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A REVIEW ON INFLUENCE OF ANTIDIABETIC MEDICATIONS ON QUALITY OF LIFE

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ABSTRACT

The term diabetes includes several different metabolic disorders that all, if left untreated, result in abnormally high concentration of a sugar called glucose in the blood. Diabetes mellitus type 1 result when the pancreas no longer produces significant amounts of the hormone insulin, usually owing to the autoimmune destruction of the insulin-producing beta cells of the pancreas. Diabetes mellitus type 2, in contrast, is now thought to result from autoimmune attacks on the pancreas and/or insulin resistance. The pancreas of a person with type 2 diabetes may be producing normal or even abnormally large amounts of insulin. Other forms of diabetes mellitus, such as the various forms of maturity onset diabetes of the young, may represent some combination of insufficient insulin production and insulin resistance. Some degree of insulin resistance may also be present in a person with type 1 diabetes. The main goal of diabetes management is, as far as possible, to restore carbohydrate metabolism to a normal state. To achieve this goal, individuals with an absolute deficiency of insulin require insulin replacement therapy, which is given through injections or an insulin pump. Insulin resistance, in contrast, can be corrected by dietary modifications and exercise. Other goals of diabetes management are to prevent or treat the many complications that can result from the disease itself and from its treatment. Diabetes mellitus is associated with a marked increased of cardiovascular events. The treatment strategy of diabetes has to be based on the knowledge of its pathophysiology. Thus, insulin is essential for treatment of type 1 diabetic patients because there is a defect in insulin secretion. However, treatment of type 2 diabetic patients is more complex because a defect in both insulin secretion and insulin action exists. Therefore, the treatment selection will depend on the stage of the disease and the individual characteristics of the patient. Management of patients with Type 2 diabetes mellitus (T2DM) demands a comprehensive approach which includes diabetes education, an emphasis on life style modification, achievement of good glycemic control, minimization of cardiovascular risk, and avoidance of drugs that can aggravate glucose or lipid metabolism, and screening for diabetes complications. Comprehensive diabetes management can delay the progression of complication and maximize the quality of life. Acquiring knowledge about diabetes is an essential part of diabetes management, and even more important is to make the patient aware of this chronic disease. "For a diabetic patient, knowledge and understanding are not a part of treatment they are the treatment".

KEYWORDS: Diabetes mellitus, autoimmune, glycemic control, cardiovascular risk etc.

INTRODUCTION

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.[1] Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications.[2] Acute complications can include diabetic ketoacidosis, nonketotic hyper osmolar coma, or death.[3] Serious long-term complications include heart disease, stroke, chronic kidney failure, foot ulcers, and damage to the eyes.[2] Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced.[4] There are three main types of diabetes mellitus.

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.[2] Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly.[2] As the disease progresses a lack of insulin may also develop.[5] 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 not enough exercise.[2] Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels.[2]

Prevention and treatment involve maintaining a healthy diet, regular physical exercise, a normal body weight, and avoiding use of tobacco. Control of blood pressure and maintaining proper foot care are important for people with the disease. Type 1 DM must be managed with insulin injections.[2] Type 2 DM may be treated with medications with or without insulin.[6] Insulin and some oral medications can cause low blood sugar.[7] Weight loss surgery in those with obesity is sometimes an effective measure in those with type 2 DM.[8] Gestational diabetes usually resolves after the birth of the baby.[9]

Signs and symptoms

The classic symptoms of untreated diabetes are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger).[10] Symptoms may develop rapidly (weeks or months) in type 1 DM, while they usually develop much more slowly and may be subtle or absent in type 2 DM. Several other signs and symptoms can mark the onset of diabetes although they are not specific to the disease. In addition to the known ones above, they include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes.

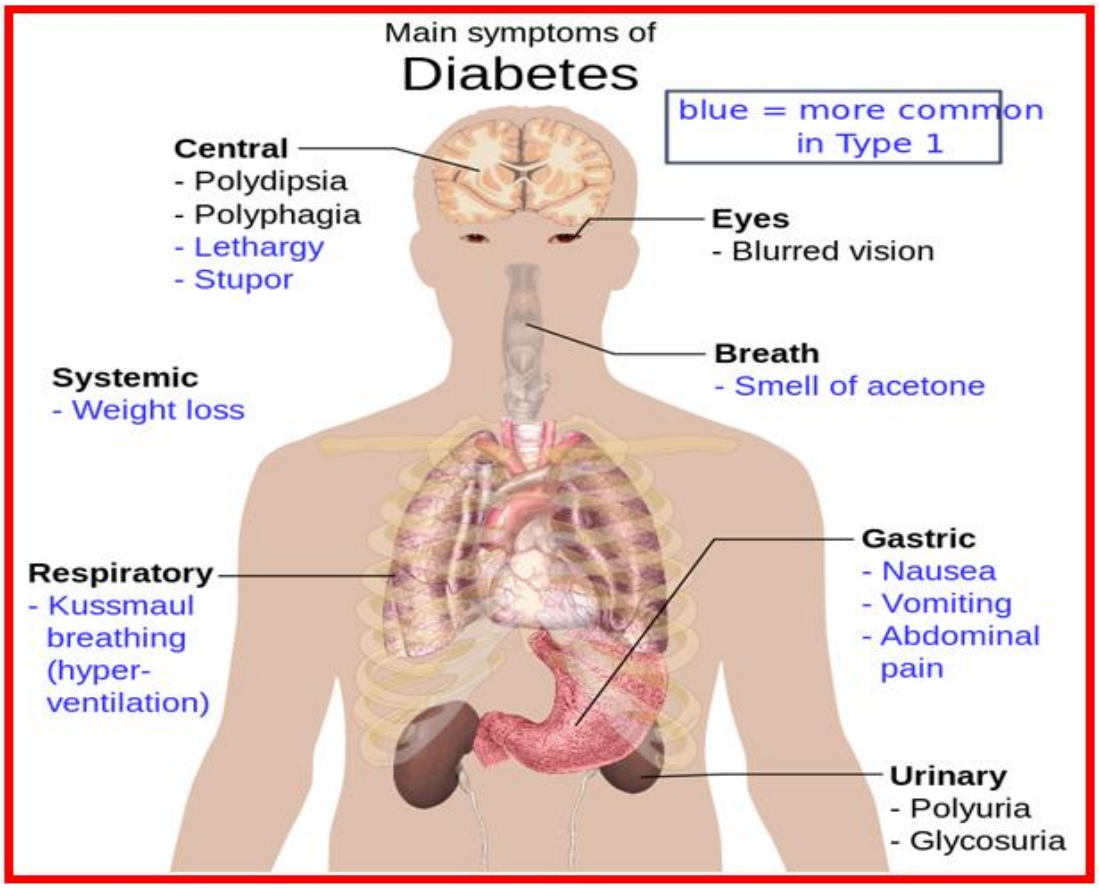

Fig: Overview of the most significant symptoms of diabetes.

