the pancreas doesn't make enough insulin during pregnancy, a woman develops gestational diabetes. Overweight or obese women have a higher chance of gestational diabetes. Also, gaining too much weight during pregnancy may increase your likelihood of developing gestational diabetes.

Gestational diabetes most often goes away after the baby is born. However, a woman who has had gestational diabetes is more likely to develop type 2 diabetes later in life. Babies born to mothers who had gestational diabetes are also more likely to develop obesity and type 2 diabetes.

Symptoms:-

Signs and symptoms of diabetes:-



1. Frequent
2. urination
3. Excessive thirst
4. Increased hunger
5. Weight loss
6. Tiredness
7. Lack of interest and concentration
8. A tingling sensation or numbness in the hands or feet
9. Blurred vision
10. Frequent infections
11. Slow-healing wounds
12. Vomiting and stomach pain Common symptoms include:
13. Being more thirsty than usual
14. Going to the toilet more often, especially at night
15. Feeling tired and lethargic
16. Always feeling hungry
17. Itching, skin infections or rashes
18. Weight changes
19. Mood swings 20. Headaches
21. Feeling dizzy
22. Pain or tingling in the legs or feet

The development of type 1 diabetes is usually sudden and dramatic while the symptoms can often be mild or absent in people with type 2 diabetes.[3]

Etiology:-

Diabetes mellitus is classified into three broad categories:-

1) Type 1

2) Type 2

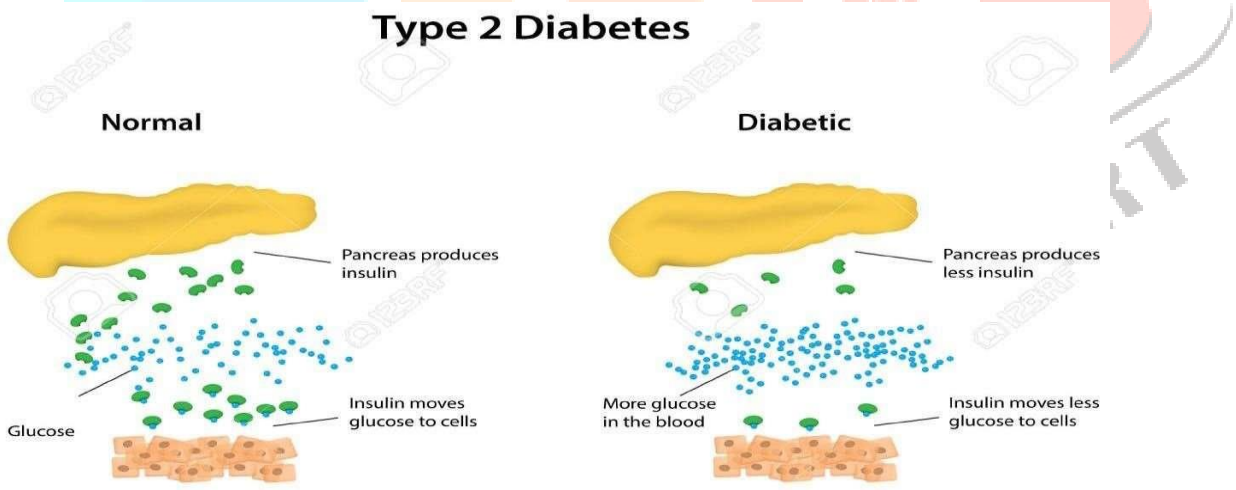
3) Gestational diabetes

1) Type 1:-

Type 1 diabetes mellitus is characterized by loss of the insulin producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immunemediated nature, in which a T-cell-mediated autoimmune attack leads to the loss of beta cells and thus insulin.

Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children Type 1 diabetes can be accompanied by irregular and unpredictable high blood sugar levels, frequently with ketosis; and sometimes with serious low blood sugar levels. Other complications include an impaired counterregulatory response to low blood sugar, infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (Addison's disease).These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.

2) Type 2:-



Type 2 DM is the most common type of diabetes mellitus .In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, high blood sugar can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce the liver's glucose production. Type 2 DM is due primarily to lifestyle factors and genetics. A number of lifestyle factors are known to be important to the development of type 2 DM, including obesity (defined by a body mass index of greater than 30), lack of physical activity, poor diet, stress, and urbanization.

Dietary factors also influence the risk of developing type 2 DM. Consumption of sugarsweetened drinks in excess is associated with an increased risk.The type of fats in the diet is also important,

with saturated fats and trans fatty acids increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk.

