

Overview of diabetes mellitus types and medications

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ABSTRACT

Insulin is a hormone produced naturally by the pancreas through β cells, whereas glucagon is a hormone secreted by the pancreas through α cells. Somatostatin is secreted by δ cells. These hormones play vital roles in metabolic actions in the human body, especially regulating glucose levels. The absence or lack of insulin causes diabetes, which is characterized by increase in level blood sugar level. Diabetes is the main reason for many diseases, such as kidney diseases, vision loss, nerve disorders, and cardiovascular difficulties. Insulin medication and other related composition and inhibition can reduce diabetes cases and lower mortality due to diabetes.

Introduction

In the 20th century, diabetes become more problematic disease and has significantly increases in the world [1]. In general, Diabetes are two types, type 1 diabetes mellitus (T1DM) which is insulin dependent and type 2 diabetes mellitus (T2DM) which is noninsulin dependent. Diabetes considered one of the most serious chronic diseases. In general, diabetes and gestational diabetes are because of medications and genetic causes. Pregnant women may diabetes which is called gestational diabetes which is consequences of carbohydrate intolerance with the first recognition of carbohydrate during pregnancy [2].

Type 1 diabetes mellitus (T1DM)

T1DM mainly appear on children, teenagers, and adults. The main reason for this type is insulin deficiency due to damage to β cells in the pancreas. β -Cell dysfunction may be caused by an impaired autoimmune system, viral infections, or exposure to ecological pollutants [3]. When β cells are damaged, the pancreas stops responding to glucose, and patients with T1DM lose weight, are always thirsty, and excessively urinate. Insulin-replacement therapy is needed to prevent high blood sugar and the deadly catabolic state of diabetic ketoacidosis in patients with T1DM [4].

β cells maintain the low levels of glucose by secreting insulin in the human body, preventing glycogenolysis, proteolysis, and lipolysis. The probability to develop T1DM is genetic predisposition, including specific HLA genotypes. The progress of diabetes in people with genetic link to it may be accelerated by external factors, such as eating habits or virus-related infection. The main cause of this disease is viral infection.

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Exogenous insulin administered through insulin-replacement therapy prevents ketoacidosis and controls hyperglycemia in people with T1DM, in addition to regulating glycosylated hemoglobin level. The aim of insulin therapy is keep blood glucose level in the body as close to the normal range as possible [5, 6].

Type 2 diabetes mellitus (T2DM)

T2DM develops in 90% of T1DM cases, occurring because of genetic issues, aging and obesity, instead of autoimmune system dysfunction. The metabolic changes are generally minor than those observed with T1DM [7].

In T2DM causes insulin deficiency because impaired β cells in the pancreas. Therefore, insulin secretion in the blood circulation is insufficient to maintain glucose homeostasis, and β cells might slowly decrease. Obesity is the main causative factor for T2DM and causes insulin resistance in the body. The main causes of T2DM are genetics, eating habits, poor exercise, poor diet, and stress. T2DM treatments maintain glucose level in the blood circulation within the normal range. Different protocols can be implemented to maintain the glucose level within the range, including losing weight through exercise, diet, and change in lifestyle. However, people suffering from T2DM need medications that control glucose level [8, 9].



Figure 1. T1DM and T2DM diabetes

Table 1. T1DM and T2DM.

	T1DM	T2DM
Aging	Generally, from born to or adult	Normally over 35 years
Nutrition	Commonly undernourished	Obesity
Predominance	(5% -10%)	(90% - 95%)
Genetic predisposition	common	More common
Deficiency	β cells are damaged which reducing the insulin production	Lack of ability of β cells to secrete suitable quantities of insulin;

Types of Insulin

Insulin treatment is important for the long-term survival of patients with T1DM and T2DM. Pregnant women with T2DM can be treated with insulin as well. However, the most common complication of using insulin is hypoglycemia, which is usually associated with high dosage of insulin or skipping meals. Insulin treatments are classified into short, intermediate, and long-acting. Short or fast-acting insulin treatments have faster onset and shorter action duration than intermediate and long-lasting insulin treatments and are sometimes known as rapid-acting insulin [10].