Diabetic emergencies

Low blood sugar is common in persons with type 1 and type 2 DM. Most cases are mild and are not considered medical emergencies. Effects can range from feelings of unease, sweating, trembling, and increased appetite in mild cases to more serious issues such as confusion, changes in behaviour such as aggressiveness, seizures, unconsciousness, and (rarely) permanent brain damage or death in severe cases.[11, 12] Moderate hypoglycaemia may easily be mistaken for drunkenness[13] rapid breathing and sweating, cold, pale skin are characteristic of hypoglycaemia but not definitive.[14] Mild to moderate cases are self-treated by eating or drinking something high in sugar. Severe cases can lead to unconsciousness and must be treated with intravenous glucose or injections with glucagon.[citation needed]. People (usually with type 1 DM) may also experience episodes of diabetic ketoacidosis, a metabolic disturbance characterized by nausea, vomiting and abdominal pain, the smell of acetone on the breath, deep breathing known as Kussmaul breathing, and in severe cases a decreased level of consciousness. A rare but equally severe possibility is hyperosmolar nonketotic

state, which is more common in type, 2 DM and is mainly the result of dehydration.[15]

Complications

All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20) but may be the first symptom in those who have otherwise not received a diagnosis before that time. The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease[16] and about 75% of deaths in diabetics are due to coronary artery disease.[17] Other "macro vascular" diseases are stroke, and peripheral vascular disease.

The primary complications of diabetes due to damage in small blood vessels include damage to the eyes, kidneys, and nerves. Damage to the eyes, known as diabetic retinopathy, is caused by damage to the blood vessels in the retina of the eye, and can result in gradual vision loss and blindness. Damage to the kidneys, known as diabetic nephropathy, can lead to tissue scarring, urine protein loss, and eventually chronic kidney disease, sometimes requiring dialysis or kidney transplant. Damage to the nerves of the body, known as diabetic neuropathy, is the most common complication of diabetes.[18] The symptoms can include numbness, tingling, pain, and altered pain sensation, which can lead to damage to the skin. Diabetes-related foot problems (such as diabetic foot ulcers) may occur, and can be difficult to treat, occasionally requiring amputation. Additionally, proximal diabetic neuropathy causes painful muscle wasting and weakness. There is a link between cognitive deficit and diabetes. Compared to those without diabetes, those with the disease have a 1.2 to 1.5-fold greater rate of decline in cognitive function.[19] Being diabetic, especially when on insulin increases the risk of falls in older people.[20]

Types

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes, and "other specific types".[4] The "other specific types" are a collection of a few dozen individual causes.[4] Diabetes is a more variable disease than once thought and people may have combinations of forms.[21] The term "diabetes", without qualification, usually refers to diabetes mellitus.

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 immune-mediated nature, in which a T-cell-mediated autoimmune attack leads to the loss of beta cells and thus insulin.[22] Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children.

"Brittle" diabetes, also known as unstable diabetes or labile diabetes is a term that was traditionally used to describe the dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used.[23] Still, 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 counter regulatory response to low blood sugar, infection, gastro paresis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (e.g., Addison's disease)[23] These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.[24]

Type 1 diabetes is partly inherited, with multiple genes, including certain HLA genotypes, known to influence the risk of diabetes. The increase of incidence of type 1 diabetes reflects the modern lifestyle.[25] In genetically susceptible people, the onset of diabetes can be triggered by one or more environmental factors[26] such as a viral infection or diet. Several viruses have been implicated, but to date there is no stringent evidence to support this hypothesis in humans.[27] Among dietary factors, data suggest that gliadin (a protein present in gluten) may play a role in the development of type 1 diabetes, but the mechanism is not fully understood.[28, 29]

Type 2: Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion.[4] The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 DM is the most common type of diabetes mellitus.[citation needed]**.** Type 2 DM is due primarily to lifestyle factors and genetics.[30] 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.[31] Dietary factors also influence the risk of developing type 2 DM. Consumption of sugar-sweetened drinks in excess is associated with an increased risk.[32, 33] 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.[30] Eating lots of white rice also may increase the risk of diabetes[34] A lack of exercise is believed to cause 7% of cases.[35]

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. However, after pregnancy approximately 5–10% of women with gestational diabetes are found to have diabetes mellitus, most commonly type 2.[36] Gestational diabetes is fully treatable, but requires careful medical supervision throughout the pregnancy. Management may include dietary changes, blood glucose monitoring, and in some cases, insulin may be required.

Maturity onset diabetes of the young: Maturity onset diabetes of the young (MODY) is an autosomal dominant inherited form of diabetes, due to one of several single-gene mutations causing defects in insulin production.[37] It is significantly less common than the three main types. The name of this disease refers to early hypotheses as to its nature. Being due to a defective gene, this disease varies in age at presentation and in severity according to the specific gene defect; thus there are at least 13 subtypes of MODY. People with MODY often can control it without using insulin.

Other types: Prediabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Many people destined to develop type 2 DM spend many years in a state of prediabetes. Latent autoimmune diabetes of adults (LADA) is a condition in which type 1 DM develops in adults. Adults with LADA are frequently initially misdiagnosed as having type 2 DM, based on age rather than cause. "Type 3 diabetes" has been suggested as a term for Alzheimer's disease as the underlying processes may involve insulin resistance by the brain.[38]

Diabetes Pathophysiology[39-45]

Diabetes occurs when there is a dis-balance between the demand and production of the hormone insulin.

Control of blood sugar: When food is taken, it is broken down into smaller components. Sugars and carbohydrates are thus broken down into glucose for the body to utilize them as an energy source. The liver is also able to manufacture glucose.

In normal persons the hormone insulin, which is made by the beta cells of the pancreas, regulates how much glucose is in the blood. When there is excess of glucose in blood, insulin stimulates cells to absorb enough glucose from the blood for the energy that they need.

Insulin also stimulates the liver to absorb and store any excess glucose that is in the blood. Insulin release is triggered after a meal when there is a rise in blood glucose. When blood glucose levels fall, during exercise for example, insulin levels fall too.

High insulin will promote glucose uptake, glycolysis (break down of glucose), and glycogenesis (formation of storage form of glucose called glycogen), as well as uptake and synthesis of amino acids, proteins, and fat.

Low insulin will promote gluconeogenesis (breakdown of various substrates to release glucose), glycogenolysis (breakdown of glycogen to release gluose), lipolysis (breakdown of lipids to release glucose), and proteolysis (breakdown of proteins to release glucose). Insulin acts via insulin receptors.