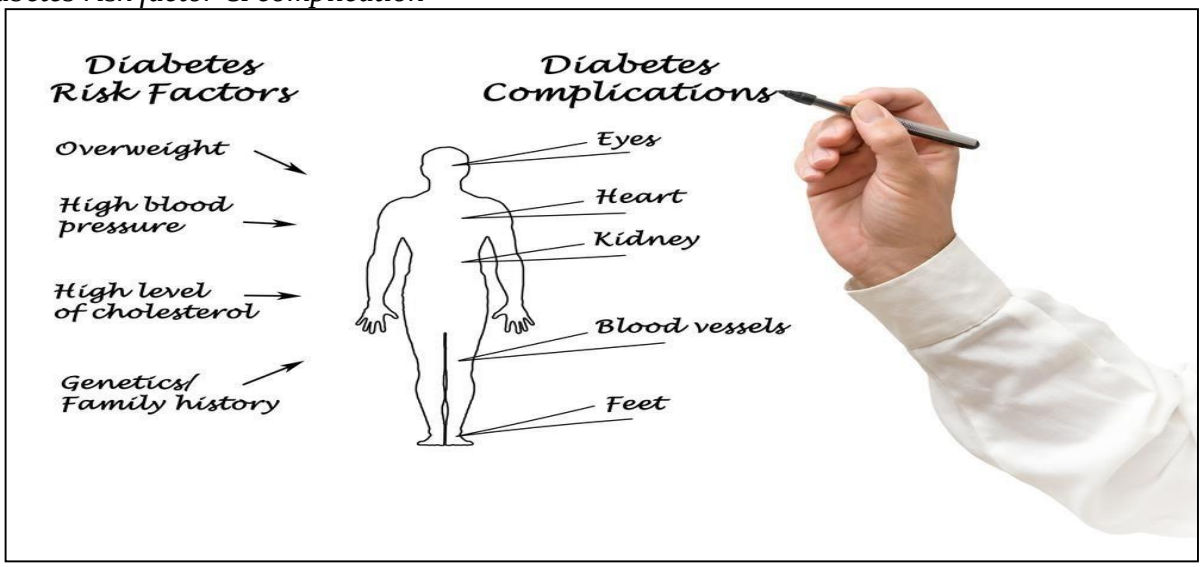
COMPARISON OF TYPE 1 & TYPE 2

Comparison of type 1 and 2 diabetes		
Feature	**Type 1 diabetes**	**Type 2 diabetes**
Onset	Sudden	Gradual
Age at onset	Any age (mostly young)	Mostly in adults
Body habitus	Thin or normal	Often obese
Ketoacidosis	Common	Rare
Autoantibodies	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
Concordance in identical twins	50%	90%
Prevalence	Less prevalent	More prevalent - 90 to 95% of U.S. diabetics

3) Gestational diabetes:

Gestational diabetes mellitus (GDM) resembles type 2 DM in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2–10% of all pregnancies and may improve or disappear after delivery.Gestational diabetes is fully treatable, but requires careful medical supervision throughout the pregnancy.[4]

Diabetes risk factor & complication



COMPLICATIONS:

Persistent hyper glycemia 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 Type1, 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.

1. 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.

2. DISEASES OF THE URINARY TRAIT:

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.

3. 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 most prevalent in elderly patients with type2, 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. Muscle pain is common.

Autonomic neuropathy may affect any part of the sympathetic or Para-sympathetic 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.

4. 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.

5. 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. [6]

3. REVIEW OF LITERATURE

1. Jagriti Upadhyay et al. Her aim of this narrative review is to summarize the pharmacologic treatment options available for patients with T2DM. Each therapeutic class is presented in detail, outlining medication effects, side effects, glycemic control, effect on weight, indications and contraindications, and use in selected populations (heart failure, renal insufficiency, obesity and the elderly). We also present representative cost for each antidiabetic category. Then, we provide an individualized guide for initiation and intensification of treatment and discuss the considerations and rationale for an individualized glycemic goal. (11)

2..Pitchai Balakumar et al. Her review discussed various presently employed and recently developed pharmacological interventions to treat diabetic nephropathy and to improve the function of diabetic kidney. In addition, the recently identified potential target sites involved in the pathogenesis of diabetic nephropathy have been delineated. (12)

3. Antea DeMarsilis et al He outline an up-to-date treatment approach that starts with identification of an individualized goal for glycemic control then selection, initiation, and further intensification of a personalized therapeutic plan for T2D. (13)