Table 2. Types of insulin treatments [11]

Fast-acting insulin:	Rapid Acting Insulin Analogs (Insulin Lyspro, Insulin Aspart, Insulin Glulisine): Have an onset of action (5-15) min., peak effect (1-2) hrs and Action duration (4-6) hrs, while regular Human Insulin: has an onset of action (1/2 -1) hr, peak effect (2-4) hrs, and action duration (6-8) hrs.
Intermediate-acting insulin:	NPH Human Insulin: Has an onset of insulin effect (1-2) hrs, a peak effect (4-6) hrs, and action duration more than 12 hrs. Pre-Mixed Insulin: Pre-mixed with either rapid- acting insulin analog or regular human insulin.
Long-acting insulin:	(Insulin Detemir, Insulin Glargine): Have an onset of insulin effect (1 1/2-2) hrs. Action duration 24 hrs for insulin glargine and (12-24) hrs for insulin detemir.

Medications

1. Sulfonylureas control glucose level by stimulating insulin secretion by pancreatic β cells. Second-generation sulfonylureas include glyburide, gliclazide, glipizide, and glimepiride, which are oral hypoglycemic agents that are widely used in T2DM treatment [12, 13]. The main mechanism action of sulfonylureas is closing ATP-sensitive K-channels in the β cell plasma membrane and initiates a chain of actions resulting in insulin release. Furthermore, sulfonylureas may decrease hepatic glucose production and enhance peripheral insulin sensitivity [14].

Oral medications bind to albumin, are metabolized by the liver, and are eliminated through the feces and urine. The duration is between 12 and 24 h. The side effects of using sulfonylureas are increased body weight, hypoglycemia, and hyperinsulinemia. Thus, it should be used carefully when renal insufficiency or hepatic dysfunction occurs because sulfonylurea accumulation may lead to hypoglycemia. Glyburide is the main component affecting people with kidney failure, considerably increasing the risk of hypoglycemia. Glimepiride or glipizide is safe for people with kidney failure and aging people. Glyburide can be transferred to the placenta and may be another source of insulin in gestational diabetes [15].

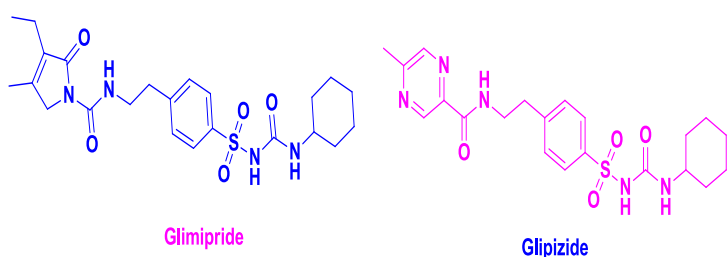


Figure 2. Structure of glimepiride and glipizide structure

2. Metformin restores the body's response to insulin, reducing the level of blood sugar produced by the liver and absorbed by the stomach or intestines. Biguanides constitute a class of medications for treating T2DM and other conditions [16], and metformin is the only biguanide available for T2DM treatment. In contrast to sulfonylureas, metformin does not enhance insulin secretion in the bloodstream. Thus, it does not cause hyperinsulinemia in the body, and the risk of hypoglycemia remains extremely low.

Metformin alters energy metabolism in cells and lowers glucose level by inhibiting hepatic gluconeogenesis and counteracting glucagon activity [17, 18]. Metformin is taken orally, not metabolized, and not bound to albumin and can thus be easily eliminated through urination. Metformin should not be used by people with kidney failure because of lactic acidosis. In addition, it should be discontinued by patients suffering from sepsis and heart failure, which ultimately lead to kidney failure [19].

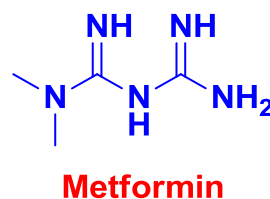


Figure 3. Metformin structure

3- Thiazolidinediones (TZDs) mainly include rosiglitazone and pioglitazone. TZDs do not enhance insulin release from β cells, and thus the risk of hyperinsulinemia is nonexistent.

TZDs lower insulin resistance by acting as agonists for the peroxisome proliferator-activated receptor γ (PPAR γ), which is a nuclear hormone receptor. PPAR γ initiates the transcription of some insulin-responsive genes, improving the insulin sensitivity of skeletal muscles, adipose tissues, and the liver [20, 21].