	Liver	**Adipose or fat Tissue**	**Muscle**
High insulin	Glycolysis Glycogenesis	Triglyceride synthesis	Amino acid uptake Protein synthesis
Low insulin	Gluconeogenesis Glycogenolysis	Lipolysis	Proteolysis

Normal Responses to Eating and Fasting: In a fed state: there is increased insulin secretion, causing glycolysis, glycogen storage, fatty acid synthesis/storage, and protein synthesis. After an overnight fast: there is low insulin and high glucagon that can cause glycogen breakdown, hepatic gluconeogenesis, and lipolysis. After a prolonged fast: there is extremely low insulin and low glucagon, this causes lipolysis to take over. Lipids are the main fuel source. Gluconeogenesis is minimized, as it causes nitrogen wasting, ammonia build-up, and loss of muscle mass.

Hormones: Hormones that raise blood sugar include glucagon, epinephrine and norepinephrine, cortisol, Growth hormone etc. These hormones are released due to *stress*. Thus during phases of stress like an infection, surgery or pregnancy diabetes control worsens and blood sugar rises.

Pathophysiology of type 1 diabetes: In this condition the immune system attacks and destroys the insulin producing beta cells of the pancreas. There is beta cell deficiency leading to complete insulin deficiency. Thus is it termed an autoimmune disease where there are anti insulin or anti-islet cell antibodies present in blood. These cause lymphocytic infiltration and destruction of the pancreas islets. The destruction may take time but the onset of the disease is rapid and may occur over a few days to weeks. There may be other autoimmune conditions associated with type 1 diabetes including vitiligo and hypothyroidism. Type 1 diabetes always requires insulin therapy, and will not respond to insulin-stimulating oral drugs.

Pathophysiology of type 2 diabetes: This condition is caused by a relative deficiency of insulin and not an absolute deficiency. This means that the body is unable to produce adequate insulin to meet the needs. There is Beta cell deficiency coupled with peripheral insulin

resistance. Peripheral insulin resistance means that although blood levels of insulin are high there is no hypoglycaemia or low blood sugar. This may be due to changes in the insulin receptors that bring about the actions of the insulin. Obesity is the main cause of insulin resistance. In most cases over time the patients need to take insulin when oral drugs fail to stimulate adequate insulin release.

	Type 1 Diabetes	**Type 2 Diabetes**
Etiology	Autoimmune	Peripheral insulin resistance
Formerly known as	IDDM	NIDDM or "adult onset" diabetes
Age of onset	Younger	Older
Obesity	Rare	Common
Family History	Rare	Common
HLA association/Genetic association	Yes	No
Ketosis	Yes	No
Insulin resistance	No	Yes
Presence of body's own insulin	No	Yes
Respond to Oral Agents	No	Yes

Pathophysiology of gestational diabetes

Gestational diabetes is caused when there are excessive counter-insulin hormones of pregnancy. This leads to a state of insulin resistance and high blood sugar in the mother. There may be defective insulin receptors.

Pathophysiology behind symptoms and complications of diabetes

- Polydipsia or increased thirst is due to high blood glucose that raises the osmolarity of blood and makes it more concentrated.
- Polyuria or increased frequency of urination is due to excess fluid intake and glucose-induced urination.
- Weight loss occurs due to loss of calories in urine.
- Polyphagia or increased hunger due to loss or excess glucose in urine that leads the body to crave for more glucose.
- Poor wound healing, gum and other infections due to increased blood glucose providing a good source of nutrition to microbes and due to a diminished immunity.
- Heart disease – this occurs due to changes in the large blood vessels leading to coronary, cerebral, and peripheral artery diseases, atherosclerosis, dyslipidemia etc.
- Eye damage – this is termed diabetic retinopathy and occurs due to damage of the fine blood vessels of the retina in the eye due to long term exposure to high blood sugar.
- Kidney damage – similar damage to small and large blood vessels of the kidneys. Initially there is proteinuria or increased outflow of protein and may lead to end stage renal disease (ESRD).
- Nerve damage – this can affect the arms and legs and is called stocking-glove numbness/tingling. It can also affect autonomic functions leading to impotence, erectile dysfunction, difficulty in digestion or gastroparesis etc.
- Diabetic foot – this occurs due to peripheral nerve damage as well as blood vessel affliction due to long term diabetes. Little trauma, sores and blisters go unnoticed due to lack of sensation and peripheral vascular disease impairs healing and allows infection.
- Diabetic Ketoacidosis is caused in type 1 diabetes where there is complete lack of insulin and reliance on fatty acids for energy. This uncontrolled lipid breakdown leads to formation of ketones and causes acidosis and ketonemia. This is a medical emergency.
- Non-Ketotic Hyperosmolarity – this is caused due to extreme rise of blood sugar. This is seen in type 2 diabetics. There is just enough insulin to suppress ketone synthesis. The high blood sugar leads to excessive concentration or osmolarity of blood which in turn leads to dieresis and collapse of the blood vessels and cardiovascular shock. This is a medical emergency.

Pharmacologic Treatment

The management of type 1 and 2 diabetes mellitus (DM) requires addressing multiple goals, with the primary goal being glycemic control. Maintaining glycemic control in patients with diabetes prevents many of the microvascular and macrovascular complications associated with diabetes. When considering appropriate pharmacologic therapy, a major factor to consider is whether the patient is insulin deficient, insulin resistant, or both. Treatment options can be divided into noninsulin therapies—insulin sensitizers, secretagogues, alpha glucosidase inhibitors, incretins, pramlintide, bromocriptine and sodium glucose cotransporter 2 (SGLT-2) inhibitors—and insulins (insulin and insulin analogs). Table 1 lists the noninsulin therapies available and Table 2 lists of the insulin therapies.[46-50]

Table 1: Non Insulin Therapies.

Class	Generic name (Brand)	Route	Comments
Insulin sensitizers			
Biguanides	Metformin (Glucophage)	Oral	Weight loss No hypoglycemia GI upset
Thiazolidinediones	Rosiglitazone (Avandia) Pioglitazone (Actos)	Oral	Weight gain Peripheral edema
Insulin secretagogues			
Sulfonylureas	Chlorpropamide (Diabinese) Glibenclamide (Glyburide) Glimepiride (Amaryl) Glipizide (Glucotrol) Tolazamide (Tolinase) Tolbutamide (Orinase)	Oral	Hypoglycemia Weight gain
Glinides	Nateglinide (Starlix) Repaglinide (Prandin)	Oral	Weight gain
Alpha-glucosidase inhibitors			
	Acarbose (Precose) Miglitol (Glyset)	Oral	GI upset No hypoglycemia
Incretins			
GLP-1 receptor agonists **Short-acting (4-6 hrs)**	Exenatide (Byetta)	SC	Weight loss GI upset
GLP-1 receptor agonists **Intermediate-acting (24 hrs)**	Liraglutide (Victoza)	SC	Weight loss Nausea
GLP-1 receptor agonists **Long-acting (7 days)**	Exenatide ER (Bydureon) Albiglutide (Tanzeum) Dulaglutide (Trulicity)	SC	Weight loss Nausea
DPP-4 inhibitors	Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta) Alogliptin (Nesina)	Oral	No hypoglycemia Nasopharyngitis Weight neutral
Pramlintide			
	Pramlinitide (Symlin)	SC	Weight loss GI upset Adjunctive tx with insulin
Rapid-release bromocriptine			
	Bromocriptine quick-release (Cycloset)	Oral	Take within 2 hrs of awakening Nausea, stuffy nose
SGLT-2 inhibitors			
	Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)	Oral	Polyuria UTIs