4. Allen C. Ho MD et al He review the evidence regarding the safety and efficacy of current anti–vascular endothelial growth factor (VEGF) pharmacotherapies for the treatment of diabetic macular edema (DME). (14) 5. Justis P. Ehlers MD et a; He searches yielded 230 citations, of which 108 were reviewed in full text. Of these, 31 were deemed appropriate for inclusion in this assessment and were assigned a level of evidence rating by the panel methodologist. (15)

6. Mattia Albiero et al He discuss state-of-the-art of the effects exerted by diabetes pharmacotherapy on such cell populations. Further, we highlight which outstanding questions remain to be addressed for a more comprehensive understanding of this topic. (16)

6.Saikat Dewanjee

et al He attempted to assess the role of autophagy and its adaptations in the diabetic heart. To delineate the molecular consequences of these events, we provided detailed insights into the autophagy regulation pieces of machinery including the mTOR/AMPK, TFEB/ZNSCAN3, FOXOs, SIRTs, PINK1/Parkin, Nrf2, miRNAs, and others in the diabetic cardiomyopathy. Given the clinical significance of autophagy in the diabetic heart, we further discussed the potential pharmacotherapeutic strategies towards targeting autophagy. Taken together, the present report meticulously assessed autophagy, its adaptations, and molecular regulations in diabetic cardiomyopathy and reviewed the current autophagy-targeting strategies.

4. DIAGNOSIS

If a diagnosis of diabetes is made, the clinician must feel confident that the diagnosis is fully established since the consequences for the individual are considerable and lifelong. The requirements for diagnostic confirmation for a person presenting with severe symptoms and gross hyperglycaemia differ from those for the asymptomatic person with bloodglucose values found to be just above the diagnostic cut–offvalue. Severe hyperglycaemia detected under conditions ofacute infective, traumatic, circulatory or other stress may be transitory and should not in itself be regarded as diagnostic of diabetes. The diagnosis of diabetes in an asymptomaticsubject should never be

made on the basis of a single abnormal blood glucose value. For the asymptomatic person,at least one additional plasma/blood glucose test result with avalue in the diabetic range is essential, either fasting, from random (casual) sample, or from the oral glucose tolerancetest (OGTT). If such samples fail to confirm the diagnosis ofdiabetes mellitus, it will usually be advisable to maintain surveillance with periodic re– testing until the diagnosticsituation becomes clear. In these circumstances, the clinicianshould take into consideration such additional factors as ethnicity, family history, age, adiposity, and concomitantdisorders, before deciding on a diagnostic or therapeutic course of action. An alternative to blood glucose estimation or the OGTT has long been sought to simplify the diagnosis of diabetes. Glycated haemoglobin, reflecting average glycaemia over a period of weeks, was thought to providesuch a test. Although in certain cases it gives equal or almost equal sensitivity and specificity to glucose measurement (6),it is not available in many parts of the world and is not well enough standardized for its use to be recommended at this time.

DIAGNOSIS DIABETES IN CHILDREN

Diabetes in children usually presents with severe symptoms, very high blood glucose levels, marked glycosuria, and ketonuria. In most children the diagnosis is confirmed without delay by blood glucose measurements, and treatment (including insulin injection) is initiated immediately, often as a life–saving measure. An OGTT is neither necessary nor appropriate for diagnosis in such circumstances. A small proportion of children and adolescents, however, present withless severe symptoms and may require fasting blood glucose measurement and/or an OGTT for diagnosis.

5. PRINCIPLES OF MANAGEMENT

It is important to define ambitious but achievable goals for each patient. In young type 1 patients there is good evidence that improved diabetic control reduces microvascular complications. It is well worth trying hard to minimize the metabolic derangement associated with diabetes mellitus in order to reduce the development of such complications. Education and support are essential to motivate the patient to learn how to adjust their insulin dose to optimize glycaemic control. This can only be achieved by the patient performing blood glucose monitoring at home and learning to adjust their insulin dose accordingly. The treatment regimen must be individualized. A common strategy is to combine injections of a short-acting insulin before each meal with a once daily injection of a long-acting insulin to provide a low steady background level during the night. Follow up must include structured care with assessment of chronic glycaemic control using HbA1c and regular screening for evidence of microvascular disease. This is especially important in the case of proliferative retinopathy and maculopathy, because prophylactic laser therapy can prevent blindness.