Pioglitazone and rosiglitazone can be consumed orally and bind to albumin. They are metabolized by the cytochrome P450 hemoprotein. Some pioglitazone metabolites have shown activity. The kidney is ineffective in eliminating pioglitazone, and most active medications and metabolites are concentrated in the bile and feces and then eliminated. Rosiglitazone metabolites are mostly excreted with the urine. Thus, adjusting the dosage of rosiglitazone in case of kidney failure is unnecessary, but it should not be administered to nursing mothers.

Some important issues regarding liver toxicity have been reported by using these medications. Obesity may occur because thiazolidinediones increases hypodermic fat and causes fluid retention that causes heart diseases [22].

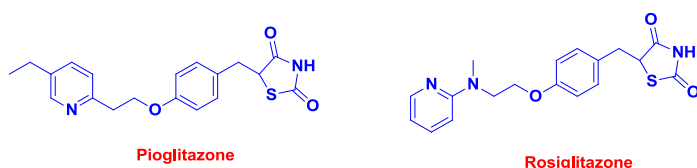


Figure 4. Structure of pioglitazone and rosiglitazone

4-Alpha-glucosidase inhibitors, such as miglitol and acarbose are used in T2DM treatment. The mechanism of this medication inside the human body is breaking down carbohydrates into simple sugars and glucose. Miglitol and acarbose reversibly inhibit α -glucosidase enzymes. At the beginning of a meal, these medications delay the digestion of carbohydrates, thus lowering glucose levels and do not induce insulin release. Therefore, these medications do not cause hypoglycemia [23,24]. Acarbose is weakly metabolized and absorbed by intestinal bacteria, and unmetabolized acarbose is eliminated with the urine. Miglitol is strongly absorbed, has no systemic effects, and is eliminated by the kidney. However, it has some side effects, such as diarrhea, flatulence, and abdominal cramping. This medication should not be administered to patients with colonic diseases, inflammatory bowel disease, ulceration, or intestinal obstruction [25].

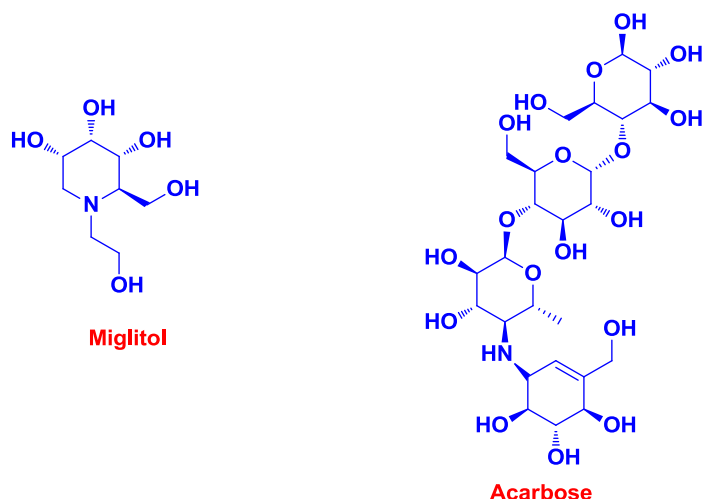


Figure 5. Structure of miglitol and acarbose

5- Sodium-glucose cotransporter 2 (SGLT2) inhibitors include dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin are novel agents for T2DM treatment. They reabsorb glucose filtered by the kidney, inhibiting its reabsorption and elimination with the urine. In addition, inhibitors also inhibit the reabsorption of sodium and cause osmotic diuresis.

Consequently, SGLT2 inhibitors may decrease systolic blood pressure, but they are ineffective for hypertension [26]. In general, medications are metabolized by glucuronidation into inactive metabolites, whereas the primary route of excretion for canagliflozin is the elimination through the feces. This medication should not be administered to people with kidney problems. The main effects of SGLT2 inhibitors are female genital mycotic infections, urinary regularity, and urinary tract infections. Hypotension also occurs, especially in patients on diuretics or old patients [27].