Abbreviations: DPP-4 = dipeptidyl peptidase-4; ER = extended release; GI=gastro intestinal; GLP-1= glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2; SC = subcutaneous injection; UTIs = urinary tract infections.

Insulin Sensitizers: Insulin sensitizers reduce glycemic load primarily by improving insulin actions in peripheral tissues. Two classes of these oral hypoglycemic drugs are available: biguanides and thiazolidinediones. They have been shown through more than a decade of clinical use to have positive, durable effects in the treatment of diabetes. These drug classes can be used as monotherapy or in combination with sulfonylurea, insulin, or with each other.

Biguanides (Metformin): Metformin was first marketed in the 1950s. Its primary mechanism of action is suppression of hepatic glucose output, but it also enhances insulin sensitivity of muscle and fat. Metformin primarily lowers fasting glycemia; however, some decreases in postprandial glucose concentrations, especially after the midday meal, are seen.

Metformin is well tolerated, with the most common side effect being gastrointestinal (GI) complaints, such as diarrhea, nausea, and abdominal discomfort, and a metallic taste. All of these symptoms improve with time and dose reduction. Metformin causes a small increase in basal and postprandial lactate concentrations in the blood, which can produce rare but life-threatening lactic acidosis (<1 in 100,000).[51, 52] It is best to avoid

metformin use in patients with hepatic impairment. Metformin is contraindicated in males with a serum creatinine 1.5 mg/dL or higher and in females with a level 1.4 mg/dL or higher.[52]

A major benefit of metformin is that it usually does not lead to hypoglycemia when used as monotherapy. It can lead to weight loss, and it has been shown to decrease plasma triglycerides concentration by 10% to 20%.[52]

Dosing is typically twice daily, but it can be dosed three times daily; the extended-release formulation is dosed once daily. The typical metformin starting dose is 500 mg/day with a maximum dose of 2,550 mg/day. Gradual titration of metformin, starting at 500 mg with breakfast and increasing by 500 mg in weekly intervals until reaching a maximum dose of 1,000 mg with breakfast and dinner, helps prevent GI side effects.[52-55]

Thiazolidinediones: Thiazolidinediones (TZDs) are agonists of peroxisome proliferator-activated receptor gamma. They primarily enhance sensitivity of muscle and fat, and, mildly, the liver, to exogenous and endogenous insulin. These effects lower fasting and postprandial blood glucose levels.

Major side effects include weight gain, with an increase in subcutaneous adiposity and fluid retention, which typically manifests as peripheral edema although heart failure has occurred on occasion. These effects are mostly seen at higher doses. As a result, these agents should be avoided in patients with functional class III or IV heart failure.

Dosing is once daily. It takes 2 to 12 weeks for TZDs to become fully effective. For rosiglitazone, the starting dose is 4 mg/day and maximum dose is 8 mg/day. For pioglitazone, the starting dose is 7.5 mg/day and the maximum dose is 45 mg/day.[56, 54,55-58]

Insulin Secretagogues: Insulin secretagogues stimulate secretion of insulin from the pancreas, thereby enhancing glucose uptake by muscles and fat and decreasing hepatic glucose production. Two types of secretagogues are marketed: sulfonylureas and glinides.

Sulfonylureas: Sulfonylureas lower fasting and postprandial glucose levels. The main adverse effects are weight gain (about 2 kg a few months after initiation) and hypoglycemia. Hypoglycemia episodes can be significant, leading to need for medical care, coma, or seizure, and are seen more often in the elderly. Benefits include a 25% reduction in microvascular complications with or without insulin, as noted in the United Kingdom Prospective Diabetes Study (UKPDS). Dosing is typically once or twice daily. Caution should be used in patients with liver or kidney dysfunction or in those who often skip meals.[60, 54, 61]

Glinides: Glinides work in a manner similar to sulfonylureas; however, they have a more rapid onset of action and shorter duration, so they are a good option for patients with erratic timing of meals. Also, the hypoglycemia risk is lower than with sulfonylureas, but they have a similar-to-lower risk of weight gain after initiating therapy. Caution must be used in patients with liver dysfunction. Dosing is before meals.[56]

Alpha-Glucosidase Inhibitors: Alpha-glucosidase inhibitors competitively block the enzyme alpha glucosidase in the brush borders of the small intestine, which delays absorption of carbohydrates (absorbed in the mid and distal portions of the small intestine instead). They primarily target postprandial hyperglycemia but do it without causing hypoglycemia. GI complaints, such as bloating, abdominal cramps, flatulence, and diarrhea, are the main side effects. Use should be avoided in patients with severe hepatic or renal impairment. Dosing must occur before carbohydrate-containing meals.[54, 55, and 56]

Incretins: Incretin-based therapies are available as injections (GLP-1 analogs) or oral formulations (DPP-4 inhibitors). These therapies differ slightly in their mechanisms of actions, as described in the following sections. All incretin-based medications carry an increased risk of acute pancreatitis. Patients must be warned about this risk and be advised to stop taking these medications and to seek medical evaluation if acute abdominal pain develops. These medications should not be given to individuals who have a history of medullary thyroid carcinomas or have multiple endocrine neoplasia type 2. This restriction is based on increased incidences of thyroid C-cell tumors observed with these medications in murine models. So far, no increased risk in humans has been observed. Nevertheless, the above groups of individuals should not use these medications.

GLP-1 Receptor Agonists[56, 58]
(Short-Acting (4-6 hrs)

Exenatide is a synthetic form of exendin 4, a hormone found in the saliva of the Gila monster, which mimics glucagon-like peptide-1 (GLP-1). GLP-1 is produced in the small intestine. It stimulates insulin secretion and inhibits glucagon secretion and hepatic glucose production in a glucose-dependent manner. It also delays gastric emptying and suppresses appetite through central pathways. It primarily decreases postprandial blood glucose levels; however, a moderate reduction in fasting blood glucose levels also can be seen. Due to its delaying effects on gastric emptying, the major side effects are GI complaints of nausea, vomiting, and diarrhea. Hypoglycemia does not occur when exenatide is used as monotherapy or with metformin, but it does occur when exenatide is combined with a sulfonylurea. Benefits include weight loss up to 2 to 3 kg in the first 6 months and up to 5.5 kg in the first 2 years.