By contrast, striving for tight control of blood sugar in type 2 patients is only appropriate in selected cases. Tight control reduces macrovascular complications, but at the expense of increased hypoglycaemic attacks, and the number of patients that needs to be treated in this way to prevent one cardiovascular event is large. In contrast, aggressive treatment of hypertension is of substantial benefit, and the target blood pressure should be lower than in non-diabetic patients (130mmHg systolic and 80 mmHg diastolic). In older type 2 patients, hypoglycaemic treatment aims to minimize symptoms of polyuria, polydipsia or recurrent Candida infection, and to prevent hyperosmolar coma.

6. PHARMACOTHERAPY OF DIABETES:-

Treatment for Type 1 Diabetes Insulin Therapy:-

Insulin is the only medication that is effective in lowering blood glucose levels in type 1 diabetes. The use of insulin requires daily management of those factors that affect the insulin dose

(food, physical activity, illness, stress). See Table 5 for common insulin preparations. Rapid-acting insulin may be given before, during, or immediately after a meal. Administration after a meal may help reduce the postprandial hyperglycemia associated with high fat meals. The number of insulin injections/day will vary; insulin may be delivered with insulin syringes, insulin pens or external insulin pumps.

- Conventional therapy– 2 daily injections of mixed insulin (rapid- or short-acting and intermediate-acting) before breakfast and the evening meal.
- Conventional therapy with a split night-time dose– 1 injection of mixed insulin (rapid- or shortacting and intermediate-acting) before breakfast, 1 injection of rapid- or short-acting insulin before the evening meal and 1 injection of intermediate-acting insulin before the bedtime snack. This regimen is used to help reduce fasting hyperglycemia associated with the long interval between the evening meal and breakfast and the duration of action of the intermediate-acting insulin and to facilitate management of the dawn phenomenon.
- Multiple daily injections (MDI) of rapid- or short-acting insulin before every meal (and sometimes large snacks) with intermediate- or long-acting insulin once or twice a day. The addition of rapid- or short-acting insulin before lunch helps reduce pre-supper hyperglycemiawith less risk of hypoglycemia associated with very large pre-breakfast doses of intermediateacting insulin. With the exception of a bedtime snack to prevent hypoglycemia during the night, snacks usually are not required with MDI– an advantage for busy teens and those who wish to maintain a target weight. This may be called intensive therapy depending on the level ofglycemic control that is targeted.
- Intensive therapy with a continuous subcutaneous insulin infusion (CSII or insulin pump)– Rapid-acting insulin is delivered constantly to meet the body's basal need to suppress hepatic glucose production. A bolus dose of insulin is given before meals and snacks based on the amount of carbohydrate eaten and the measured level of blood glucose. This regimen is for motivated teens who are willing to test frequently (>4 times/day), monitor carbohydrate intake accurately, adjust insulin doses and commit to frequent contact with the diabetes team.

TABLE 5
Description of Commonly Used Insulin Preparations

Common Description	Name	Onset (hrs)	Peak (hrs)	Effective Duration (hrs)
Rapid-acting	Lispro	0.25	1-2	2-3
Short-acting	Regular	0.5-1	2-3	3-6
Intermediate-acting	NPH	2-4	4-10	10-16
Intermediate-acting	Lente	3-4	4-12	12-18
Long-acting	Ultralente	6-10	12-18	18-20
Long-acting	Glargine	1	None	24

Adapted From: Orr, DP. Contemporary management of adolescents with diabetes mellitus. Part 1: Type 1 diabetes. Adolescent Health Update 2000;12(2), Table 3, p 7.

The insulin dose depends on basal needs, food intake (especially the total amount of carbohydrate) and amount of physical activity. Changes in the dose of rapid- or short-acting insulin can be made according to a sliding scale that increases the dose for higher blood glucose levels and decreases the dose when blood glucose levels are lower. In addition, average blood glucose levels at various times of day can be calculated to further adjust the insulin recommended (rapid, short, intermediate and/or longacting preparations). Self-blood glucose testing is recommended before

each meal and the bedtime snack to help assess the dose and make changes as needed. Testing at 2:00-3:00 am is useful for evaluating night-time hypoglycemia and fasting hyperglycemia (dawn phenomenon).

A variety of blood glucose testing meters are available. Many contain memory to store the date, times and test results. Some can be downloaded to personal computers that graphically display blood glucose readings. New meters are available that allow the user to obtain blood from other areas beside the fingertips.