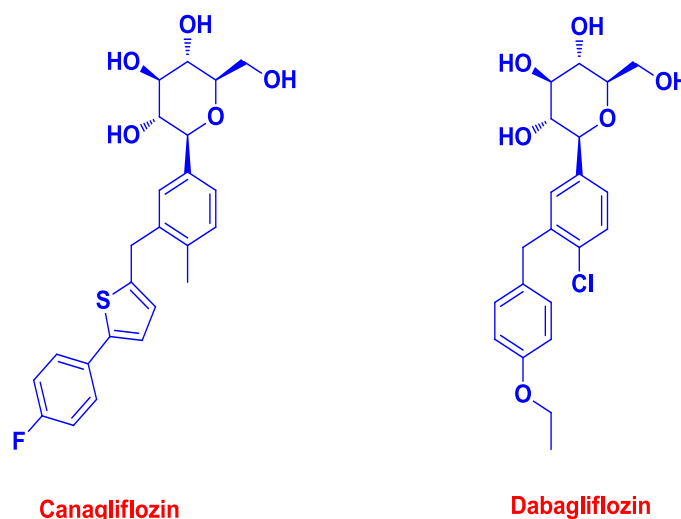


Figure 6. Structure of canagliflozin and dabagliflozin.

Diabetic diseases

Kidney disease

Diabetic nephropathy, which is also called diabetic kidney disease, is the main complication of T1DM and T2DM. In the USA, one of three people living with diabetes has diabetic nephropathy. Given that this disease affects the capability of the kidney to eliminate waste through the urine. Therefore, this disease can be prevented by controlling blood sugar level [28].

Diabetic nephropathy causes

Uncontrolled diabetes can cause severe damage to blood vessel clusters in the kidneys. Damaged kidneys cause high blood pressure, which then adversely affects the kidneys [29].

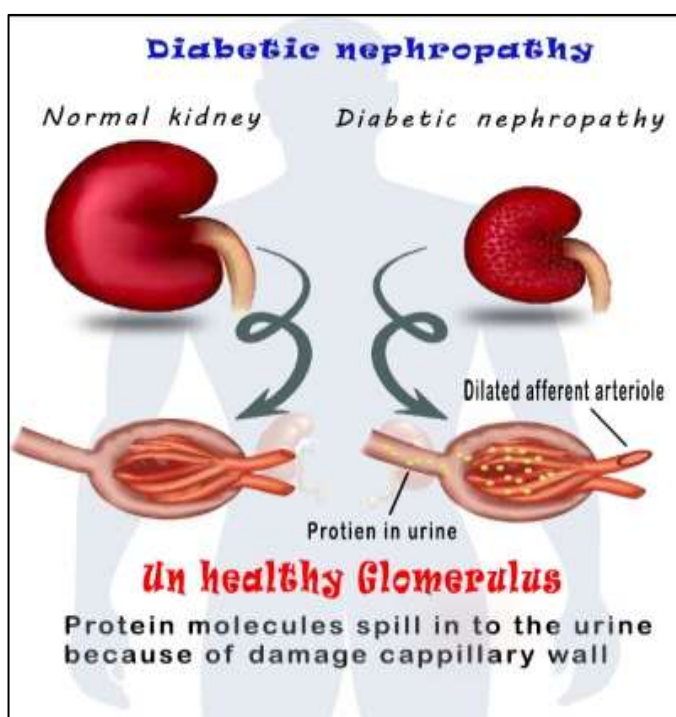


Figure 7. Difference between normal and unhealthy kidney

Conclusions

Diabetes is a chronic disease, and patients with T1DM and T2DM should comply with their respective doctors' advice and recommended medications. In addition, patients should perform exercises and follow specific diets to keep fit and prevent the complications of this disease. Furthermore, patients should receive excessive doses to prevent hypoglycemia, take medications on time. Owing to complexities associated with modern dye formulations, forensic fiber analysis remains a vital tool to the pursuit of justice. Its contribution to the exoneration of individuals under suspicion cannot be overstated, and its role within the broader framework of forensic science remains indispensable to crime resolution and fair and just legal systems

Reference

[1] Stetson, B., McDonough, S., & Mokshagundam, S. P. (2015). Nutrition Issues and Recommendations in the Management of Diabetes and Prediabetes in Older Adults. *Preventive Nutrition: The Comprehensive Guide for Health Professionals*, 399-424. https://doi.org/10.1007/978-3-319-22431-2_21

[2] American Diabetes Association. (2018). 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. *Diabetes care*, 41(Supplement_1), S13-S27., <https://doi.org/10.2337/dc18-S002>