Dosing is twice daily by subcutaneous injection. The initial starting dose is 5 µg. If this dose is tolerated, titrate after 1 month to 10 µg.

Intermediate-Acting (24 hrs)
Liraglutide is a GLP-1 analogue derived from human GLP-1. It is administered once a day as a subcutaneous injection from its pen device. Timing is independent of meals. Half-life is about 13 hours. Its beneficial effects and side effects are similar to those of exenatide, but it may be slightly more powerful in its actions. The initial dose is 0.6 mg/day for a week. If there are no side effects, the dose is increased to 1.2 mg/day (the dose at which most clinical benefits are seen). For most patients, dose will be increased to 1.8 mg/day after another week if there are no side effects.

Long-Acting (7 days)
Exenatide also is available as a once per week injection, supplied as a kit containing 2 mg of extended-release exenatide. If a dose is missed, it should be administered as soon as noticed provided that next dose is scheduled 3 or more days later. Albiglutide is a newer GLP-1 analog that has a half-life of 4 to 7 days. It is given as 30 or 50 mg weekly injections. Dulaglutide is another long-acting GLP-1 analog. It is given as 0.75 and 1.5 mg weekly injections.

DPP-4 Inhibitors: Dipeptidyl peptidase-4 (DPP-4) is a cell membrane protein that rapidly degrades GLP-1 and glucose-dependent insulinotropic polypeptide. Suppression of DPP-4 leads to higher levels of insulin secretion and suppression of glucagon secretion in a glucose-dependent manner.The DPP-4 inhibitors act primarily on postprandial blood glucose levels, but reductions in fasting glycemia are also seen. These agents are generally well tolerated, with the most common side effect being headache. An increase in nasopharyngitis also has been seen. Benefits include that it is weight neutral and does not cause hypoglycemia as monotherapy or when combined with metformin or thiazolidinediones. When combined with sulfonylurea or insulin, it increases the risk of hypoglycaemia. Four DPP-4 inhibitors are approved by the US Food and Drug Administration (FDA) for use in type 2 DM: sitagliptin, saxagliptin, linagliptin, and alogliptin. These agents are indicated for use as monotherapy or in combination with other agents such as metformin, sulfonylureas, thiazolidinediones, or insulin.

Sitagliptin dosing is 100 mg orally once daily with or without meals. Dose reduction is needed in patients with renal impairment. For patients with a creatinine clearance of 30 to 50 mL/min, dosing is 50 mg once daily. For patients with a creatinine clearance less than 30 mL/min, dosing is 25 mg once daily. Saxagliptin dosing is 2.5 or 5 mg orally once daily with or without meals. The 2.5 mg daily dose is used in patients whose estimated glomerular filtration rate (eGFR) is <50 mg/mL and those using the strong inhibitors of P450 3A4/5 (eg, ketoconazole, ritonavir). Linagliptin dosing is 5 mg orally once daily with or without meals. Dose reduction is not needed in renal impairment. Alogliptin dosing is 25 mg orally once daily with or without meals. Dose reduction is needed in renal impairment. In patients with a creatinine clearance 30 to 60 mL/min, dosing is 12.5 mg once daily. In patients with a creatinine clearance below 30 mL/min, dosing is 6.25 mg once daily.

Pramlintide: Pramlintide is a synthetic form of amylin, a hormone secreted by beta cells that acts to suppress glucagon secretion, slow gastric emptying, and suppress appetite through central pathways. It acts primarily on postprandial blood glucose levels. Efficacy data from well-conducted studies are lacking. Dosage varies in different patients. The major side effects are GI complaints, especially nausea and hypoglycemia. Benefits of therapy include weight loss of 1 to 1.5 kg over 6 months and up to 4.5 kg after chronic therapy. Pramlintide is FDA approved only as adjunctive therapy with insulin, but it is used off-label in patients with either type 1 DM or type 2 DM. Pramlintide can reduce insulin requirements by up to 50%. The starting dose for patients with type 2 DM is generally 60 µg subcutaneously before meals. In patients with type 1 DM, the starting dose is 15 µg before each meal. Pramlintide can be used by patients taking insulin, metformin, or sulfonylureas.

Bromocriptine: Fast release bromocriptine improves glycemic control in patients with type 2 DM when taken within the 2 hours of waking up. Mechanism of action is not known. Improvement in Hba1c is 0.6-0.7%. It is sold as 0.8 mg tablet and therapeutic dose varies from 1.6-4.8 mg. Nausea is main side effect.

SGLT-2 Inhibitors: The SGLT-2 inhibitors are the newest group of FDA-approved medications for type 2 DM. SGLT-2 is a protein acting as sodium-glucose cotransporter in the kidney's proximal tubules whose main function is reabsorption of the filtered glucose from the urine back into the circulation. It is responsible for about 90% of total glucose reabsorption. Inhibition of this protein leads to the excretion of glucose in the urine at much lower blood glucose levels than normal (at approximately 120 mg/dL instead of 180 mg/dL).

The most common side effects of SGLT-2 inhibitors are vaginal yeast infections and urinary tract infections. The greatest risk is seen in female patients and in uncircumcised males. Polyuria also may occur.

Additional benefits are weight loss (two-thirds of weight loss is related to loss of fat tissue and one-third is related to loss of water) and lower blood pressure. These medications are not indicated in children, in patients with type 1 DM, frequent ketones in their blood or urine, or severe renal impairment. Patients should be advised to expect glucose to be in the urine and, thus, urine glucose strips will usually have a positive reading.

Three SGLT-2 inhibitors are currently available: canagliflozin, dapagliflozin, and empagliflozin. Canagliflozin is dosed at 100 mg/day before the first meal of the day and can be increased to 300 mg/day, if tolerated. Canagliflozin should not be used in patients with eGFR less than 45 mL/min/1.73m^2 and should be limited to 100 mg in those with eGFR 45 to 60 mL/min/1.73m^2. Dapagliflozin is dosed at 5 mg/day and can be increased to 10 mg/day, if tolerated. It should not be used if eGFR is less than 60 mL/min/1.73m^2. Empagliflozin is dosed at 10 or 25 mg once a day. It should not be started if eGFR is less than 60 mL/min/1.73m^2. If eGFR decreases below 60 mL/min/1.73m^2 while patient takes this medication, it should be continued at 10 mg/day and stopped if eGFR decreases below 45 mL/min/1.73m^2. At this time, empagliflozin is the only antidiabetic medication shown to decrease cardiovascular risk in patients with type 2 DM.