Average blood glucose levels over the last 3 months are measured by a blood test called glycatedhemoglobin. Different assays are available, each with their own normal (nondiabetic) range; hemoglobinA1c (HbA1c) is the preferred method. It is recommended to use the same laboratory to avoid confusion. The teen should have the test performed before visiting the physician to facilitate early discussion of results and if necessary, strategies to improve control. The 1994 Diabetes Control and Complications Trial (DCCT) that included 195 adolescents (13-18 years old) demonstrated that better blood glucose control significantly reduced the risk for long-term complications.5 Based upon the DCCT results, the target

HbA1c is 7%.[7]

TREATMENT FOR TYPE 2 DIABETES GLUCOSE LOWERING THERAPY

It is best to treat type 2 diabetes as vigorously as possible to avoid or delay the long term consequences of elevated blood glucose levels, high blood pressure, and dyslipidemia. Treatment focuses on discovering the most effective method to lower blood glucose levels, whether it is lifestyle modifications, insulin therapy, oral agents, or any combination of these factors. The diabetes team must work with the teen and the family to educate them about the importance of good control and to make the necessary adjustments in treatment every 4-6 weeks until acceptable control is achieved.

- At diagnosis, teens with type 2 diabetes who are acutely ill with significant hyperglycemia

(>300 mg/dl) and ketosis require insulin therapy. Insulin regimens are similar to those for teens with type 1 diabetes. In the less ill teen, initial treatment with medical nutrition therapy and exercise or a glucose lowering oral agent may be appropriate. In both circumstances, target blood glucose goals are similar to those with type 1 diabetes and treatment recommendations may change depending on blood glucose control.

- Glucose-lowering oral agents may be effective with type 2 diabetes. See Table 10 for the types currently available in the US.

- The biguanide, metformin, is often the first oral agent used with teens. Metformin is effective at reducing blood glucose levels without the risk of hypoglycemia. It does not cause weight gain and it helps reduce total cholesterol, LDL cholesterol, and triglyceride levels. Nausea and abdominal discomfort may occur with initial use. Starting at low doses (500 mg/day) and increasing graduallyto a maximum daily dose of 2200 mg may minimize these side effects. Because the kidney metabolizes biguanides, they should not be used if the teen is dehydrated. In young women with diabetes and polycystic ovary syndrome, metformin may normalize

ovulatory abnormalities, thereby increasing the risk for pregnancy in those who are sexually active and necessitating preconception counseling.

TABLE 10
Glucose-Lowering Oral Agents Commonly Used for Treatment of Type 2 Diabetes.

Type of Agent	Mechanism of Action	Generic Names
Biguanides	Decrease hepatic glucose production, increase muscle insulin sensitivity	Metformin
Sulfonylureas	Increase insulin secretion	Glyburide Glipizide Glimepiride
Meglitinide	Short-term promotion of glucose-stimulated insulin secretion	Repaglinide
Glucosidase inhibitors	Decrease digestion and absorption of carbohydrate	Acarbose Miglitol
Thiazolidenediones	Increase insulin action in muscle, adipose tissue and probably the liver	Rosiglitazone Pioglitazone

- The other oral agents are used infrequently with teens due to concerns with hypoglycemiaandweight gain (sulfonylureas), more severe gastrointestinal symptoms (glucosidase inhibitors) andsafety (thiazolidinediones).
- Combination regimens that include insulin with an oral agent may be used to help lowerbloodglucose levels. Combination therapy usually requires less insulin, however blood glucose monitoring is still essential.

Blood glucose monitoring is recommended to evaluate treatment. Teens whose diabetes is controlled with life style changes or oral agents are encouraged to perform blood glucose testing before breakfast and one other time during the day. Teens on insulin therapy need to test 2-4 times/day depending on the insulin regimen. In addition, blood glucose monitoring 2 hours after a meal provides information about the effectiveness of lifestyle changes. If 2 hour post-meal blood glucose levels are >180 mg/dl, the teen needs to decrease carbohydrate goals, increase activity or adjust medications. HbA1c are monitored quarterly. As in type 1 diabetes, a large clinical study, the United Kingdom Prospective Diabetes Study, has shown that better glycemic control (HbA1c < 7.0%) results in reduced cardiovascular and microvascular complications.

7. ORAL HYPOGLYCAEMIC DRUGS AND

TYPE 2 DIABETES

Oral hypoglycaemic drugs are useful in type 2 diabetes as adjuncts to continued dietary restraint. They fall into four groups: 1. biguanides (metformin);

2. sulphonylureas and related drugs;

3. thiazolidinediones (glitazones);

4. α-glucosidase inhibitors (acarbose).

Most type 2 diabetic patients initially achieve satisfactory control with diet either alone or combined with one of these agents. The small proportion who cannot be controlled with drugs atthis stage (primary failure) require insulin. Subsequent failure after initially adequate control (secondary failure) occurs in about one-third of patients, and is treated with insulin. Inhaled insulin is effective but expensive. Its bioavailability is affected by smoking and by respiratory infections, and currently should only be used with great caution in patients with asthma/ COPD.