[3] Spaight, C., Gross, J., Horsch, A., & Puder, J. J. (2016). Gestational diabetes mellitus. *Novelties in diabetes*, 31, 163-178. <https://doi.org/10.1159/000439413>

[4] Chetan, M. R., Thrower, S. L., & Narendran, P. (2019). What is type 1 diabetes?. *Medicine*, 47(1), 5-9.. <https://doi.org/10.1016/j.mpmed.2018.10.006>

[5] Kakleas, K., Soldatou, A., Karachaliou, F., & Karavanaki, K. (2015). Associated autoimmune diseases in children and adolescents with type 1 diabetes mellitus (T1DM). *Autoimmunity reviews*, 14(9), 781-797. <https://doi.org/10.1016/j.autrev.2015.05.002>

[6] Krzewska, A., & Ben-Skowronek, I. (2016). Effect of associated autoimmune diseases on type 1 diabetes mellitus incidence and metabolic control in children and adolescents. *BioMed research international*, 2016(1), 6219730. <https://doi.org/10.1155/2016/6219730>

[7] Ozougwu, J. C., Obimba, K. C., Belonwu, C. D., & Unakalamba, C. B. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *J Physiol Pathophysiol*, 4(4), 46-57. <https://doi.org/10.5897/JPAP2013.0001>

[8] DeFronzo, R. A., Ferrannini, E., Groop, L., Henry, R. R., Herman, W. H., Holst, J. J., ... & Weiss, R. (2015). Type 2 diabetes mellitus. *Nature reviews Disease primers*, 1(1), 1-22., <https://doi.org/10.1038/nrdp.2015.19>

[9] Thevenod, F. (2008). Pathophysiology of diabetes mellitus type 2: roles of obesity, insulin resistance and β -cell dysfunction. In *Diabetes and Cancer* (Vol. 19, pp. 1-18). <https://doi.org/10.1159/isbn.978-3-8055-8641-2>

[10] Janež, A., Guja, C., Mitrakou, A., Lalic, N., Tankova, T., Czupryniak, L., ... & Smircic-Duvnjak, L. (2020). Insulin therapy in adults with type 1 diabetes mellitus: a narrative review. *Diabetes Therapy*, 11, 387-409. <https://doi.org/10.6084/m9.figshare.11310668>

[11] Sinha, B. (2020). Profile of Insulins. *Insulin Therapy Made Easy*, 15.