Insulin therapy: Insulin was the first treatment for diabetes. It was discovered in 1921, and clinical testing in humans started in 1922. Insulin therapy remains the most effective method of reducing hyperglycemia. There is no upper limit in dosing for therapeutic effect, so it can be used to bring any elevated HbA1c level down to near normal. Other benefits of insulin include its effects on reducing triglycerides levels and increasing HDL. Hypoglycemia is a concern, although the actual risk of severe episodes is small. Studies have shown that insulin-induced hypoglycemic episodes requiring therapy occur in 1 to 3 per 100,000 patient-years. Weight gain can occur after initiation and is typically about 2 to 4 kg.[56] Insulin therapy remains the most effective method of reducing hyperglycaemia. There is no upper limit in dosing for therapeutic effect, so it can be used to bring any elevated HbA1c level down to near normal. Other benefits of insulin include its effects on reducing triglycerides levels and increasing HDL. Hypoglycaemia is a concern, although the actual risk of severe episodes is small. Studies have shown that insulin-induced hypoglycemic episodes requiring therapy occur in 1 to 3 per 100,000 patient-years. Weight gain can occur after initiation and is typically about 2 to 4 kg. Most brands of insulin are available in both vial and pen form for delivery.

Table 2: Lists of Insulin Formulations.

Insulin (Brand)	Onset	Peak	Effective Duration
Rapid-acting			
Aspart (Novolog)	5-15 min	30-90 min	<5 hr
Lispro (Humalog)	5-15 min	30-90 min	<5 hr
Glulisine (Apidra)	5-15 min	30-90 min	<5 hr
Short-acting			
Regular insulin (Humulin R, Novolin R)	30-60 min	2-3 hr	5-8 hr
Intermediate, basal			
Insulin NPH	2-4 hr	4-10 hr	10-16 hr
Long-acting, basal			
Insulin glargine (Lantus, Toujeo, Basaglar)	2-4 hr	No peak	20-24 hr
Insulin detemir (Levemir)	3-8 hr	No peak	17-24 hr
Insulin degludec (Tresiba)	1 hr		>25 hr
Premixed			
75% Insulin lispro protamine/25% insulin lispro (Humalog mix 75/25)	5-15 min	Dual	10-16 hr
50% Insulin lispro protamine/50% insulin lispro (Humalog mix 50/50)	5-15 min	Dual	10-16 hr
70% Insulin lispro protamine/30% insulin aspart (Novolog mix 70/30)	5-15 min	Dual	10-16 hr
70% NPH insulin/30% regular	30-60 min	Dual	10-16 hr
Inhaled			
Technosphere insulin-inhalation system (Afrezza))			

NPH=Neutral protamine Hagedorn.

Initiation and Titration of Therapy: Several different regimens are used to administer insulin therapy (Table 3). All patients with type 1 DM require insulin therapy, which is available as basal-bolus therapy or insulin pump. Patients with type 2 DM often require insulin, which can be combined with oral hypoglycemic agents. Regimens used are basal insulin only, twice-daily premixed insulin, basal-bolus, and insulin pump therapy.

TABLE 3: REGIMENS FOR INSULIN THERAPY

Insulin Regimen	HbA1c (%)	Medication	Pattern	Diet	Lifestyle	Monitoring
Basal-only	>7.5-10	Oral medications adequately control postprandial glucose excursions	High fasting glucose with minimal glucose rise during the day	Small, regular meals; large meals will result in postprandial hyperglycemia	Reluctance to do MDI; requires oral agents	Fasting
Basal-bolus (MDI)	>7.5		Regimen can be matched to any pattern to achieve glycemic control	Regimen can be matched to any diet to achieve glycemic control	Erratic schedule, motivated to achieve tight glycemic control	Frequent blood glucose monitoring (minimum before meals and bedtime)
Once- or Twice-Daily Premixed						
Rapid-acting analogue and intermediate acting	>7.5	Oral agent failure (maximum tolerated dosages, contraindications, cost issues)	Any fasting glucose; glucose rises during the day	Large suppers, small lunches	Consistent daily routine, reluctance to do MDI	Fasting and pre-supper (if insulin is administered twice daily)
Regular and NPH	>7.5	Oral agent failure (maximum tolerated dosages, contraindications, cost issues)	Any fasting glucose; glucose rises during the day	Isocaloric meals or larger lunches	Consistent daily routine, reluctance to do MDI	Fasting and pre-supper (if insulin is administered twice daily)

Abbreviations: HbA1c=hemoglobin A1c; MDI=multiple daily injections; NPH=Neutral protamine Hagedorn.

Type I Diabetes

Basal–Bolus: The basal-bolus regimen combines a long-acting agent (administered once or twice daily) that provides basal insulin needs and a rapid-acting agent for prandial coverage. Traditionally, when initiating therapy with glargine or detemir as the basal insulin, 50% of the total daily dose is given as basal insulin and the rest as prandial insulin divided equally before meals. The prandial insulin dose can be fixed, but it is better to determine the dose based on the carbohydrate content of the meal. This requires learning carbohydrate counting and knowing the insulin dose required to cover the carbohydrates. A diabetic educator can help patients adjust their insulin dose based on carbohydrate consumptions. The starting daily insulin dose is typically 0.3 U/kg total daily (divided between long-acting and rapid-acting). A key to achieving glycemic control is appropriate SMBG by the patient and frequent adjustment of the regimen.[59]

Table 4: Summary of Initial Dose, Titration of Insulin Therapy: Type 1 DM.

Type 1 Diabetes Mellitus	
Initial basal dose (detemir or glargine) 10 units or 0.15 units/kg (whichever is greater)	Adjustments (desired range 90-140 mg/dL): Increase/decrease by 3 units every 3 days if out of range
Initial basal coverage (NPH insulin): 10 units or 0.15 units/kg divided into 2 doses; 1 at breakfast and 1 at dinner	Adjustments (desired range 90-140 mg/dL): Increase/decrease by 10% every 3 days, if out of range
Meal coverage (regular insulin, glulisine, aspart, lispro) 4 units per or 0.15 units/kg divided among 3 meals	Adjustments (postprandial <180 mg/dL): Increase/decrease by 1 unit or 10% (whichever is greater)
Carbohydrate counting (1 unit per 15 g of carbohydrate)	Increase to 1 unit per 10 g of carbohydrates or decrease to 1 unit per 20 g of carbohydrates

NPH = neutral protamine Hagedorn.

Insulin Pump Therapy: The insulin pump allows administration of different basal insulin rates during different periods of the day. It also allows administration of the meal bolus as a single discrete bolus or as an extended bolus (square bolus) over a specific time period, which provides a better match between insulin delivery and glucose absorption from the meal in patients with gastric emptying abnormalities. Use of insulin pump therapy is increasing in all diabetic populations. It should be considered in these populations.