1. BIGUANIDES: METFORMIN

Metformin is the only biguanide available in the UK. It is used in type 2 diabetic patients inadequately controlled by diet. Its anorectic effect aids weight reduction, so it is a first choice drug for obese type 2 patients, provided there are no contraindications. It must not be used in patients at risk of lactic acidosis and is contraindicated in:

• renal failure (it is eliminated in the urine, see below);

• alcoholics;

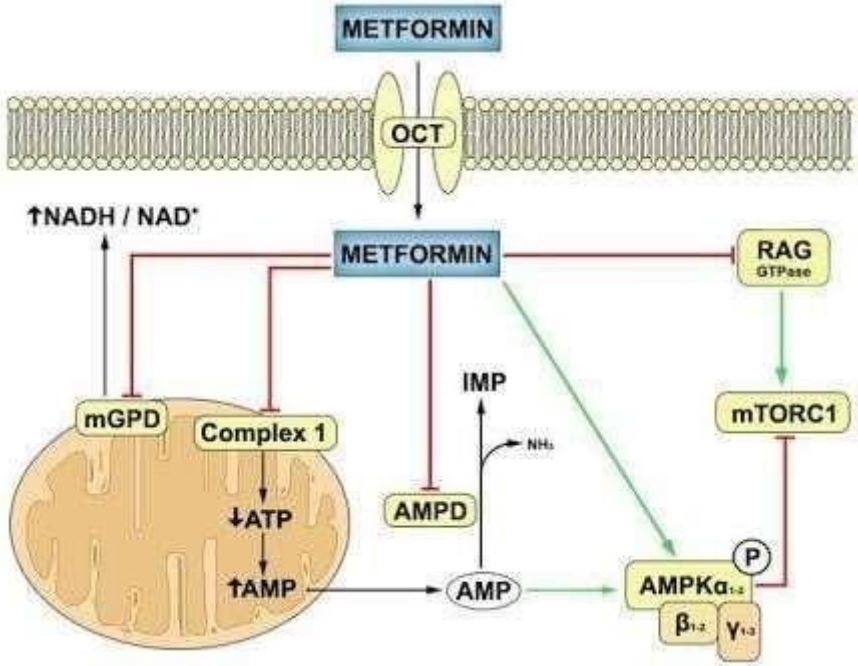
• cirrhosis;

• chronic lung disease (because of hypoxia);

• cardiac failure (because of poor tissue perfusion);

• congenital mitochondrial myopathy (which is often accompanied by diabetes);

• acute myocardial infarction and other serious intercurrent illness (insulin should besubstituted).



Metformin should be withdrawn and insulin substituted before major elective surgery. Plasma creatinine and liver function tests should be monitored before and during its use.

MECHANISM OF ACTION:

This remains uncertain. Biguanides do not produce hypoglycaemia and are effective in pancreatectomized animals. Effects of metformin include:

• reduced glucose absorption from the gut;

• facilitation of glucose entry into muscle by a non-insulinresponsive mechanism;

• inhibition of gluconeogenesis in the liver;

• Suppression of oxidative glucose metabolism and enhanced anaerobic glycolysis.

ADVERSE EFFECTS

Metformin causes nausea, a metallic taste, anorexia, vomiting and diarrhoea. The symptoms are worst when treatment is initiated and a few patients cannot tolerate even small doses. Lactic acidosis, which has a reported mortality in excess of 60%,is uncommon provided that the above contraindications are respected. Treatment is by reversal of hypoxia and circulatorycollapse and peritoneal or haemodialysis to alleviate sodiumoverloading and removing the drug. Phenformin (withdrawnin the UK and USA) was more frequently associated with thisproblem than metformin. Absorption of vitamin B12 is reducedby metformin, but this is seldom clinically important.

Uses

Metfromin 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. [8]

2. THIAZOLIDINEDIONES:-

Thiazolidinediones (TZDs), also known as "glitazones," bind to PPARγ a type of nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. These PPARs act on peroxysome proliferator responsive elements (PPRE).[The PPREs influence insulin-sensitive genes, which enhance production of mRNAs of insulin-dependent enzymes. The final result is better use of glucose by the cells.

Typical reductions in glycated hemoglobin (A1C) values are 1.5–2.0%.