- [12] Cheng, A. Y., & Fantus, I. G. (2005). Oral antihyperglycemic therapy for type 2 diabetes mellitus. *Cmaj*, 172(2), 213-226. <https://doi.org/10.1503/cmaj.1031414>
- [13] Lv, W., Wang, X., Xu, Q., & Lu, W. (2020). Mechanisms and characteristics of sulfonylureas and glinides. *Current topics in medicinal chemistry*, 20(1), 37-56. <https://doi.org/10.2174/1568026620666191224141617>
- [14] Sola, D., Rossi, L., Schianca, G. P. C., Maffioli, P., Bigliocca, M., Mella, R., ... & Derosa, G. (2015). State of the art paper Sulfonylureas and their use in clinical practice. *Archives of medical science*, 11(4), 840-848. <https://doi.org/10.5114/aoms.2015.53304>
- [15] Davis, S. N. (2004). The role of glimepiride in the effective management of type 2 diabetes. *Journal of Diabetes and its Complications*, 18(6), 367-376. <https://doi.org/10.1016/j.jdiacomp.2004.07.001>
- [16] Bailey, C. J. (2017). Metformin: historical overview. *Diabetologia*, 60(9), 1566-1576. <https://doi.org/10.1007/s00125-017-4318-z>
- [17] Henquin, J. C. (2000). Triggering and amplifying pathways of regulation of insulin secretion by glucose. *Diabetes*, 49(11), 1751-1760. <https://doi.org/10.2337/diabetes.49.11.1751>
- [18] Rena, G., Hardie, D. G., & Pearson, E. R. (2017). The mechanisms of action of metformin. *Diabetologia*, 60(9), 1577-1585. <https://doi.org/10.1007/s00125-017-4342-z>
- [19] Lv, Z., & Guo, Y. (2020). Metformin and its benefits for various diseases. *Frontiers in endocrinology*, 11, 191. <https://doi.org/10.3389/fendo.2020.00191>
- [20] Kahn, C. R., Chen, L., & Cohen, S. E. (2000). Unraveling the mechanism of action of thiazolidinediones. *The Journal of clinical investigation*, 106(11), 1305-1307. <https://doi.org/10.1172/JCI11705>
- [21] Hauner, H. (2002). The mode of action of thiazolidinediones. *Diabetes/metabolism research and reviews*, 18(S2), S10-S15. <https://doi.org/10.1002/dmrr.249>
- [22] Reginato, M. J., & Lazar, M. A. (1999). Mechanisms by which thiazolidinediones enhance insulin action. *Trends in Endocrinology & Metabolism*, 10(1), 9-13. [https://doi.org/10.1016/S1043-2760\(98\)00110-6](https://doi.org/10.1016/S1043-2760(98)00110-6)
- [23] Ismail, D. T. S. E. S., & Deshmukh, D. S. A. (2012). Comparative study of effect of alpha glucosidase inhibitors–Miglitol, acarbose and voglibose on postprandial Hyperglycemia and glycosylated hemoglobin in type-2 Diabetes Mellitus. *diabetes*, 7(8). <https://doi.org/10.22376/ijpbs>
- [24] Ueno, H., Tsuchimochi, W., Wang, H. W., Yamashita, E., Tsubouchi, C., Nagamine, K., ... & Nakazato, M. (2015). Effects of miglitol, acarbose, and sitagliptin on plasma insulin and gut peptides in type 2 diabetes mellitus: a crossover study. *Diabetes Therapy*, 6, 187-196. <https://doi.org/10.1007/s13300-015-0113-3>
- [25] Derosa, G., & Maffioli, P. (2012). α -Glucosidase inhibitors and their use in clinical practice. *Archives of medical science: AMS*, 8(5), 899. <https://doi.org/10.5114/aoms.2012.31621>
- [26] Scheen, A. J. (2010). Dipeptidylpeptidase-4 inhibitors (gliptins) focus on drug-drug interactions. *Clinical pharmacokinetics*, 49, 573-588. <https://doi.org/10.2165/11532980-000000000-00000>
- [27] Rosenthal, N., Meininger, G., Ways, K., Polidori, D., Desai, M., Qiu, R., ... & Demarest, K. (2015). Canagliflozin: a sodium glucose co- transporter 2 inhibitor for the treatment of type 2 diabetes mellitus. *Annals of the New York Academy of Sciences*, 1358(1), 28-43. <https://doi.org/10.1111/nyas.12852>
- [28] Fu, H., Liu, S., Bastacky, S. I., Wang, X., Tian, X. J., & Zhou, D. (2019). Diabetic kidney diseases revisited: A new perspective for a new era. *Molecular metabolism*, 30, 250-263. <https://doi.org/10.1016/j.molmet.2019.10.005>
- [29] Gross, J. L., De Azevedo, M. J., Silveiro, S. P., Canani, L. H., Caramori, M. L., & Zelmanovitz, T. (2005). Diabetic nephropathy: diagnosis, prevention, and treatment. *Diabetes care*, 28(1), 164-176. <https://doi.org/10.2337/diacare.28.1.164>

نظرة عامة على انواع وادوية داء السكر

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الملخص:

الأنسولين هو هرمون يفرزه البنكرياس بشكل طبيعي من خلال خلايا β ، بينما الجلوكاجون هو هرمونات يفرزها البنكرياس أيضاً من خلال خلايا α ، والسوماتوستاتين الذي تفرزه خلايا δ . تلعب هذه الهرمونات دوراً حيوياً في التحكم في العمليات الأيضية في جسم الإنسان، وخاصة مستويات الجلوكوز. يؤدي نقص الأنسولين كلياً أو جزئياً إلى ما يسمى بمرض السكري، وهو ارتفاع مستوى السكر في الدم. يعد مرض السكري السبب الرئيسي للعديد من الأمراض مثل أمراض الكلى وفقدان البصر واضطرابات الأعصاب وأمراض القلب والأوعية الدموية. يمكن لأدوية الأنسولين والتركيبات والمثبطات الأخرى ذات الصلة أن تقلل من مرضى السكري وتخفف معدل الوفيات الناتج من مرض السكر.

كلمات مفتاحية: أنواع مرض السكري، أنواع الأنسولين، مثبطات مرض السكري.