- Patients unable to achieve target goals with basal-bolus regimens.
- Patients with frequent hypoglycemia, dawn phenomenon, or brittle diabetes.
- Pregnant patients.
- Patients with insulin sensitivity or those requiring more intense monitoring due to complications.
- Patients who are able to monitor blood glucose several times during the day and to make insulin dose adjustments.

Type 2 Diabetes: The ADA and the AACE have published different algorithms for initiation and maintenance of therapy in patients with type 2 DM [61, 51]. No studies have compared the efficacy of these algorithms. Table 5 lists the initial dose and titration of insulin therapy for type 2 DM. The starting daily insulin dose is typically 0.5 U/kg total, divided between long-acting and rapid-acting. Therapy can be combined with oral insulin sensitizers but not secretagogues.

Table 5: Summary of Initial Dose, Titration of Insulin Therapy: Type 2 DM.

Type 2 Diabetes Mellitus	
Initial basal dose (detemir or glargine) 15 units or 0.25 units/kg (whichever is greater)	Adjustments (desired range 90-140 mg/dL): Increase/decrease by 3 units or 10% (whichever is greater) every 3 days, if out of range
Initial basal coverage (NPH insulin) 15 units or 0.25 units/kg divided into 2 doses; 1 given at breakfast and 1 at dinner	Adjustments (desired range 90-140 mg/dL): Increase/decrease by 10% every 3 days, if out of range
Meal coverage (regular insulin, glulisine, aspart, lispro) 6 units per meal or 0.25 units/kg divided between 3 meals	Adjustments (postprandial <180 mg/dL): Increase/decrease by 2 units or 10% (whichever is greater)
Carbohydrate counting (1 unit per 10 g of carbohydrate)	Increase to 1 unit per 5 g of carbohydrate or decrease to 1 unit per 15 g of carbohydrate

NPH = neutral protamine Hagedorn.

Gestational Diabetes: In patients with gestational diabetes, insulin therapy is indicated when exercise and nutritional therapy are ineffective in controlling prandial and fasting blood glucose levels. Basal therapy alone may be sufficient, but basal-bolus regimens are often required.

CONCLUSION

From the above review data here we concluded that the glycemic control is crucial for preventing microvascular and macrovascular complications of diabetes. Type 2 diabetes is a progressive disease and requires therapy intensification with time. Insulin sensitizers and incretin-based therapy should be used early in the course of the disease. Type 1 diabetes requires insulin therapy. Multiple daily doses of insulin providing basal, prandial, and supplemental insulin are a mainstay of insulin treatment.

REFERENCES

1. "About diabetes". World Health Organization. Archived from the original on 31 March 2014. Retrieved 4 April 2014.
2. "Diabetes Fact sheet N°312". WHO. October 2013. Archived from the original on 26 August 2013. Retrieved 25 March 2014.
3. Kitabchi, AE; Umpierrez, GE; Miles, JM; Fisher, JN (Jul 2009). "Hyperglycemic crises in adult patients with diabetes.". Diabetes Care, 32(7): 1335–43. doi:10.2337/dc09-9032. PMC 2699725Freely accessible. PMID 19564476.
4. Shoback, edited by David G. Gardner, Dolores (2011). "Chapter 17". Greenspan's basic & clinical endocrinology (9th ed.). New York: McGraw-Hill Medical. ISBN 0-07-162243-8.
5. RSSDI textbook of diabetes mellitus. (Rev. 2nd ed.). New Delhi: Jaypee Brothers Medical Publishers, 2012; 235. ISBN 9789350254899.
6. "The top 10 causes of death Fact sheet N°310". World Health Organization, Oct 2013.
7. Rippe, edited by Richard S. Irwin, James M. (2010). Manual of intensive care medicine (5th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 549. ISBN 9780781799928.
8. Picot, J; Jones, J; Colquitt, JL; Gospodarevskaya, E; Loveman, E; Baxter, L; Clegg, AJ (September 2009). "The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation". Health Technology Assessment (Winchester, England), 13(41): 1–190, 215–357, iii–iv. doi:10.3310/hta13410. PMID 19726018.
9. Cash, Jill (2014). Family Practice Guidelines (3rd ed.). Springer. p. 396. ISBN 9780826168757.
10. Cooke DW, Plotnick L (November 2008). "Type 1 diabetes mellitus in pediatrics". Pediatr Rev, 29(11): 374–84; quiz 385. doi:10.1542/pir.29-11-374. PMID 18977856.