Some examples are:

Rosiglitazone (Avandia): the European Medicines Agency recommended in September 2010 that it be suspended from the EU market due to elevated cardiovascular risks. Pioglitazone (Actos)

Troglitazone (Rezulin): used in 1990s, withdrawn due to hepatitis and liver damage risk.

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. (4) They act most effectively in combination with other oral antidiabetic agents including Sulfonyl urea and metformin.

USE

Thiazolidine diones improves glycaemic control in patients with insulin resistance by reducing HbA1C levels upto 1.5%. The combination of Thiazolidine diones with metformin is preferred to combination wtith Sulfonyl urea, especially in obese patients.

3. SULPHONYLUREAS AND RELATED DRUGS

Sulphonylureas (e.g. tolbutamide, glibenclamide, gliclazide) are used for type 2 diabetics who have not responded adequately to diet alone or diet and metformin with which they are additive. They improve symptoms of polyuria and polydipsia, but (in contrast to metformin) stimulate appetite. Chlorpropamide, the longest-acting agent in this group, has a higher incidence of adverse effects (especially hypoglycaemia) than other drugs of this class and should be avoided. This is because of a protracted effect and reduced renal clearance in patients with renal dysfunction and the elderly; thus it is hardly ever used. Tolbutamide and gliclazide are shorter acting than glibenclamide, so there is less risk of hypoglycaemia, and for this reason they are preferred in the elderly. Related drugs (e.g. repaglinide, nateglinide) are chemically distinct, but act at the same receptor. They are shorter acting even than tolbutamide, but more expensive. They are given before meals.

MECHANISM OF ACTION

The hypoglycaemic effect of these drugs depends on the presence of functioning B cells. Sulphonylureas, like glucose, depolarize B cells and release insulin. They do this by binding to sulphonylurea receptors (SUR) and blocking ATP-dependent potassium channels (KATP); the resulting depolarization activates voltage-sensitive Ca2channels, in turn causing entry of Ca2 ions and insulin secretion.

ADVERSE EFFECTS

Sulphonylureas can cause hypoglycaemia. Chlorpropamide, the longest-acting agent, was responsible for many cases. It alsocauses flushing in susceptible individuals when ethanol is consumed,and can cause dilutionalhyponatraemia (by potentiatingADH, see Chapter 42). Allergic reactions to sulphonylureasinclude rashes, drug fever, gastrointestinal upsets, transient jaundice (usually cholestatic) and haematopoietic changes,including thrombocytopenia, neutropenia and pancytopenia.Serious effects other than hypoglycaemia are uncommon.

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 thiazolidine dione is also used

4. THIAZOLIDINEDIONES (GLITAZONES)

Glitazones (e.g. piolitazone, rosiglitazone) were developed from the chance finding that a fibrate drug increased insulin sensitivity.Glitazones lower blood glucose and haemoglobin A1c (HbA1c) in type 2 diabetes mellitus patients who are inadequately controlled on diet alone or diet and other oral hypoglycaemic drugs. An effect on mortality or diabetic complications has yet to be established, but they have rapidly become very widely used.

MECHANISM OF ACTION

Glitazones bind to the peroxisome-proliferating activator receptor γ (PPARγ), a nuclear receptor found mainly in adipocytes and also in hepatocytes and myocytes. It works slowly, increasing the sensitivity to insulin possibly via effects of circulating fatty acids on glucose metabolism. Adverse effects

The first two glitazones caused severe hepatotoxicity and are not used. Hepatotoxicity has not proved problematic with rosiglitazone or pioglitazone, although they are contraindicated in patients with hepatic impairment and liver function should be monitored during their use. The most common adverse effects are weight gain (possibly partly directly related to their effect onadipocytes) and fluid retention due to an effect of PPARγ receptors on renal tubular sodium ion absorption. They can also exacerbate cardiac dysfunction and are therefore contraindicated inheart failure. Recently, an association with increased bone fractures and osteoporosis has been noted. They are contraindicated during pregnancy. A possible increase in myocardial infarctionwith rosiglitazone has been noted, but the data are controversial.

USE

Thiazolidine diones improves glycaemic control in patients with insulin resistance by reducing HbA1C levels upto 1.5%. The combination of Thiazolidine diones with metformin is preferred to combination wtith Sulfonyl urea, especially in obese patients.

III 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. [9]

8. CONCLUSION

There is now overwhelming evidence that long term treatment with inhaled corticosteroids provide no significant clinical benefit to patient with COPD. The disease process in COPD appears to be steroid resistant yet patients with COPD are often treated with high doses of ICS for want of any effective therapy in the disease. This must be associated with a high risk of adverse systemic affects and involve unnecessary expense. Inhaled corticosteroids treatment should not be routinely recommended for the management of COPD, unless there is co-existing asthma.

The Guidelines recommended that in ICS should be prescribed for patience with an FEV1 less than 50%, who have two or more exacerbation, requiring treatment with antibiotics/oral corticosteroids in a 12 months period. The term of treatment is to reduce exacerbation rate & slow decline in health status & not to improve lung function. Although maintenance dose of CS therapy in COPD is usually recommended some patience with Advanced COPD may require maintenance dose of oral corticosteroid. In such case the dose of oral CS should be kept as low as possible.

There is need for further studies to investigate the efficacy and safety of long term use of ICS for the management of COPD.[10]

9. REFERENCES

1. American Diabetes Association. Economic consequences of diabetes mellitus in the U.S. in 1997. DiabetesCare 1998;21(2):296-309.

2. Rosenbloom AL, Joe JR, Young RS, Winter WE. Emerging epidemic of type 2 diabetes in youth.DiabetesCare 1999;22(2):345-354.

3. Pinhas-Hamiel O, Dolan L, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of noninsulin-dependent diabetes mellitus among adolescents. J Pediatr 1999;128:608-615.

4. American Diabetes Association. Type 2 diabetes in children and adolescents.Pediatrics 2000;105(3 Pt1):671-680.

5. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment onthedevelopment and progression of long-term complications in adolescents with insulin-dependent diabetesmellitus: Diabetes Control and Complications Trial. J Pediatr 1994;125(2):177188.

6. Gillespie SJ, Kulkarni KD, Daly AE.Using carbohydrate counting in diabetes clinical practice. J AmDietAssoc 1998;98(8):897-905.

7. Grey M, Boland EA, Davidson M, Yu C, Tamborlane WV. Coping skills training for youths with diabeteson intensive therapy.ApplNurs Res 1999;12(1):3-12.

8. American Diabetes Association. Implications of the United Kingdom Prospective DiabetesStudy.Diabetes Care 2001;24:S28-S32

.

9. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reductionin the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med2002;346(6):393-403.

10. Clinical Pharmacy and Therapeuties by Roger Walker

11. Upadhyay, J., Polyzos, S. A., Perakakis, N., Thakkar, B., Paschou, S. A., Katsiki, N., … Mantzoros, C. S. (2018). Pharmacotherapy of type 2 diabetes: An update. Metabolism, 78

12. Balakumar, P., Arora, M. K., Ganti, S. S., Reddy, J., & Singh, M. (2009). Recent advances in pharmacotherapy for diabetic nephropathy: Current perspectives and future directions. Pharmacological Research, 60(1), 24–32. doi:10.1016/j.phrs.2009.02.002

13. Antea DeMarsilis[a] · Niyoti Reddy[b] · Chrysoula Boutari[c] · Andreas Filippaios[a] · Elliot Stern thal[d] · Niki Katsiki[e,f] nikikatsiki@nutr.ihu.gr · Christos Mantzoros[a]Pharmacotherapy of type 2 diabetes: An update and future directions

14. Ho, A. C., Scott, I. U., Kim, S. J., Brown, G. C., Brown, M. M., Ip, M. S., & Recchia, F. M. (2012). Anti–Vascular Endothelial Growth Factor Pharmacotherapy for Diabetic Macular Edema. Ophthalmology, 119(10), 2179–2188. doi:10.1016/j.ophtha.2012.07.058

15. Justis P. Ehlers MD [1], Steven Yeh MD [2 3], Maureen G. Maguire PhD [4], Justine R. Smith MBBS, PhD [5], Prithvi Mruthyunjaya MD, MHS [6], Nieraj Jain MD [3], Leo A. Kim MD, PhD [7], Christina Y. Weng MD, MBA [8], Christina J. Flaxel MD [9], Scott D. Schoenberger MD [10], Stephen J. Kim MD [11] ·Intravitreal Pharmacotherapies for Diabetic Macular Edema: A Report by the American Academy of Ophthalmology

16. Mattia Albiero [1 2], Benedetta Maria Bonora [1 2], Gian Paolo Fadini.Diabetes pharmacotherapy and circulating stem/progenitor cells. State of the art and evidence gaps

17. Dewanjee, S., Vallamkondu, J., Kalra, R. S., John, A., Reddy, P. H., & Kandimalla, R. (2021). Autophagy in the diabetic heart: A potential pharmacotherapeutic target in diabetic cardiomyopathy. Ageing Research Reviews, 68,
101338. doi:10.1016/j.arr.2021.101338