11. Kenny C (April 2014). "When hypoglycemia is not obvious: diagnosing and treating under-recognized and undisclosed hypoglycemia". Primary care diabetes, 8(1): 3–11. doi:10.1016/j.pcd.2013.09.002. PMID 24100231.
12. Verrotti A, Scaparrotta A, Olivieri C, Chiarelli F (December 2012). "Seizures and type 1 diabetes mellitus: current state of knowledge". European Journal of Endocrinology, 167(6): 749–58. doi:10.1530/EJE-12-0699. PMID 22956556. Archived from the original on 2014-11-07.
13. Hsieh, Arthur. "Drunk versus diabetes: How can you tell?". Retrieved 29 June 2016.
14. "Symptoms of Low Blood Sugar". WebMD. Retrieved 29 June 2016.
15. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN (July 2009). "Hyperglycemic crises in adult patients with diabetes". Diabetes Care, 32(7): 1335–43. doi:10.2337/dc09-9032. PMC 2699725Freely accessible. PMID 19564476.
16. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J (2010). "Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies". The Lancet, 375(9733): 2215–22. doi:10.1016/S0140-6736(10)60484-9. PMC 2904878Freely accessible. PMID 20609967.
17. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW (29 January 2013). "2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.". Circulation, 127(4): e362–425. doi:10.1161/CIR.0b013e3182742cf6. PMID 23247304.
18. "Diabetes Programme". World Health Organization. Retrieved 22 April 2014.
19. Cukierman, T (8 Nov 2005). "Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies". Springer-Verlag. Retrieved 28 Apr 2013.
20. Yang, Y; Hu, X; Zhang, Q; Zou, R (November 2016). "Diabetes mellitus and risk of falls in older adults: a systematic review and meta-analysis.". Age and ageing, 45(6): 761–767. PMID 27515679.
21. Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L (2014). "The many faces of diabetes: a disease with increasing heterogeneity". Lancet, 383(9922): 1084–94. doi:10.1016/S0140-6736(13)62219-9. PMID 24315621.
22. Rother KI (April 2007). "Diabetes treatment—bridging the divide". The New England Journal of Medicine, 356(15): 1499–501. doi:10.1056/NEJMp078030. PMC 4152979Freely accessible. PMID 17429082.
23. "Diabetes Mellitus (DM): Diabetes Mellitus and Disorders of Carbohydrate Metabolism: Merck Manual Professional". Merck Publishing. April 2010. Retrieved 2010-07-30.
24. Dorner M, Pinget M, Brogard JM (May 1977). "Essential labile diabetes". MMW Munch Med Wochenschr (in German), 119(19): 671–4. PMID 406527.
25. Phillips JE, Couper JJ, Penno MA, Harrison LC, ENDIA Study Group (2016). "Type 1 diabetes: a disease of developmental origins.". Pediatr Diabetes (Review). doi:10.1111/pedi.12425. PMID 27526948.
26. Petzold A, Solimena M, Knoch KP (2015). "Mechanisms of Beta Cell Dysfunction Associated With Viral Infection.". Curr Diab Rep (Review), 15(10): 73. doi:10.1007/s11892-015-0654-x. PMC 4539350Freely accessible. PMID 26280364. "So far, none of the hypotheses accounting for virus-induced beta cell autoimmunity has been supported by stringent evidence in humans, and the involvement of several mechanisms rather than just one is also plausible.".
27. Butalia S, Kaplan GG, Khokhar B, Rabi DM (Aug 18, 2016). "Environmental Risk Factors and Type 1 Diabetes: Past, Present, and Future". Can J Diabetes (Review). 40: 586–593. doi:10.1016/j.jcjd.2016.05.002. PMID 27545597.
28. Serena G, Camhi S, Sturgeon C, Yan S, Fasano A (2015). "The Role of Gluten in Celiac Disease and Type 1 Diabetes.". Nutrients, 7(9): 7143–62. doi:10.3390/nu7095329. PMC 4586524Freely accessible. PMID 26343710. open access publication – free to read.
29. Visser J, Rozing J, Sapone A, Lammers K, Fasano A (2009). "Tight junctions, intestinal permeability, and autoimmunity: celiac disease and type 1 diabetes paradigms.". Ann N Y Acad Sci, 1165: 195–205. doi:10.1111/j.1749-6632.2009.04037.x. PMC 2886850Freely accessible. PMID 19538307.
30. Risérus U, Willett WC, Hu FB (January 2009). "Dietary fats and prevention of type 2 diabetes". Progress in Lipid Research, 48(1): 44–51. doi:10.1016/j.plipres.2008.10.002. PMC 2654180Freely accessible. PMID 19032965.
31. Williams textbook of endocrinology (12th ed.). Philadelphia: Elsevier/Saunders, 1371–1435. ISBN 978-1-4377-0324-5.
32. Malik VS, Popkin BM, Bray GA, Després JP, Hu FB (2010-03-23). "Sugar Sweetened Beverages, Obesity, Type 2 Diabetes and Cardiovascular Disease risk". Circulation, 121(11): 1356–64.

doi:10.1161/CIRCULATIONAHA.109.876185. PMC 2862465Freely accessible. PMID 20308626.
33. Malik VS, Popkin BM, Bray GA, Després JP, Willett WC, Hu FB (November 2010). "Sugar-Sweetened Beverages and Risk of Metabolic Syndrome and Type 2 Diabetes: A meta-analysis". Diabetes Care, 33(11): 2477–83. doi:10.2337/dc10-1079. PMC 2963518Freely accessible. PMID 20693348.
34. Hu EA, Pan A, Malik V, Sun Q (2012-03-15). "White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review". BMJ (Clinical research ed.). 344: e1454. doi:10.1136/bmj.e1454. PMC 3307808Freely accessible. PMID 22422870.
35. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT (1 July 2012). "Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy". The Lancet, 380(9838): 219–29. doi:10.1016/S0140-6736(12)61031-9. PMC 3645500Freely accessible. PMID 22818936.
36. "National Diabetes Clearinghouse (NDIC): National Diabetes Statistics 2011". U.S. Department of Health and Human Services. Retrieved 22 April 2014.
37. "Monogenic Forms of Diabetes". National institute of diabetes and digestive and kidney diseases. US NIH. Retrieved 12 March 2017.
38. de la Monte, SM. "Type 3 diabetes is sporadic Alzheimer′s disease: mini-review.". European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology, December 2014; 24(12): 1954–60. doi:10.1016/j.euroneuro.2014.06.008. PMC 4444430Freely accessible. PMID 25088942.
39. www.diabetes.org.uk/.../.
40. www.bbc.co.uk/.../aboutdiabetes_what.shtml.
41. http://www.nhs.uk/Conditions/Diabetes/Pages/Diabetes.aspx.
42. http://www.patient.co.uk/doctor/diabetes-mellitus.
43. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002194/.
44. http://www.diabeteswellness.net/Portals/0/files/DRWFUSdiabetes.pdf.
45. http://www.cdc.gov/chronicdisease/resources/publications/AAG/ddt.htm.
46. Mitka M. Report quantifies diabetes complications. JAMA, 2007; 297: 2337–2338.
47. Welschen LM, Bloemendal E, Nijpels G, et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. Diabetes Care, 2005; 28: 1510–1517.
48. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) [published erratum appears in Lancet 1998; 352:1558]. Lancet, 1998; 352: 854–865.
49. Chase HP, Jackson WE, Hoops SL, Cockerham RS, Archer PG, O'Brien D. Glucose control and the renal and retinal complications of insulin-dependent diabetes. JAMA, 1989; 261: 1155–1160.
50. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med, 1993; 329: 977–986.
51. Salpeter S, Greyber E, Pasternak G, Salpeter E: Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev CD002967, 2006.
52. Bailey CJ, Turner RC. Metformin. N Engl J Med, 1996; 334: 574–579.
53. Bailey CJ. Biguanides and NIDDM. Diabetes Care, 1992; 15: 755–772.
54. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetes Care, 2006; 29: 1963–1972.
55. Nathan DM. Clinical practice: initial management of glycemia in type 2 diabetes mellitus. N Engl J Med, 2002; 347: 1342–1349.
56. American Diabetes Association. Standards of medical care in diabetes—2015. Diabetes Care, 2015; 38(suppl 1): S33–S40.
57. Dormandy JA, Charbonnel C, Eckland DJ, et al; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet, 2005; 366: 1279–1289.
58. Fonseca VA, Kulkarni KD. Management of type 2 diabetes: oral agents, insulin, and injectables. J Am Diet Assoc, 2008; 108(4 suppl 1): S29–S33.
59. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy—update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care, 2008; 31: 173–175.
60. Saudek CD, Derr RL, Kalyani RR. Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. JAMA, 2006; 295: 1688–1697.
61. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [erratum published in Lancet 1999; 354:602]. Lancet, 1998; 352: 837–853.